CHAPTER 03
MANUFACTURING, SALE / DISTRIBUTION

The pharmaceutical industry develops, produces, and markets drugs licensed for use as medications. Pharmaceutical companies can deal in generic and/or brand medications. They are subject to a variety of laws and regulations regarding the patenting, testing and marketing of drugs.

The earliest drugstores date back to the Middle Ages. The first known drugstore was opened by Arabian pharmacists in Baghdad in 754, and many more soon began operating throughout the medieval Islamic world and eventually medieval Europe. By the 19th century, many of the drug stores in Europe and North America had eventually developed into larger pharmaceutical companies.

Most of today's major pharmaceutical companies were founded in the late 19th and early 20th centuries. Key discoveries of the 1920s and 1930s, such as insulin and penicillin, became mass-manufactured and distributed. Switzerland, Germany and Italy had particularly strong industries, with the UK, US, Belgium and the Netherlands following suit.

Legislation was enacted to test and approve drugs and to require appropriate labeling. Prescription and non-prescription drugs became legally distinguished from one another as the pharmaceutical industry matured. The industry got underway in earnest from the 1950s, due to the development of systematic scientific approaches, understanding of human biology (including DNA) and sophisticated manufacturing techniques.

Numerous new drugs were developed during the 1950s and mass-produced and marketed through the 1960s. These included the first oral contraceptive, 'The Pill', Cortisone, blood-pressure drugs and other heart medications. MAO Inhibitors, chlorpromazine (Thorazine), Haldol (Haloperidol) and the tranquilizers ushered in the age of psychiatric medication. Valium (diazepam), discovered in 1960, was marketed from 1963 and rapidly became the most prescribed drug in history, prior to controversy over dependency and habituation.

Attempts were made to increase regulation and to limit financial links between companies and prescribing physicians, including by the relatively new U.S. Food and Drug Administration (FDA). Such calls increased in the 1960s after the thalidomide tragedy came to light, in which the use of a new tranquilizer in pregnant women caused severe birth defects. In 1964, the World Medical Association issued its Declaration of Helsinki, which set standards for clinical research and demanded that subjects give their informed consent before enrolling in an experiment. Pharmaceutical companies became required to prove 'efficacy' in clinical trials before marketing drugs.

Cancer drugs were a feature of the 1970s. From 1978, India took over as the primary center of pharmaceutical production without patent protection.

The industry remained relatively small scale until the 1970s when it began to expand at a greater rate. Legislation allowing for strong patents, to cover both the process of manufacture and the specific products, came into force in most countries by the mid 1980s. Industry entered the 1980s pressured by economics and a host of new regulations, both safety and environmental, but
also transformed by new DNA chemistries and new technologies for analysis and computation. Drugs for heart disease and for AIDS were a feature of the 1980s, involving challenges to regulatory bodies and a faster approval process.

**Managed care** and Health Maintenance Organizations (HMOs) spread during the 1980s as part of an effort to contain rising medical costs, and the development of preventative and maintenance medications became more important. A new business atmosphere became institutionalized in the 1990s, characterized by mergers and takeovers, and by a dramatic increase in the use of contract research organizations for clinical development and even for basic R&D. The pharmaceutical industry confronted a new business climate and new regulations, born in part from dealing with world market forces and protests by activists in developing countries. **Animal Rights** activism was also a problem.

Marketing changed dramatically in the 1990s, partly because of a new consumerism. The Internet made possible the direct purchase of medicines by drug consumers and of raw materials by drug producers, transforming the nature of business. In the US, Direct-to-consumer advertising proliferated on radio and TV because of new FDA regulations in 1997 that liberalized requirements for the presentation of risks. The new antidepressants, the SSRIs, notably Fluoxetine (Prozac), rapidly became bestsellers and marketed for additional disorders.

Drug development progressed from a hit-and-miss approach to rational drug discovery in both laboratory design and natural-product surveys. Demand for nutritional supplements and so-called alternative medicines created new opportunities and increased competition in the industry. Controversies emerged around adverse effects, notably regarding Vioxx in the US, and marketing tactics. Pharmaceutical companies became increasingly accused of **disease mongering** or over-medicalizing personal or social problems.

**Drug discovery** is the process by which potential drugs are discovered or designed. In the past most drugs have been discovered either by isolating the active ingredient from traditional remedies or by serendipitous discovery. Modern **biotechnology** often focuses on understanding the **metabolic pathways** related to a **disease state or pathogen**, and manipulating these pathways using **molecular biology** or **Biochemistry**. A great deal of early-stage drug discovery has traditionally been carried out by universities and research institutions.

**Drug development** refers to activities undertaken after a compound is identified as a potential drug in order to establish its suitability as a medication. Objectives of drug development are to determine appropriate **Formulation and Dosing**, as well as to establish **safety**. Research in these areas generally includes a combination of in **vivo** studies, **in vitro** studies, and clinical trials. The amount of capital required for late stage development has made it a historical strength of the larger pharmaceutical companies. (http://csdd.tufts.edu)

Often, large multinational corporations exhibit **vertical integration**, participating in a broad range of drug discovery and development, manufacturing and quality control, marketing, sales, and distribution. Smaller organizations, on the other hand, often focus on a specific aspect such as discovering drug candidates or developing formulations. Often, collaborative agreements between research organizations and large pharmaceutical companies are formed to explore the potential of new drug substances.

**The cost of innovation**: Drug discovery and development is very expensive; of all compounds investigated for use in humans only a small fraction are eventually **approved**. The cost of developing a successful new drug (New chemical entity or NCE), has been estimated at about 1 billion USD (not
including marketing expenses). A study reported that the cost for discovering, developing and launching (which factored in marketing and other business expenses) a new drug (along with the prospective drugs that fail) rose over a five year period to nearly $1.7 billion in 2003. Because of the very long time needed for discovery, development, and approval of pharmaceuticals, these costs can accumulate to nearly half the total expense.

Controversy about drug development and testing: There have been increasing accusations and findings that clinical trials conducted or funded by pharmaceutical companies are much more likely to report positive results for the preferred medication.

Drug researchers not directly employed by pharmaceutical companies often look to companies for grants, and companies often look to researchers for studies that will make their products look favorable. Sponsored researchers are rewarded by drug companies, for example with support for their conference/symposium costs. Lecture scripts and even journal articles presented by academic researchers may actually be ‘ghost-written’ by pharmaceutical companies. Some researchers who have tried to reveal ethical issues with clinical trials or who tried to publish papers that show harmful effects of new drugs or cheaper alternatives have been threatened by drug companies with lawsuits.

Product approval in the US: In the United States, new pharmaceutical products must be approved by the Food and Drug Administration (FDA) as being both safe and effective. This process generally involves submission of an Investigational New Drug (IND) filing with sufficient pre-clinical data to support proceeding with human trials. Following INC approval, three phases of progressively larger human clinical trials may be conducted. Phase I generally studies ‘toxicity’ using healthy volunteers. Phase II can include ‘Pharmacokinetics’ and ‘Dosing’ in patients, and Phase III is a very large study of efficacy in the intended patient population.

A fourth phase of post-approval surveillance is also often required due to the fact that even the largest clinical trials cannot effectively predict the prevalence of rare side-effects. Post-marketing surveillance ensures that after marketing the safety of a drug is monitored closely. In certain instances, its indication may need to be limited to particular patient groups, and in others the substance is withdrawn from the market completely. The FDA provides information about approved drugs at the Orange Book site.

Legal issues: Where pharmaceutics have been shown to cause side-effects, civil action has occurred, especially in countries where tort payouts are likely to be large. Due to high-profile cases leading to large compensations, most pharmaceutical companies endorse tort reform. Recent controversies have involved Rofecoxib (Vioxx) and Serotonin Reuptake Inhibitors (SSRI) antidepressants.

Product approval elsewhere: In many non-US western countries a ‘fourth hurdle’ of cost effectiveness analysis has developed before new technologies can be provided. This focuses on the efficiency (in terms of the cost per Quality-Adjusted Life Year- QALY) of the technologies in question rather than their efficacy. In England National Institute for Health and Clinical Excellence (NICE) approval requires technologies be made available by the National Health Service (NHS), whilst similar arrangements exist with the Scottish Medical Consortium in Scotland and the Pharmaceutical Benefits Advisory Committee in Australia. A product must pass at the threshold for cost-effectiveness if it is to be approved. Treatments must represent ‘value for money’ and a net benefit to society. There is much speculation that a NICE style framework may be implemented in the USA to ensure Medicare and Medicaid spending is focused to maximize benefit to patients and not excessive profits for the pharmaceutical industry. In the UK, the British National Formulary is the core guide for pharmacists and clinicians.
Patents and generics: Depending on a number of considerations, a company may apply for and be
granted a patent for the drug, or the process of producing the drug, granting exclusivity rights typically
for about 20 years. However, only after rigorous study and testing, which takes 10 to 15 years on
average, will governmental authorities grant permission for the company to market and sell the drug.
Patent protection enables the owner of the patent to recover the costs of research and development
through high profit margins for the branded drug. When the patent protection for the drug expires, a
generic drug is usually developed and sold by a competing company.

Marketing: Pharmaceutical companies commonly spend a large amount on advertising, marketing and
lobbying. In the US, drug companies spend about $19 billion a year on promotions. Advertising is
common in healthcare journals as well as through more mainstream media routes. In some countries,
notably the US, pharmaceutical companies also employ lobbyists to influence politicians.

To retail pharmacies and stores: Commercial stores and pharmacies are a major target of non-
prescription sales and marketing for pharmaceutical companies.

Controversy about drug marketing and lobbying: There has been increasing controversy
surrounding pharmaceutical marketing and influence. There have been accusations and findings of
influence on doctors and other health professionals through drug representatives, including the
constant provision of marketing 'gifts' and biased information to health professionals; highly prevalent
advertising in journals and conferences; funding independent healthcare organizations and health
promotion campaigns; lobbying physicians and politicians, more than any other industry in the US;
sponsorship of medical schools or nurse training; sponsorship of continuing educational events, with
influence on the curriculum; and hiring physicians as paid consultants on medical advisory boards.

Developing world: The role of pharmaceutical companies in the developing world is a matter of some
debate, ranging from those highlighting the aid provided to the developing world, to those critical of the
use of the poorest in human clinical trials, often without adequate protections, particularly in states
lacking a strong rule of law. Other criticisms include an alleged reluctance of the industry to invest in
treatments of diseases in less economically advanced countries.

Patents: Under World Trade Organization (WTO) rules, a developing country has options for
obtaining needed medications under compulsory licensing or importation of cheaper versions of the
drugs, even before patent expiration (WTO Press Release). Pharmaceutical companies often offer
much needed medication at no or reduced cost to the developing countries. In March 2001, South
Africa was sued by 41 pharmaceutical companies for their Medicines Act, which allowed the import
and generic production of cheap AIDS drugs. The case was later dropped after protest around the
world. (http://en.wikipedia.org/wiki/Pharmaceutical_industry)

3.1 United States of America

In U.S. Drugs must be manufactured in accordance with standards called Good Manufacturing
Practices, and the FDA inspects manufacturing facilities before a drug can be approved. If a facility
isn't ready for inspection, approval can be delayed. Any manufacturing deficiencies found would need
to be corrected before approval.

FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with
its Current Good Manufacturing Practice (CGMP) regulations.
The approval process for new drug and generic drug marketing applications includes a review of the manufacturer’s compliance with the CGMP. Decisions regarding compliance with CGMP regulations are based upon inspection of the facilities, sample analyses, and compliance history of the firm. This information is summarized in reports which represent several years’ history of the firms.

FDA can issue a warning letter or initiate other regulatory actions against a company that fails to comply with Current Good Manufacturing Practice regulations. Failure to comply can also lead to a decision by FDA not to approve an application to market a drug. (www.fda.gov/cder/regulatory/applications/compliance.htm)

OVER THE COUNTER (NON PRESCRIPTION) DRUGS:

Over-the-counter and prescription drugs, including generic drugs, are regulated by FDA's Center for Drug Evaluation and Research (CDER). This work covers more than just medicines.

For example, fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered “drugs.”

Two regulatory mechanisms exist for the legal marketing of OTC drug products:

1. NDA (regulations described in 21 Code of Federal Regulations; (CFR) Part 314)
2. OTC drug monograph (regulations described in 21 CFR Part 330)

OTC drug products marketed under either mechanism must meet established standards for safety and effectiveness, neither mechanism establishes higher standards for safety or effectiveness than the other. Under both mechanisms, products must be manufactured according to Current Good Manufacturing Practices (cGMPs) and must comply with the labeling content and format requirements.

1. NDA. Legal marketing is under the authority of an approved product-specific New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA). An OTC drug product with active ingredient(s), dosage form, dosage strength, or route of administration new to the OTC marketplace is regulated under the NDA process. For example, a drug product previously available only by prescription (Rx) can be marketed OTC under an approved “Rx-to-OTC switch” NDA.

FDA must approve the NDA for an OTC drug product before that product can be marketed OTC. A drug manufacturer submits data in an NDA demonstrating a drug product is safe and effective for use by consumers without the assistance of a healthcare professional. FDA must review the data within an established timeframe, and the data submitted in an NDA remains confidential.

The drug manufacturer can only market the product with the specific formulation and exact labeling approved by FDA. To make a change, the manufacturer must submit an NDA supplement and FDA must approve that supplement.

2. OTC Drug Monograph. Legal marketing is in compliance with an OTC drug monograph. Unlike NDAs which are based on drug products, monographs specify the active ingredients that can be contained within OTC drug products. An OTC drug product containing ingredients that comply with standards established in an applicable monograph is considered to be “Generally Recognized as Safe and Effective” (GRASE) and does not require specific FDA approval before marketing. For example, OTC sunscreen drug products can be legally marketed if they contain...
ingredients which comply with the standards established in the OTC sunscreen monograph for formulation, labeling, and testing. (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm106386.htm)

Over-the-Counter (Non Prescription) drugs play an increasingly vital role in America’s health care system. OTC drug products are those drugs that are available to consumers without a prescription. There are more than 80 therapeutic categories of OTC drugs, ranging from acne drug products to weight control drug products. As with prescription drugs, Centre for Drug Evaluation and Research (CDER) oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks.

SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

Subpart A--General Provisions

Sec. 314.2 Purpose.

The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to establish an effective system for FDA's surveillance of marketed drugs. These regulations shall be construed in light of these objectives.

Sec. 314.3 Important Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (sections 201-901 (21 U.S.C. 301-392)).

Application means the application described under 314.50, including all amendments and supplements to the application.

Approval letter means a written communication to an applicant from FDA approving an application or an abbreviated application.

Assess the effects of the change means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

Complete response letter means a written communication to an applicant from FDA usually describing all of the deficiencies that the agency has identified in an application or abbreviated application that must be satisfactorily addressed before it can be approved.

Efficacy supplement means a supplement to an approved application proposing to make one or more related changes from among the following changes to product labeling:
1) Add or modify an indication or claim;
2) Revise the dose or dose regimen;
3) Provide for a new route of administration;
4) Make a comparative efficacy claim naming another drug product;
5) Significantly alter the intended patient population;
6) Change the marketing status from prescription to over-the-counter use;
7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of part 314; or
8) Incorporate other information based on at least one adequate and well-controlled clinical study.

**Listed drug** means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

**Original application** means a pending application for which FDA has never issued a complete response letter or approval letter, or an application that was submitted again after FDA had refused to file it or after it was withdrawn without being approved.

**Specification** means the quality standard (i.e., tests analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

The list means the list of drug products with effective approvals published in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication.

**Part 210 - CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL**

210.1 Status of Current Good Manufacturing Practice regulations. (a) The regulations set forth in this part and in Parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in Parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

210.2 Applicability of Current Good Manufacturing Practice regulations. (a) The regulations in this part and in Parts 211 through 226 of this chapter as they may pertain to a drug and in Parts 600
through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in Parts 211 through 226 and Parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

210.3 Definitions.

Some of the important definitions and interpretations contained in section 201 of the act are:

**Batch** means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

**Component** means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

**Drug product** means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

**Active ingredient** means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

**Inactive ingredient** means any component other than an "active ingredient."

**In-process material** means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

**Lot** means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

**Lot number, control number, or batch number** means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.

**Manufacture, processing, packing, or holding of a drug product** includes packaging and labeling operations, testing, and quality control of drug products.

**Quality control unit** means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS


Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.


Subpart D--Equipment: Equipment design, size, and location, Equipment construction, Equipment cleaning and maintenance, Automatic, mechanical, and electronic equipment, Filters.

Subpart E--Control of Components and Drug Product Containers and Closures: General requirements, Receipt and storage of untested components, drug product containers, and closures, Testing and approval or rejection of components, drug product containers, and closures, Use of approved components, drug product containers, and closures, Retesting of approved components, drug product containers, and closures, Rejected components, drug product containers, and closures & Drug product containers and closures.

Subpart F--Production and Process Controls: Written procedures; deviations, Charge-in of components, Calculation of yield, Equipment identification, Sampling and testing of in-process materials and drug products, Time limitations on production, Control of microbiological contamination & Reprocessing.

Subpart G--Packaging and Labeling Control: Materials examination and usage criteria, Labeling issuance, Packaging and labeling operations, Tamper-evident packaging requirements for over-the-counter (OTC) human drug products, Drug product inspection & Expiration dating.

Subpart H--Holding and Distribution: Warehousing procedures & Distribution procedures.
Subpart I—Laboratory Controls: General requirements, Testing and release for distribution, Stability testing, Special testing requirements, Reserve samples, Laboratory animals & Penicillin contamination.

Subpart J—Records and Reports: General requirements, Equipment cleaning and use log, Component, drug product container, closure, and labeling records, Master production and control records, Batch production and control records, Production record review, Laboratory records, Distribution records & Complaint files.


Subpart A-General Provisions

211.1 Scope

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter, as they pertain to drug products, and in parts 600 through 680 of this chapter, as they pertain to biological products for human use, shall be considered to supplement, not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter or in parts 600 through 680 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the regulation in this part.

(c) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

211.3 Definitions: The definitions set forth in 210.3 of this chapter apply in this part.

Subpart B—Organization and Personnel

211.22 Responsibilities of quality control unit: There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

211.25 Personnel qualifications: Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good
manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

211.28 Personnel responsibilities: Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel; such as head, face, hand, and arm coverings; shall be worn as necessary to protect drug products from contamination; Personnel shall practice good sanitation and health habits. Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas;

Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

Subpart C-Buildings and Facilities

211.42 Design and construction features: Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mix-ups.

211.44 Lighting: Adequate lighting shall be provided in all areas.

211.46 Ventilation, air filtration, air heating and cooling: Adequate ventilation shall be provided, adequate control over air pressure; micro-organisms, dust, humidity, and temperature shall be provided; Air filtration systems, including preilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas; adequate exhaust systems or other systems adequate to control contaminants. Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.
211.48 Plumbing: Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product; drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break.

211.50 Sewage and refuse: Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

211.52 Washing and toilet facilities: Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

211.67 Equipment cleaning and maintenance: Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product.

211.68 Automatic, mechanical, and electronic equipment: Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems. If used, shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

211.72 Filters: Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products.

Subpart E-Control of Components and Drug Product Containers and Closures

211.80 General requirements: There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures, stored in a manner to prevent contamination; Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.
Each container or grouping of containers for components or drug product containers, or closures shall be identified as to its status i.e., quarantined, approved, or rejected.

211.82 Receipt and storage of untested components, drug product containers, and closures: Apart from visual examination, Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the above general requirements.

211.84 Testing and approval or rejection of components, drug product containers, and closures: Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

211.86 Use of approved components, drug product containers, and closures: Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first.

211.87 Retesting of approved components, drug product containers, and closures: Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit.

211.89 Rejected components, drug product containers, and closures: Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.94 Drug product containers and closures: Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product. Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

Subpart F-Production and Process Controls

211.100 Written procedures; deviations: There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall be written including any changes, approved by the quality control unit and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

211.101 Charge-in of components: Written production and control procedures shall include the following, amongst others:

The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient. Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. Weighing, measuring, or subdividing operations for components shall be adequately supervised and verified by a second person.

211.103 Calculation of yield: Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.
211.105 Equipment identification: All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

211.110 Sampling and testing of in-process materials and drug products: To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall include, but are not limited to, the following, where appropriate:

1) Tablet or capsule weight variation;
2) Disintegration time;
3) Adequacy of mixing to assure uniformity and homogeneity;
4) Dissolution time and rate;
5) Clarity, completeness, or pH of solutions.

In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods. Rejected in-process materials shall be identified and controlled under a quarantine system.

211.111 Time limitations on production: When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product, deviation shall be justified and documented.

211.113 Control of microbiological contamination: Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

211.115 Reprocessing: Written procedures shall be established and followed prescribing a system for reprocessing batches. Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G-Packaging and Labeling Control

211.122 Materials examination and usage criteria: There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel. Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.
Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

211.125 Labeling issuance: Strict control shall be exercised over labeling issued for use in drug product labeling operations. Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

Procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued.

All excess labeling bearing lot or control numbers shall be destroyed. Returned labeling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.

Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

211.130 Packaging and labeling operations: There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products. Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

211.132 Tamper-resistant packaging requirements for over-the-counter (OTC) human drug products: General. The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-resistant packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or throat lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated or misbranded or both.

Requirement for tamper-resistant package. Each manufacturer and packer who packages an OTC drug product for retail sale shall package the product in a tamper-resistant package. A tamper-resistant package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. The tamper-resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution.

Labeling. Each retail package of an OTC drug product covered by this section, is required to bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. For example, the labeling statement on a bottle with a shrink band could say "For your protection, this bottle has an imprinted seal around the neck."

Request for exemptions from packaging and labeling requirements. A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under section 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from Tamper-Resistant Rule." The petition is required to contain the following:
(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.

(2) The reasons that the drug product's compliance with the tamper-resistant packaging or labeling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

211.134 Drug product inspection: Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label. Results of these examinations shall be recorded in the batch production or control records.

211.137 Expiration dating: To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing. Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in section 211.166.

If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products. Homeopathic drug products shall be exempt from the requirements of this section.

New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations.

Pending consideration of a proposed exemption, published in the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

Subpart H-Holding and Distribution

211.142 Warehousing procedures: Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

- Quarantine of drug products before release by the quality control unit;
- Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

211.150 Distribution procedures: Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

- A procedure whereby the oldest approved stock of a drug product is distributed first; and
- A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall, if necessary.

Subpart I-Laboratory Controls
211.160 General requirements: The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit, and shall be documented at the time of performance.

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules.

211.165 Testing and release for distribution: For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release.

The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented.

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed.

211.166 Stability testing: There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted.
For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

211.167 Special testing requirements: For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

211.170 Reserve samples: An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary containing the active ingredient. The retention time shall be as prescribed.

An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. The retention time shall be as prescribed.

211.173 Laboratory animals: Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

Subpart J-Records and Reports

211.180 General requirements: (a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating 3 years after distribution of the batch.

Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such
records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection.

Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.

Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.

Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

211.182 Equipment cleaning and use log: A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

211.184 Component, drug product container, closure, and labeling records: These records shall include the following:

The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known. The results of any test or examination performed and the conclusions derived there from.

An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component.

Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with these provisions. The disposition of rejected components, drug product containers, closure, and labeling.

211.186 Master production and control records: To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed. Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;
(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to sec. 211.192 is required;

(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations,

**Prescription Drug Approval:** Drug companies seeking FDA approval to sell a new prescription drug in the United States must test it in various ways. First are laboratory and animal tests. Next are tests in humans to see if the drug is safe and effective when used to treat or diagnose a disease.

After testing the drug, the company then sends FDA an application called a New Drug Application (NDA). Some drugs are made out of biologic materials. Instead of an NDA, new biologic drugs are approved using a Biologies License Application (BLA). Whether an NDA or a BLA, the application includes

- the drug’s test results
- manufacturing information to demonstrate the company can properly manufacture the drug
- the company’s proposed label for the drug. The label provides necessary information about the drug, including uses for which it has been shown to be effective, possible risks, and how to use it.

If a review by FDA physicians and scientists shows the drug’s benefits outweigh its known risks and the drug can be manufactured in a way that ensures a quality product, the drug is approved and can be marketed in the United States (http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194949.htm.)

**Prescription Drug Marketing Act of 1987**

To amend the Federal Food, Drug, and Cosmetic Act to ban the reimportation of drugs produced in the United States, to place restrictions on the distribution of drug samples, to ban certain resales of drugs by hospitals and other health care entities, and for other purposes.
Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE: REFERENCE.

(a) SHORT TITLE.--This Act may be cited as the "Prescription Drug Marketing Act of 1987".

(b) Reference.-- Whenever in this Act an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act.

SEC. 2. FINDINGS. The Congress finds the following:

(1) American consumers cannot purchase prescription drugs with the certainty that the products are safe and effective.

(2) The integrity of the distribution system for prescription drugs is insufficient to prevent the introduction and eventual retail sale of substandard, ineffective, or even counterfeit drugs.

(3) The existence and operation of a wholesale submarket, commonly known as the "diversion market", prevents effective control over or even routine knowledge of the true sources of prescription drugs in a significant number of cases.

(4) Large amounts of drugs are being reimported to the United States as American goods returned. These imports are a health and safety risk to American consumers because they may have become sub potent or adulterated during foreign handling and shipping.

(5) The ready market for prescription drug reimports has been the catalyst for a continuing series of frauds against American manufacturers and has provided the cover for the importation of foreign counterfeit drugs.

(6) The existing system of providing drug samples to physicians through manufacturer's representatives has been abused for decades and has resulted in the sale to consumers of misbranded, expired, and adulterated pharmaceuticals.

(7) The bulk resale of below wholesale priced prescription drugs by health care entities, for ultimate sale at retail, helps fuel the diversion market and is an unfair form of competition to wholesalers and retailers that must pay otherwise prevailing market prices.

(8) The effect of these several practices and conditions is to create an unacceptable risk that counterfeit, adulterated, misbranded, sub potent, or expired drugs will be sold to American consumers.

Definition of a Combination Product

As defined in 21 CFR section 3.2(e), the term combination product includes:

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Overview of the Office of Combination Products

Combination products (i.e., drug-device, drug-biologic, and device-biologic products) are increasingly incorporating cutting edge, novel technologies that hold great promise for advancing patient care. For example, innovative drug delivery devices have the potential to make treatments safer or more effective, or more convenient or acceptable to patients. Drug-eluting cardiovascular stents have the potential to reduce the need for surgery by preventing the restenosis that sometimes occurs following stent implantation. Drugs and biologics can be used in combination to potentially enhance the safety and/or effectiveness of either product used alone. Biologics are being incorporated into novel orthopedic implants to help facilitate the regeneration of bone required to permanently stabilize the implants.

Stakeholders report that FDA can expect to receive significantly more combination products for review as technological advances continue to merge therapeutic products and blur the historical lines of separation between FDA's medical product Centers. Since combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different FDA Centers, they also raise challenging regulatory, policy, and review management issues. A number of criticisms have been raised regarding FDA's regulation of combination products. These include concerns about the consistency, predictability, and transparency of the assignment process; issues related to the management of the review process when two (or more) FDA Centers have review responsibilities for a combination product; lack of clarity about the post market regulatory controls applicable to combination products; and lack of clarity regarding certain Agency policies, such as when applications to more than one Agency Center are needed.

To address these concerns, FDA's Office of Combination Products (OCP) was established on Dec. 24, 2002, as required by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). The law gives the Office broad responsibilities covering the regulatory life cycle of drug-device, drug-biologic, and device-biologic combination products. However, the primary regulatory responsibilities for, and oversight of, specific combination products will remain in one of three product centers -- the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, or the Center for Devices and Radiological Health -- to which they are assigned.

Office duties include:

assigning an FDA Center to have primary jurisdiction for review of a combination product ensuring timely and effective premarket review of combination products by overseeing reviews involving more than one agency center ensuring consistency and appropriateness of postmarket regulation of
combination products resolving disputes regarding the timeliness of premarket review of combination products updating agreements, guidance documents or practices specific to the assignment of combination products submitting annual reports to Congress on the Office's activities and impact. The Office also has assumed the functions of the Combination Products Program begun in 2002 within the FDA Office of the Ombudsman. Among these functions: working with FDA Centers to develop guidance or regulations to clarify the agency regulation of combination products serving as a focal point for combination products issues for internal and external stakeholders.

Laws, Regulations, Policies and Procedures for Drug Applications

*Code of Federal Regulations* for Investigational New Drugs (INDs), New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)

*Manual of Policies and Procedures (MaPPs)*

*Code of Federal Regulations* for Investigational New Drugs (INDs), New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)

The following *Code of Federal Regulations* sections provide regulations for INDs and NDAs. All parts of section 21 of the *Code of Federal Regulations* are also available.

- CFR Sections for INDs
- CFR Sections for NDAs
- CFR Sections for ANDAs

*Manual of Policies and Procedures (MaPPs)*.

The following MaPPs provide official instructions for internal practices and procedures followed by CDER staff to help standardize the IND and NDA review process. All CDER MaPPs are available from the MaPP Index webpage.

- MaPPs for INDs
- MaPPs for NDAs
- MaPPs for ANDAs

Drug Application Regulatory Compliance

Compliance Questions and Answers

Introduction

FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.
Federal Regulations

Code of Federal Regulations (CFR). The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA’s portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains most regulations pertaining to food and drugs. The regulations document the actions of drug sponsors that are required under Federal law.


* Federal Register Notices for Proposed Changes and Final Changes to CGMP. The Office of the compliance, Division of Manufacturing and Product Quality web page provides links to in-process changes in cGMP regulations announced in the Federal Register.

Drug Application Forms and Electronic Submissions

* Investigational New Drug Forms (IND)
* New Drug Application Forms (NDA)
* Abbreviated New Drug Application Forms (ANDA) for Generic Drug Products
* Orphan Drug Products (for rare diseases and disorders)

Electronic Regulatory Submissions and Review (ERSR)

Investigational New Drug Forms (IND)

* FDA 1571. Investigational New Drug Application
* FDA 1572. Statement of Investigator
* Instructions for completing FDA forms 1571 and 1572
* FDA Form Distributions Page. includes links to:
  Certification: Financial Interest and Arrangements of Clinical Investigators
  Disclosure: Financial Interest and Arrangements of Clinical Investigators
  MedWatch: FDA Medical Product Reporting Program – Voluntary
  MedWatch: FDA Medical Products Reporting Program - Mandatory

For electronic form submissions, see Electronic Regulatory Submissions and Review

New Drug Application Forms (NDA)

* Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
* Form FDA-3397 User Fee Cover Sheet
* Form FDA-3331. New Drug Application Field Report

For electronic form submissions, see Electronic Regulatory Submission and Review
Abbreviated New Drug Application Forms (ANDA) for Generic Drug Products

* FDA Form 356h. Application to Market a New Drug for Human Use/Antibiotic Drug for Human Use
* The CDER Office of Generic Drugs has developed a guidance document entitled Providing Regulatory Submissions in Electronic Format — ANDAs [PDF version] (Issued 6/2002, Posted 6/27/2002) to assist applicants making regulatory submissions in electronic format of abbreviated new drug applications. This guidance should be used in conjunction with the following guidances:
  * Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations.
  * Regulatory Submissions in Electronic Format; New Drug Applications.

For electronic form submissions, see Electronic Regulatory Submissions and Review

Orphan Drug Products (for rare diseases and disorders)

* There is no form, but there is a prescribed format for application for orphan drug status. The section from the regulations that describes the format can be found on this website on the Orphan Drug Act and Related Law and Regulations page.

Electronic Regulatory Submission and Review (ERSR)

* Regulations and Instructions for Submitting Drug Applications Electronically. This webpage provides for information on CDER's program to enable the electronic submission of regulatory information to the Center and the review of it by CDER staff.

Drug Registration and Listing: Section 510 of the Federal Food, Drug, and Cosmetic Act requires manufacturers, repackers, and relabelers that engage in the manufacture, preparation, propagation, compounding, or processing of human or veterinary drugs and human biological products to register their establishment(s) and submit a listing of every product in commercial distribution with the FDA. This information helps FDA maintain a catalog of all human and veterinary drugs and biologics in commercial distribution in the United States.

The Act: Section 510 of the Food, Drug and Cosmetic Act - Registration of Producers of Drugs and Devices.

The Regulations

* Proposed 21 CFR 207 - Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution
* FDA News: FDA Proposes New Rule to Automate Drug Registration and Listing
* Federal Register Notice, 71FR51275:
  * 21 CFR 207 - Registration of Producers of Drugs And Listing of Drugs in Commercial Distribution

Federal Register Notices

* Proposed 21 CFR 207 - Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution:
  Federal Register Notice, 71FR51276:
Forms Needed to Register and List

Form FDA 2656 - Registration of Drug Establishment/Labeler Code Assignment

This form is used by manufacturers, repackers, and relabelers to register establishments and by private label distributors to obtain a labeler code. This form is also used to provide updates in registration information annually or at the discretion of the registrant, when any changes occur.

Form FDA 2657 - Drug Product Listing

This form is used by registrants to report within 5 days of beginning the manufacturing, repackaging, or relabeling of drug or biological products a listing for every product in commercial distribution, and private label distributors who elect to submit listing information to FDA for products they distribute. This form is also used to provide updates to product listing information every June and December or at the discretion of the registrant, when any change occurs.

Form FDA 2658 - Registered Establishment's Report of Private Label Distributors

This form is used by manufacturers to report product listing information for those private label distributors who do not elect to list the products they distribute, and to update product listing information for private label distributors, every June and December or, at the discretion of the registrant, when any change occurs.

Guidance Documents

Forms for Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution.

Foreign Establishment Registration (Effective May 24, 2002)

According to the Federal Register Notice, November 27, 2001 (Vol. 6, No. 228), http://www.fda.gov/ohrms/dockets/98fr/112701a.htm, effective May 24, 2002, all foreign drug establishments (registrants) are required to register with the Food and Drug Administration (FDA) and identify a United States agent.

The United States agent must be included as part of their initial and updated registration information.

1) Each registrant will designate only one United States agent and this agent should represent the registrant and all products that will be imported or offered for import into the United States by the registrant.

2) The registrant shall report changes in the United States agent’s name, address, or phone number to FDA within 10-business days of the change.

3) All drug registration and listing deficiencies will be mailed back to the US agent, irrespective of who submitted the forms.

4) To designate a United States agent, the registrant should submit a letter, on the registrant’s letterhead to the FDA that includes the following information:
1. Name, street address, telephone phone number, fax number and e-mail address of the United States agent
2. Signed by a senior corporate official located at the foreign establishment
3. Include the telephone number of an registrant's official contact or senior corporate official

**The United States Agent:** (from CFR 207.40)

1. May be an individual, firm or company
2. Must be physically located in the United States but may not be a Post Office Box
3. Shall assist FDA in communications with the registrant
4. Respond to questions concerning the registrant's products that are imported or offered for import into the United States
5. Assist FDA in scheduling inspections of the registrant's foreign establishment

One may obtain forms for registering a foreign establishment from [www.hhs.gov/forms](http://www.hhs.gov/forms). A copy of the guidance documents for annual registration of foreign establishments is available at [http://www.fda.gov/cder/drugs/registration_listing.htm](http://www.fda.gov/cder/drugs/registration_listing.htm).

Submit the forms (Form FDA 2656, Registration of Drug Establishment/Labeler Code Assignment and Form FDA 2657, Drug Product Listing), and the United States Agent letter to:

CDER/Drug Registration and Listing HFD-337
5600 Fishers Lane
Rockville, MD 20857

**CHAPTER V - DRUGS AND DEVICES**

**SUBCHAPTER A - DRUGS AND DEVICES**

**ADULTERATED DRUGS AND DEVICES**

**REGISTRATION OF PRODUCERS OF DRUGS AND DEVICES**

**SEC. 510. [360]** (a) As used in this section –

(1) the term "manufacture, preparation, propagation, compounding, or processing" shall include repackaging or otherwise changing the container, wrapper, or labeling of any drug package or device package in furtherance of the distribution of the drug or device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user; and

(2)(a) the term "name" shall include in the case of a partnership the name of each partner and, in the case of a corporation, the name of each corporate officer and director, and the State of incorporation

(b) On or before December 31 of each year every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices shall register with the Secretary his name, places of business, and all such establishments.

(c) Every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices in any establishment which he owns or operates in any State shall immediately register with the Secretary his name, place of business, and such establishment.

(d) Every person duly registered in accordance with the foregoing subsections of this section shall immediately register with the Secretary any additional establishment which he owns or operates in any
State and in which he begins the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices.

(e) The Secretary may assign a registration number to any person or any establishment registered in accordance with this section. The Secretary may also assign a listing number to each drug or class of drugs listed under subsection (j). Any number assigned pursuant to the preceding sentence shall be the same as that assigned pursuant to the National Drug Code.

(f) The Secretary shall make available for inspection, to any person so requesting, any registration filed pursuant to this section; except that any list submitted pursuant to paragraph (3) of subsection (j) and the information accompanying any list or notice filed under paragraph (1) or (2) of that subsection shall be exempt from such inspection unless the Secretary finds that such an exemption would be inconsistent with protection of the public health.

(g) The foregoing subsections of this section shall not apply to:

1. **pharmacies** which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail;

2. **practitioners** licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice;

3. **persons** who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in research, teaching, or chemical analysis and not for sale;

4. any **distributor** who acts as a wholesale distributor of devices, and who does not manufacture, repackage, process, or relabel a device; or

5. such other classes of persons as the **Secretary may by regulation exempt** from the application of this section upon a finding that registration by such classes of persons in accordance with this section is not necessary for the protection of the public health.

(h) Every establishment in any State registered with the Secretary pursuant to this section shall be subject to inspection pursuant to section 704 and every such establishment engaged in the manufacture, propagation, compounding, or processing of a drug or drugs classified in class II or III shall be so inspected by one or more officers or employees duly designated by the Secretary at least once in the two-year period beginning with the date of registration of such establishment pursuant to this section and at least once in every successive two-year period thereafter.

(i) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States shall register with the Secretary the name and place of business of the establishment and the name of the United States agent for the establishment.

(2) The establishment shall also provide the information required by subsection (j).

(3) The Secretary is authorized to enter into cooperative arrangements with officials of foreign countries...
to ensure that adequate and effective means are available for purposes of determining, from time to

time, whether drugs manufactured, prepared, propagated, compounded, or processed by an

establishment described in paragraph (1), if imported or offered for import into the United States, shall

be refused admission on any of the grounds set forth in section 801(a). (j)(1) Every person who

registers with the Secretary under subsection (b), (c), or (d) shall, at the time of registration under any

such subsection, file with the Secretary a list of all drugs Such list shall be prepared in such form and

manner as the Secretary may prescribe and shall be accompanied by other documents and/or

information as required by the Secretary.

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN

SERVICES

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN

COMMERCIAL DISTRIBUTION

TITLE 21—FOOD AND DRUGS

HUMAN SERVICES

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN

COMMERCIAL DISTRIBUTION—Table of Contents

Subpart A—General

Sec. 207.3 Definitions.

(a) The following definitions apply to this part:

(1) Act means the Federal Food, Drug, and Cosmetic Act approved June 25, 1938 (52 Stat. 1040 et

seq., as amended (21 U.S.C. 301-392)), except as otherwise provided.

(2) Advertising and labeling include the promotional material described in Sec. 202.1(1) (1) and (2)

respectively.

(3) Any material change includes any change in the identity or quantity of the active ingredient(s),

any change in the identity or quantity of the inactive ingredient(s) where quantitative listing of all

ingredients is required by Sec. 207.31(a)(2), any significant change in the labeling of a prescription

drug, and any significant change in the label or package insert of an over-the-counter drug. Changes

that are not significant include changes in arrangement or printing or changes of an editorial nature.

(4) Bulk drug substance means any substance that is represented for use in a drug and that, when

used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a

finished dosage form of the drug, but the term does not include intermediates used in the synthesis of

such substances.

(5) Commercial distribution means any distribution of a human drug except for investigational use

and any distribution of an animal drug or an animal feed bearing or containing an animal drug for

noninvestigational uses, but the term does not include internal or interplant transfer of a bulk drug

substance between registered domestic establishments within the same parent, subsidiary,

and/or affiliate company.
(6) **Drug product salvaging** means the act of segregating drug products that may have been subjected to improper storage conditions, such as extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation, for the purpose of returning some or all of the products to the marketplace.

(7) **Establishment** means a place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for a registered drug establishment (e.g., consulting laboratories), manufacturers of medicated feeds and of vitamin products that are drugs in accordance with section 201(g) of the act, human blood donor centers, and animal facilities used for the production or control testing of licensed biologicals, and establishments engaged in drug product salvaging.

(8) **Manufacturing or processing** means the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(9) **Representative sampling of advertisements** means typical advertising material that gives a balanced picture of the promotional claims used for the drug.

**General**

**Sec. 207.7 Establishment registration and product listing for human blood and blood products and for medical devices.**

Owners and operators of human blood and blood product establishments shall register and list their products with the Division of Product Certification, Office of Biological Product Review (HFB-240), Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892, on Form FDA-2830 (Blood Establishment Registration and Product Listing), in accordance with part 607. Such owners and operators who also manufacture or process other drug products at the same establishment shall, in addition, register and list all such other drug products with the Drug Listing Branch in accordance with this part.

**Exemptions**

**Sec. 207.10 Exemptions for domestic establishments.** The following classes of persons are exempt from registration and drug listing in accordance with this part:

(a) **Pharmacies that operate under applicable local laws** regulating dispensing of prescription drugs and that do not manufacture or process drugs for sale other than in the regular course of the practice of the profession of pharmacy, including dispensing and selling drugs at retail.

(b) **Hospitals, clinics, and public health agencies** that maintain establishments in conformance with any applicable local laws regulating the practices of pharmacy or medicine and that regularly engage in...
dispensing prescription drugs, other than human blood or blood products, upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care.

(c) Practitioners who are licensed by law to prescribe or administer drugs and who manufacture or process drugs solely for use in their professional practice.

(d) Persons who manufacture or process drugs not for sale but solely for use in research, teaching, or chemical analysis.

(e) Manufacturers of harmless inactive ingredients that are excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs, and who otherwise would not be required to register under this part.

(f) Any manufacturer of a virus, serum, toxin, or analogous product intended for treatment of domestic animals who holds an unsuspended and unrevoked license issued by the Secretary of Agriculture.

(g) Carriers, in their receipt, carriage, holding, or delivery of drugs in the usual course of business as carriers.

Procedures for Domestic Drug Establishments

Sec. 207.20 Who must register and submit a drug list.

(a) Owners or operators of all drug establishments, not exempt, that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register and to submit a list of every drug in commercial distribution (except that listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments). Such owners or operators are required to register and to submit a list of every drug in commercial distribution whether or not the output of such establishment or any particular drug so listed enters interstate commerce, except that drug listing is not required at this time for the manufacturing, preparation, propagation, compounding, or processing of an animal feed. No owner or operator may register an establishment, if any part of the establishment is registered by any other owner or operator.

(b) Owners or operators of establishments not otherwise required to register under section 510 of the act that distribute under their own label or trade name a drug manufactured or processed by a registered establishment may elect to submit listing information directly to FDA and to obtain a Labeler Code. A distributor who submits drug listing information shall include the registration number of the drug establishment that manufactured, prepared, propagated, compounded, or processed each drug listed.

(c) Before beginning manufacture or processing of a drug subject to one of the following applications, an owner or operator of an establishment is required to register before the agency approves it: A new drug application, a new animal drug application, a medicated feed mill license application, or a biologics license application.

(d) No registration fee is required.

(e) Registration and listing do not constitute an admission, or agreement, or determination that a product is a drug.
Procedures for Domestic Drug Establishments

Sec. 207.21 Times for registration and drug listing.

(a) The owner or operator of an establishment entering into the manufacture or processing of a drug or drugs shall register the establishment within 5 days after the beginning of the operation and shall submit a list of every drug in commercial distribution at that time. If the owner or operator of the establishment has not previously entered into such an operation, the owner or operator shall register within 5 days after submitting a new drug application, new animal drug application, medicated feed mill license application, or a biologics license application.

Procedures for Domestic Drug Establishments

Sec. 207.22 How and where to register and list drugs.

An establishment shall register the first time on Form FDA-2656 (Registration of Drug Establishment), obtainable on request from the Drug Listing Branch (HFD-334), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or from FDA district offices. An establishment whose drug registration for that year was validated under Sec. 207.35 shall make subsequent annual registration on Form FDA-2656 as described in Sec. 207.21(a) by mailing the completed form to the above address within 30 days after receipt from FDA.

Procedures for Domestic Drug Establishments

Sec. 207.25 Information required in registration and drug listing.

(a) Form FDA-2656 (Registration of Drug Establishment) provides for furnishing or confirming information required by the act. This information includes, for each establishment, the name and full address of the drug establishment; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned, partnership or corporation); and the name of the owner or operator of the establishment.

(b) Form FDA-2657 (Drug Product Listing) provides that information required by the act be furnished as follows:

(1) A list of drugs, including bulk drug substances and Type A articles for use in the manufacture of animal feeds as well as finished dosage forms, by established name and by proprietary name, that are being manufactured or processed for commercial distribution and that have not been included in any list previously submitted to FDA.

(2) For each drug listed that the registrant regards as subject to section 505 or 512 of the act, the new drug application number, abbreviated new drug application number, or new animal drug application number and a copy of all current labeling, except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement.

(3) For each drug listed that the registrant regards as subject to section 351 of the Public Health Service Act, the license number of the manufacturer.

(4) For each human prescription drug listed that the registrant regards as not subject to section 505 of the act or 351 of the Public Health Service Act, and that is not manufactured by a registered blood bank, a copy of all current labeling and a representative sampling of advertisements.
(5) For each human over-the-counter drug listed, or each animal drug listed, that the registrant regards a copy of label, the package insert, and a representative sampling of any other labeling.

(6) For each prescription or over-the-counter drug so listed that the registrant regards and that is not manufactured by a registered blood bank, a quantitative listing of the active ingredient(s). Unless the quantitative listing is expressed as a percentage in the official compendium or the ingredient is a nonantibiotic ingredient in a Type A medicated article for use in the manufacture of animal feeds, the quantity of an ingredient shall be expressed in terms of the amount, not the percent, of that ingredient in each dosage unit or, if the drug is not in unit dosage form, the amount of the ingredient in a specific unit of weight or measure of the drug.

(7) For each drug listed, the registration number of every drug establishment within the parent company at which it is manufactured or processed.

(8) For each drug listed, the National Drug Code (NDC) number. If FDA has not assigned an NDC Labeler Code, the registrant shall include a Product Code and Package Code and FDA will assign a Labeler Code.

c) For each drug product listed that is subject to the imprinting requirements of part 206 of this chapter, including products that are exempted, drug companies must submit a document that provides the name of the product, its active ingredient(s), dosage strength, National Drug Code number, the name of its manufacturer or distributor, its size, shape, color, and code imprint (if any), and any other characteristic that identifies the product as unique.

**Procedures for Domestic Drug Establishments**

Sec. 207.26 Amendments to registration.

Changes in individual ownership, corporate or partnership structure location or drug-handling activity, shall be submitted by Form FDA-2656 (Registration of Drug Establishment) as amendment to registration within 5 days of such changes. A change in a registered establishment’s firm name within 6 months of the registration of the establishment is required to be supported by a signed statement of the establishment’s owner or operator that the change is not made for the purpose of changing the name of the manufacturer of a drug product. Changes in the names of officers and directors of the corporations do not require such amendment but must be shown at time of annual registration.

**Procedures for Domestic Drug Establishments**

Sec. 207.30 Updating drug listing information.

Any material change in any information previously submitted; When no changes have occurred since the previously submitted list, no report is required.

**Procedures for Domestic Drug Establishments**

Sec. 207.31 Additional drug listing information.

(a) In addition to the information routinely required by Secs. 207.25 and 207.30, FDA may require submission of the following information by letter or by Federal Register notice:
(1) For a particular prescription drug so listed that the registrant regards as not subject to section 505 of the act, upon request by FDA for good cause, a copy of all advertisements.

(2) For a particular drug product so listed that the registrant regards as not subject to section 505 or 512 of the act, upon a finding by FDA that it is necessary to carry out the purposes of the act, a quantitative listing of all ingredients.

(3) For a particular drug product, upon request by FDA, a brief statement of the basis for the registrant's belief that the drug product is not subject to section 505 or 512 of the act.

(4) For each registrant, upon a finding by FDA that it is necessary to carry out the purposes of the act, a list of each listed drug product containing a particular ingredient.

(b) It is requested but not required that a qualitative listing of the inactive ingredients be submitted for all listed drugs in the format prescribed in Form FDA-2657 (Drug Product Listing).

(c) It is requested but not required that a quantitative listing of the active ingredients be submitted for all drugs listed that are subject to section 505 or 512 of the act or section 351 of the Public Health Service Act.

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

Procedures for Domestic Drug Establishments

Sec. 207.35 Notification of registrant; drug establishment registration number and drug listing number.

(a) FDA will provide to the registrant a validated copy of Form FDA-2656 (Registration of Drug Establishment) as evidence of registration. This validated copy will be sent to the mailing address shown on the form. FDA will assign a permanent registration number to each drug establishment registered in accordance with these regulations.

(b) Using the National Drug Code (NDC) numbering system, FDA assigns a drug listing number to each drug or class of drugs listed as follows:

1. If a drug is already listed in the National Drug Code System or in the National Health Related Items Code System, the number is the same as that assigned under those codes. FDA adds a lead zero to the first three characters of the code, which identifies the manufacturer or distributor, to expand the "Labeler Code" segment to four characters. The National Drug Code, Product Code, and Package Code configurations used to describe these drugs, or any drugs added to the product line, remain the same, i.e., a four-character Product Code and a two-character Package Code. A manufacturer or distributor may either retain alphanumeric characters that are already used in the Product Code and Package Code segments of the National Drug Code or convert these alphanumeric characters to all numeric digits. The manufacturer or distributor shall inform FDA of a decision to convert the alphanumeric characters to all numeric digits.

2. If a registered establishment or distributor has not previously participated in the National Drug Code System or in the National Health Related Items Code System, FDA uses the National Drug Code numbering system in assigning a number, as follows (only numerals are used):
(i) The first 5 numeric characters of the 10-character code identify the manufacturer or distributor and are known as the Labeler Code. FDA will expand the Labeler Code from five to six numeric characters when the available five-character code combinations are exhausted. FDA will assign Labeler Code numbers and provide them to the registrant along with the validated copy of Form FDA-2656. Any registered firm that does not have an assigned Labeler Code will be assigned one when registration and listing information are submitted.

(ii) The last 5 numeric characters of the 10-character code identify the drug and the trade package size and type. The segment that identifies the drug formulation is known as the Product Code and the segment that identifies the trade package size and type is known as the Package Code. The manufacturer or distributor will assign the Product Code and the Package Code before drug listing and include these codes in Form FDA-2657 (Drug Product Listing). The manufacturer or distributor may use either of two methods in assigning the Product and Package Codes: a 3-2 Product-Package Code configuration (e.g., 542-12) or a 4-1 Product-Package Code configuration (e.g., 5421-2). A manufacturer or distributor with a given Labeler Code shall use only one such Product-Package Code configuration and shall use this same configuration in assigning the Product-Package Codes for all drugs included in the drug listing. The manufacturer or distributor shall report to FDA the Product-Package Code configuration used in assigning these codes.

(iii) If the drug formulation is a Type A medicated article intended for use in the manufacture of an animal feed, FDA assigns a separate Product Code only for each variation of level of active drug ingredient.

(3) FDA requests but does not require that the NDC number appear on all drug labels and in other drug labeling, including the label of any prescription drug container furnished to a consumer. If the NDC number is shown on a drug label, it shall be placed as follows:

(i) The NDC number shall appear prominently in the top third of the principal display panel of the label on the immediate container and of any outside container or wrapper. Instead of appearing in the top third of the label, the NDC number may appear as part of and contiguous to any bar-code symbol for any drug product if two conditions are met. First, the symbol appears prominently on the immediate container and on any outside container or wrapper and in a conspicuous location; this condition is not satisfied by the appearance of the symbol only on the natural bottom of a container or wrapper. Second, the bar-code symbol is compatible with the NDC, i.e., the symbol provides a format capable of encoding the numeric characters of an NDC Number. The term principal display panel, as used in this paragraph, means that part of a label most likely to be displayed, presented, shown, or examined under customary conditions of display to the consumer (for over-the-counter drug products) or to the dispenser (for prescription drug products).

(ii) The NDC number shall be preceded by the prefix "NDC" or "N" when it is used on a label or in labeling. The prefix used for a drug product shall be used consistently on the label of the immediate container, outside container, or wrapper, if any, and on other labeling for that drug product.

(iii) The Product-Package Code configuration shall be indicated and the segments of the number shall be separated by a dash, e.g., NDC 15643-542-12 or N 15643-542-12.

(iv) All 10 characters shall appear and the leading zeros in any segment of the NDC number shall be shown, except that leading zeros may be omitted from any segment of the NDC number when the NDC number is used for product identification by direct imprinting on dosage forms or in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear both required and optional labeling information.
(v) The placing of the assigned NDC number on a label or in other labeling does not require the submission of a supplemental new drug application, supplemental new animal drug application.

(4) (i) If any change occurs in those product characteristics that clearly distinguish one drug product version from another, the registrant shall assign a new NDC number to the new product version and submit that information to FDA. Such a change includes, but is not limited to, a change in active ingredient(s); strength or concentration of active ingredient(s); dosage form; route of administration, if it also includes a change in product formulation; product name; and a change in marketing status from prescription to over-the-counter or over-the-counter to prescription. If, by notice in the Federal Register, FDA requires a change in drug product characteristics and determines the change will require assignment of a new product code to the reformulated product, FDA will announce its determination in the Federal Register publication that requires the change, setting forth its reasoning and justification for its determination. If a change only in the trade package is involved, the registrant may revise the trade package code without the assignment of a new product code segment, but shall inform FDA of the new code for the trade package and the characteristics of the new trade package.

(ii) When a registrant has discontinued a drug product, its product code may be reassigned to another drug product 5 years after the expiration date of the discontinued product, or, if there is no expiration date, 5 years after the last shipment of the discontinued product into commercial distribution. Reuse of product codes may occur, under the specified conditions, regardless of the NDC, Product Code, and Package Code configuration used.

(c) Although registration and drug listing are required to engage in the drug activities described in Sec. 207.20, validation of registration and the assignment of a drug listing number do not, in themselves, establish that the holder of the registration is legally qualified to deal in such drugs.

 Procedures for Domestic Drug Establishments

Sec. 207.37 Inspection of registrations and drug listings.

(a) A copy of the Form FDA-2656 (Registration of Drug Establishment) filed by the registrant will be available for inspection in accordance with the act, at the Drug Listing Branch Center for Drug Evaluation and Research, Food and Drug Administration.

Procedures for Domestic Drug Establishments

Sec. 207.39 Misbranding by reference to registration or to registration number.

Registration of a drug establishment or drug wholesaler, or assignment of a registration number, or assignment of a National Drug Code (NDC) number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of registration or possession of registration number or NDC number is misleading and constitutes misbranding.

Procedure for Foreign Drug Establishments

Sec. 207.40 Drug listing requirements for foreign drug establishments.

(a) Every foreign drug establishment whose drugs are imported or offered for import into the United States shall comply with the drug listing requirements in subpart C of this part, unless exempt under subpart B of this part, whether or not it is also registered.

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(b) No drug, unless it is listed as required in subpart C of this part, may be imported from a foreign drug establishment into the United States except a drug imported or offered for import under the investigational use provisions of part 312 of this chapter. Foreign drug establishments shall submit the drug listing information in the English language.

(c) Every foreign drug establishment shall submit, as part of drug listing, the name and address of the establishment and the name of the individual responsible for submitting drug listing information. The establishment shall report to FDA any changes in this information at the intervals for updating drug listing information.

Under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, chapter I, subchapter C of title 21 of the Code of Federal Regulations is amended by adding new part 205 to read as follows:

PART 205 - GUIDELINES FOR STATE LICENSING OF WHOLESALE PRESCRIPTION DRUG DISTRIBUTORS

205.1 Scope. This part applies to any person, partnership, corporation, or business firm in a State engaging in the wholesale distribution of human prescription drugs in interstate commerce.

205.2 Purpose. The purpose of this part is to implement the Prescription Drug Marketing Act of 1987 by providing minimum standards, terms, and conditions for the licensing by State licensing authorities of persons who engage in wholesale distributions in interstate commerce of prescription drugs.

205.3 Definitions.

Drug sample means a unit of a prescription drug that is not intended to be sold and is intended to promote the sale of the drug.

Manufacturer means anyone who is engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a prescription drug.

Prescription drug means any human drug required by Federal law or regulation to be dispensed only by a prescription, including finished dosage forms and active ingredients subject to section 503(b) of the Federal Food, Drug, and Cosmetic Act.

Wholesale distribution means distribution of prescription drugs to persons other than a consumer or patient, but does not include:

(1) Intracompany sales;

(2) The purchase or other acquisition by a hospital or other health care entity that is a member of a group purchasing organization of a drug for its own use from the group purchasing organization or from other hospitals or health care entities that are members of such organizations;

(3) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization described in section 501(c)(3) of the Internal Revenue Code of 1954 to a nonprofit affiliate of the organization to the extent otherwise permitted by law;

(4) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug among hospitals or other health care entities that are under common control; for purposes of this section, "common
control" means the power to direct or cause the direction of the management and policies of a person or an organization, whether by ownership of stock, voting rights, by contract, or otherwise;

(5) The sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug for emergency medical reasons; for purposes of this section, "emergency medical reasons" includes transfers of prescription drugs by a retail pharmacy to another retail pharmacy to alleviate a temporary shortage;

(6) The sale, purchase, or trade of a drug, an offer to sell, purchase, or trade a drug, or the dispensing of a drug pursuant to a prescription;

(7) The distribution of drug samples by manufacturers' representatives or distributors' representatives; or

(8) The sale, purchase, or trade of blood and blood components intended for transfusion.

Wholesale distributor means any one engaged in wholesale distribution of prescription drugs, including, but not limited to, manufacturers; repackers; own-label distributors; private-label distributors; jobbers; brokers; warehouses, including manufacturers' and distributors' warehouses, chain drug warehouses, and wholesale drug warehouses; independent wholesale drug traders; and retail pharmacies that conduct wholesale distributions.

205.4 Wholesale drug distributor licensing requirement. Every wholesale distributor in a State who engages in wholesale distribution of prescription drugs in interstate commerce must be licensed by the State licensing authority in accordance with this part before engaging in wholesale distribution of prescription drugs in interstate commerce.

205.5 Minimum required information for licensure. (a) The State licensing authority shall require the following minimum information from each wholesale drug distributor as part of the license described in section 205.4 and as part of any renewal of such license:

(1) The name, full business address, and telephone number of the licensee;

(2) All trade or business names used by the licensee;

(3) Addresses, telephone numbers, and the names of contact persons for all facilities used by the licensee for the storage, handling, and distribution of prescription drugs;

(4) The type of ownership or operation (i.e., partnership, corporation, or sole proprietorship); and

(5) The name(s) of the owner and/or operator of the licensee, including:

   (i) If a person, the name of the person;

   (ii) If a partnership, the name of each partner, and the name of the partnership;

   (iii) If a corporation, the name and title of each corporate officer and director, the corporate names, and the name of the State of incorporation; and

   (iv) If a sole proprietorship, the full name of the sole proprietor and the name of the business entity.

(b) The State licensing authority may provide for a single license for a business entity operating more than one facility within that State, or for a parent entity with divisions, subsidiaries, and/or affiliate
companies within that State when operations are conducted at more than one location and there exists joint ownership and control among all the entities.

(c) Changes in any information in paragraph (a) of this section shall be submitted to the State licensing authority as required by such authority.

205.6 Minimum qualifications. (a) The State licensing authority shall consider, at a minimum, the following factors in reviewing the qualifications of persons who engage in wholesale distribution of prescription drugs within the State:

(1) Any convictions of the applicant under any Federal, State, or local laws relating to drug samples, wholesale or retail drug distribution, or distribution of controlled substances;

(2) Any felony convictions of the applicant under Federal, State, or local laws;

(3) The applicant's past experience in the manufacture or distribution of prescription drugs, including controlled substances;

(4) The furnishing by the applicant of false or fraudulent material in any application made in connection with drug manufacturing or distribution;

(5) Suspension or revocation by Federal, State, or local government of any license currently or previously held by the applicant for the manufacture or distribution of any drugs, including controlled substances;

(6) Compliance with licensing requirements under previously granted licenses, if any;

(7) Compliance with requirements to maintain and/or make available to the State licensing authority or to Federal, State, or local law enforcement officials those records required under this section; and

(8) Any other factors or qualifications the State licensing authority considers relevant to and consistent with the public health and safety.

(b) The State licensing authority shall have the right to deny a license to an applicant if it determines that the granting of such a license would not be in the public interest.

205.7 Personnel. The State licensing authority shall require that personnel employed in wholesale distribution have appropriate education and/or experience to assume responsibility for positions related to compliance with State licensing requirements.

205.8 Violations and penalties. (a) State licensing laws shall provide for the suspension or revocation of licenses upon conviction of violations of Federal, State, or local drug laws or regulations, and may provide for fines, imprisonment, or civil penalties.

(b) State licensing laws shall provide for suspension or revocation of licenses, where appropriate, for violations of its provisions.

205.50 Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records.

The State licensing law shall include the following minimum requirements for the storage and handling
of prescription drugs, and for the establishment and maintenance of prescription drug distribution records by wholesale drug distributors and their officers, agents, representatives, and employees:

(a) Facilities. All facilities at which prescription drugs are stored, warehoused, handled, held, offered, marketed, or displayed shall:

(1) Be of suitable size and construction to facilitate cleaning, maintenance, and proper operations;

(2) Have storage areas designed to provide adequate lighting, ventilation, temperature, sanitation, humidity, space, equipment, and security conditions;

(3) Have a quarantine area for storage of prescription drugs that are outdated, damaged, deteriorated, misbranded, or adulterated, or that are in immediate or sealed, secondary containers that have been opened;

(4) Be maintained in a clean and orderly condition; and

(5) Be free from infestation by insects, rodents, birds, or vermin of any kind.

(b) Security. (1) All facilities used for wholesale drug distribution shall be secure from unauthorized entry.

(i) Access from outside the premises shall be kept to a minimum and be well-controlled.

(ii) The outside perimeter of the premises shall be well-lighted.

(iii) Entry into areas where prescription drugs are held shall be limited to authorized personnel.

(2) All facilities shall be equipped with an alarm system to detect entry after hours.

(3) All facilities shall be equipped with a security system that will provide suitable protection against theft and diversion. When appropriate, the security system shall provide protection against theft or diversion that is facilitated or hidden by tampering with computers or electronic records.

(c) Storage. All prescription drugs shall be stored at appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the United States Pharmacopeia / National Formulary (USP/NF).

(1) If no storage requirements are established for a prescription drug, the drug may be held at "controlled" room temperature, as defined in an official compendium, to help ensure that its identity, strength, quality, and purity are not adversely affected.

(2) Appropriate manual, electromechanical, or electronic temperature and humidity recording equipment, devices, and/or logs shall be utilized to document proper storage of prescription drugs.

(3) The record keeping requirements in paragraph (f) of this section shall be followed for all stored drugs.

(d) Examination of materials. (1) Upon receipt, each outside shipping container shall be visually examined for identity and to prevent the acceptance of contaminated prescription drugs or prescription
drugs that are otherwise unfit for distribution. This examination shall be adequate to reveal container
damage that would suggest possible contamination or other damage to the contents.

(2) Each outgoing shipment shall be carefully inspected for identity of the prescription drug products
and to ensure that there is no delivery of prescription drugs that have been damaged in storage or held
under improper conditions.

(3) The recordkeeping requirements in paragraph (f) of this section shall be followed for all incoming
and outgoing prescription drugs.

(e) Returned, damaged, and outdated prescription drugs. (1) Prescription drugs that are outdated,
damaged, deteriorated, misbranded, or adulterated shall be quarantined and physically separated from
other prescription drugs until they are destroyed or returned to their supplier.

(2) Any prescription drugs whose immediate or sealed outer or sealed secondary containers have been
opened or used shall be identified as such, and shall be quarantined and physically separated from
other prescription drugs until they are either destroyed or returned to the supplier.

(3) If the conditions under which a prescription drug has been returned cast doubt on the drug's safety,
identity, strength, quality, or purity, then the drug shall be destroyed, or returned to the supplier, unless
examination, testing, or other investigation proves that the drug meets appropriate standards of safety,
identity, strength, quality, and purity. In determining whether the conditions under which a drug has
been returned cast doubt on the drug's safety, identity, strength, quality, or purity, the wholesale drug
distributor shall consider, among other things, the conditions under which the drug has been held,
stored, or shipped before or during its return and the condition of the drug and its container, carton, or
labeling, as a result of storage or shipping.

(4) The recordkeeping requirements in paragraph (f) of this section shall be followed for all outdated,
damaged, deteriorated, misbranded, or adulterated prescription drugs.

(f) Record keeping. (1) Wholesale drug distributors shall establish and maintain inventories and
records of all transactions regarding the receipt and distribution or other disposition of prescription
drugs. These records shall include the following information:

(i) The source of the drugs, including the name and principal address of the seller or transferor, and the
address of the location from which the drugs were shipped;

(ii) The identity and quantity of the drugs received and distributed or disposed of; and

(iii) The dates of receipt and distribution or other disposition of the drugs.

(2) Inventories and records shall be made available for inspection and photocopying by authorized
Federal, State, or local law enforcement agency officials for a period of 2 years following disposition of
the drugs.

(3) Records described in this section that are kept at the inspection site or that can be immediately
retrieved by computer or other electronic means shall be readily available for authorized inspection
during the retention period. Records kept at a central location apart from the inspection site and not
electronically retrievable shall be made available for inspection within 2 working days of a request by
an authorized official of a Federal, State, or local law enforcement agency.

(g) Written policies and procedures. Wholesale drug distributors shall establish, maintain, and
adhere to written policies and procedures, which shall be followed for the receipt, security, storage, inventory, and distribution of prescription drugs, including policies and procedures for identifying, recording, and reporting losses or thefts, and for correcting all errors and inaccuracies in inventories. Wholesale drug distributors shall include in their written policies and procedures the following:

(1) A procedure whereby the oldest approved stock of a prescription drug product is distributed first. The procedure may permit deviation from this requirement, if such deviation is temporary and appropriate.

(2) A procedure to be followed for handling recalls and withdrawals of prescription drugs. Such procedure shall be adequate to deal with recalls and withdrawals due to:

(i) Any action initiated at the request of the Food and Drug Administration or other Federal, State, or local law enforcement or other government agency, including the State licensing agency;

(ii) Any voluntary action by the manufacturer to remove defective or potentially defective drugs from the market; or

(iii) Any action undertaken to promote public health and safety by replacing of existing merchandise with an improved product or new package design.

(3) A procedure to ensure that wholesale drug distributors prepare for, protect against, and handle any crisis that affects security or operation of any facility in the event of strike, fire, flood, or other natural disaster, or other situations of local, State, or national emergency.

(4) A procedure to ensure that any outdated prescription drugs shall be segregated from other drugs and either returned to the manufacturer or destroyed. This procedure shall provide for written documentation of the disposition of outdated prescription drugs. This documentation shall be maintained for 2 years after disposition of the outdated drugs.

(h) Responsible persons. Wholesale drug distributors shall establish and maintain lists of officers, directors, managers, and other persons in charge of wholesale drug distribution, storage, and handling, including a description of their duties and a summary of their qualifications.

(i) Compliance with Federal, State, and local law. Wholesale drug distributors shall operate in compliance with applicable Federal, State, and local laws and regulations.

(1) Wholesale drug distributors shall permit the State licensing authority and authorized Federal, State, and local law enforcement officials to enter and inspect their premises and delivery vehicles, and to audit their records and written operating procedures, at reasonable times and in a reasonable manner, to the extent authorized by law.

(2) Wholesale drug distributors that deal in controlled substances shall register with the appropriate State controlled substance authority and with the Drug Enforcement Administration (DEA), and shall comply with all applicable State, local, and DEA regulations.

(j) Salvaging and reprocessing. Wholesale drug distributors shall be subject to the provisions of any applicable Federal, State, or local laws or regulations that relate to prescription drug product salvaging or reprocessing, including parts 207, 210, and 211 of this chapter. [www.fda.gov]

3.2 EUROPE
European Medicines Agency is a decentralized body of the European Union with headquarters in London. The EMEA began its activities in 1995, when the European system for authorizing medicinal products was introduced, providing for a centralized and a mutual recognition procedure. The EMEA has a role in both, but is primarily involved in the centralized procedure. Where the centralized procedure is used, companies submit one single marketing authorization application to the EMEA. A single evaluation is carried out through the committee for Medicinal Products for Human Use (CHMP) or committee for Medicinal Products for Veterinary Use (CVMP). If the relevant committee concludes that quality, safety and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the commission to be transformed into a single market authorization valid for the whole of the European Union.

In 2001, the Committee on Orphan Medicinal Products (COMP) was established, charged with reviewing designation applications from persons or companies who intend to develop medicines for rare diseases (So-called 'Orphan drugs'). The Committee on Herbal Medicinal Products (HMPC) was established in 2004 and provides scientific opinions on traditional herbal medicines.

A network of some 3500 European experts underpins the scientific work of the EMEA and its committees.

Following countries are Head of Agencies in European Union:

1. Austria  2. France  3. Latvia  4. Poland
25. Finland  26. Italy  27. Norway  28. United Kingdom

(www.emea.europa.eu)

3.2.1 United Kingdom

The Medicines and Healthcare products Regulatory Agency (MHRA) has no interest in early stages of drug development until the company wishes to start clinical trials in patients. It is at this stage of development that the company will have sufficient evidence to indicate whether the product is going to be licensable medicine.

The applicant will be hoping to obtain a marketing authorization as quickly as possible. To minimize delays, it is important that adequate information is provided to demonstrate that the products is of adequate quality for its intended use, that it is sufficiently safe and that it is effective. No other factors are considered when assessing the application (for example comparative efficacy or cost benefit).

There are number of different types of applications, depending on the nature of active ingredient of the product. These vary from applications for products containing new active substances, those whose active ingredients have previously been evaluated before known as abridged applications, to those
biological and biotechnology products manufactured by recombinant DNA technology, products where genetic manipulations of cells is required, or a monoclonal antibodies.

Following types of licenses and certificates are granted by the Licensing Authority and provides information thereon:

- Clinical trials
- Marketing Authorisations
- Parallel imports
- Homoeopathic medicines
- Traditional Herbal Medicines Registration Scheme
- Manufacturer’s licenses and wholesale dealer’s licenses
- Export certificates.

Before assessment of the application can begin, validation takes place. Marketing Authorisations are granted for period up to five years and have to be renewed at the end of this time.

Before a medicine can be marketed or sold in the UK, a number of licenses are required. The companies that are involved in all stages of manufacturing and distribution of the product need to have the relevant license for the activity in question (manufacturer’s and/or wholesale dealers license). UK legislation (The Medicines Act 1968 "the Act" in respect of relevant medicinal products is in accordance with European Community Directives 2001/83/EC, as amended, and Directive 2003/94/EC.* These products must, unless exempt, have market authorization before they are placed on the market, and the manufacturer or importer (where import is from a third country) must hold an appropriate manufacturing authorization. In the UK, this manufacturing authorization is a ‘MANUFACTURER’S LICENSE’ (ML), which is a requirement under section 8(2) of the Act as amended. The single market now extends additionally to members of European Economic Area, i.e. Member States of European Community plus Norway, Iceland And Liechtenstein.

For the manufacture or assembly of unlicensed relevant products which are exempt from marketing authorization requirements (“specials”) the appropriate authorization is a “manufacturer’s (specials) license (MS).” For guidance on the particular conditions relating to manufacturer’s (specials) licenses reference to MHRA’s Guidance Note 14.

Medicinal products manufactured in the UK must be produced on a site that holds an appropriate manufacturer’s license (ML). Any company or individual wishing to wholesale deal (defined as selling, supplying or procuring to anyone other than the end user) medicinal products within the EU must hold a wholesale dealer’s license (WL). The administrative activities for issuing and maintaining manufacturer’s and wholesale dealer’s licenses are carried out by the Licensing section in the inspection and Enforcement Division and in fulfilling its role the Section works very closely with the Medicines Inspectorate.

MEDICINES THAT DO NOT NEED A LICENSE (Exemptions from licensing )

The Medicines Act contains certain important exemptions from licensing and makes provision for further exemptions to be included in statutory orders. This section outlines three of the more important exemptions;

(1) the manufacture and supply of unlicensed relevant medicinal products for individual patients (‘specials’);

(2) the importation and supply of unlicensed relevant medicinal products for individual patients; and
(3) herbal remedies exemptions.

THE MANUFACTURE AND SUPPLY OF UNLICENSED RELEVANT MEDICINAL PRODUCTS FOR INDIVIDUAL PATIENTS ('SPECIALS')

Some patients may have special clinical needs that cannot be met by licensed medicinal products. So that these special needs may be met, the law allows manufacture and supply of unlicensed medicinal products (commonly known as 'Specials') subject to certain conditions.

The supply of unlicensed relevant medicinal products for individual patients' provides guidance to manufacturers about the conditions under which they may manufacture and supply 'specials' and their legal obligations.

HERBAL MEDICINES EXEMPTIONS Products exempt from licensing include herbal medicines which satisfy the conditions laid down in section 12 of the Medicines Act 1968. Section 13(2) of the Act defines a herbal remedy as:

'...a medicinal product consisting of a substance produced by subjecting a plant or plants to drying, crushing, or any other process, or of a mixture whose sole ingredients are two or more substances so produced, or of a mixture whose sole ingredients are one or more substances so produced and water or some other inert substance.'

Section 12(1) allows a person to make, sell and supply a herbal remedy during the course of their business provided the remedy is manufactured or assembled on the premises and that it is supplied as a consequence of a consultation between the person and their patient. Section 12(2) allows the manufacture, sale or supply of herbal remedies where:

* the process to which the plant or plants are subjected consists only of drying, crushing or comminuting;
* the remedy is sold without any written recommendation as to its use; and
* the remedy is sold under a designation which only specifies the plants(s) and the process, and does not apply any other name to the remedy.

UNLICENSED HERBAL REMEDIES: These products don't have to meet specific standards of safety and quality and so standards can vary widely. In addition they are not required to be accompanied by the necessary information to use them safely such safety warnings and contraindications.

REGISTERED TRADITIONAL HERBAL MEDICINES: a SIMPLIFIED REGISTRATION SCHEME, THE traditional Herbal Medicines Registration Scheme, began in October 30 2005. It may took some months before the first registered products appeared on the market and a seven-year transitional period will mean that products did not require to be registered until 30 April 2011. Products registered under the Scheme will however need to meet specific standards of safety and quality and be accompanied by agreed indications and systematic patient information allowing the safe use of the product.

LICENSED HERBAL MEDICINES: Some herbal medicines in the UK hold a product license or marketing authorization just like any other medicine. These are required to demonstrate safety, quality and efficacy (or effectiveness) and be accompanied by the necessary information for safe usage. These products can be identified by a distinctive nine number Product License (PL) number on the product container or packaging which is pre-fixed by the letters PL.
The Licensing Authority for the purposes of the Act, legislation made under the Act and this guidance refers to the U K Ministers designated by the Act, acting either alone or jointly. The MHRA is the government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by Ministers.

' REVIEW OF EU MEDICINES LEGISLATION ('2001 REVIEW')' In October 2001 the commission published its proposals to amend the body of legislation covering the EU medicines regulatory regime (Regulation 2309/93 and Directives 2001/82/EC and 2001/83/EC). Regulation 2309/93 established a centralized authorization procedure for human and veterinary medicinal products and established the European Medicines Agency (EMEA). Directives 2001/82/EC and Directive 2001/83/EC set out the community codes for medicinal products for veterinary and human use. The Directives lay down provisions governing the marketing authorization, manufacture and distribution of such products. Following detailed negotiations between the council of the European Union and the European Parliament, agreement on the proposed legislative amendments was reached in early 2004.

The agreed texts were adopted by the Council and the European Parliament on 31st March 2004 as:


The following regulation was adopted on 14th June 2007 and compliments Regulation 726/2004 by providing an EU penalties regime in respect of failures to comply with various aspects of the regulation:

"Regulation (EC) No. 658/2007"

IMPLEMENTATION OF THE NEW EU LEGISLATION Regulation 726/2004 is directly applicable in national law and its main provisions have applied in the UK from 20th November 2005. The provisions of Directive 2004 had to be transposed into national law by 30th October 2005. The four statutory instruments listed below were made and laid before Parliament using the negative procedure, in order to implement the provisions of Directive 2004/27/EC. They into force on 30th October 2005.

> The Medicines (Homoeopathic Medicinal Products for Human Use) Amendment Regulations 2005 (SI 2005/2753)
> The Medicines (Marketing Authorisations Etc.) Amendment Regulations 2005 (SI 2005/2759)


Manufacturer’s License (ML) may be granted for the manufacture and assembly of medicinal products, or for just assembly. The ML also covers the activity of import from a third country. The ML may be granted for the following activities:
MANUFACTURE: In relation to medicinal products, includes any process carried out in the course of making the product, but does not include dissolving or dispersing the product in, or diluting or mixing it with, some other substance used as a vehicle for the purpose of administering it;

A ML is required for both total and partial manufacture the various processes of dividing up, packaging or presentation and for import from a third country. However such a license is not required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, SOLELY for retail supply, by or under the supervision of a pharmacist in registered pharmacy or hospital. And/or

ASSEMBLY: in relation to a medicinal product, means enclosing the product (with or without other medicinal products of same description) in a container which is labeled before the product is sold or supplied, or, where the product is already enclosed in the container in which it is to be sold or supplied, labeling the container before the product is sold or supplied in.

The over-labeling of medicinal products is an assembly activity and is therefore licensable.

IMPORT FROM THIRD COUNTRY: means import from any country other than EEA State.

EXPORT TO THIRD COUNTRY: A ML is required for the manufacture of medicinal products intended for export to a third country.

BATCH CERTIFICATION: in relation to medicinal products, concerns the activities conducted by a qualified person, in determining that a batch of a finished medicinal product is certified within the EEA before release for sale or supply in accordance with the requirements of the marketing authorization. The MHRA may issue a manufacturer’s license solely for the purpose of batch certification to authorize the holder to certify and release batches of products for which he holds the Marketing Authorisation, where the medicinal product has been manufactured by a contract manufacturer. The QP named on the manufacturer’s license granted solely for the purpose of batch certification may either take responsibility for all manufacturing stages conducted by the contract manufacturer or may take account of the confirmation of the batch by the contract manufacturer’s QP.

A ML holder may store and distribute any relevant medicinal product manufactured or assembled pursuant to his license, without the need for an additional wholesale dealer’s license. However certain obligations, referred under sections 5 and 6 must be complied with.

In arriving at a decision whether or not to grant a license, the assessors frequently take independent expert advice on matters relating to safety, quality and efficacy from medicines advisory bodies. These advisory bodies were appointed under section 4 (S4) of the Medicines Act and includes the Commission of Human Medicines. These bodies consist of independent experts who are appointed by Ministers. They do not include members of staff of the MHRA. Secretariat support to the advisory bodies is provided by the MHRA.

MANUFACTURER’S AND WHOLESALE DEALER’S LICENSES: CHANGES FROM AUGUST 2006
In August 2006 the MHRA changed the style and types of licenses issued to manufacturers and wholesale dealers of medicinal products.

The reasons for the changes are two fold:

* Legislative requirements
* The UK’s implementation of a new format of manufacturer’s license that will be common across the EU.
The major noticeable difference will be for holders of Manufacturer's Licenses and Wholesale Dealer’s (import) licenses where MHRA will now issue licenses in the style of the MIA. The MIA (Manufacturer's/Importer’s Authorisation) is the community format for Manufacturers Authorisation as defined by the European Medicines Agency (EMEA) and this single license will encompass those activities previously covered by two licenses (the Manufacturer's and Wholesale Dealer's import licenses).

It is not necessary for any license-holder to take any action with respect to these changes. In most instances licenses that are currently held will remain valid and the intention will be to only issue licenses in the new format when the existing license is varied.

(www.mhra.gov.uk)

3.2.2 GERMANY

Section 2: The term 'medicinal product' Medicinal products are substances and preparations made from substances which, by application on or in the human or animal body, are intended

1. to cure, alleviate, prevent or diagnose diseases, suffering, bodily injury or disease symptoms,
2. to diagnose the nature, the state or the functions of the body or the mental health conditions,
3. to substitute active substances or body fluids produced in the human or animal body,
4. to ward off pathogens, parasites or substances alien to the body or to destroy them or render them harmless,
5. to influence either the nature, the state or the functions of the body or mental health conditions.

Section 3: The term 'substance': For the purpose of the present Act, substances has been defined.

Section 4: Definitions of additional terms: Finished medicinal products are medicinal products which are manufactured before hand and placed on the market in packaging intended for distribution to the consumer or other medicinal products intended for distribution to the consumer, in the preparation of which any form of industrial process is used or medicinal products which are produced commercially, except in pharmacies. Finished medicinal products are not intermediate products intended for further processing by a manufacturer.

Manufacturing is the producing, preparing, formulating, treating or processing, filling as well as decanting, packaging, labeling and release of medicinal products.

Quality is the nature of a medicinal product, determined by identity, content, purity and other chemical, physical and biological properties or by the manufacturing procedure.

A batch is the quantity of a medicinal product produced from the same amount of starting material in a standard manufacturing process or, in the case of a continuous manufacturing process, within a specific period of time.

Marketing is the keeping in stock for sale or for other forms of supply, the exhibiting and offering for sale and the distribution to others.

In the case of medicinal products requiring a marketing authorisation or registration, the pharmaceutical entrepreneur shall be the holder of the marketing authorisation or registration. The pharmaceutical entrepreneur is also any person who places medicinal products on the market under his own name.
Active substances are substances which are intended for use as medically active constituents in the manufacture of medicinal products or which, through their use in the manufacture of medicinal products, are intended to become medically active substances.

Wholesale trade in medicinal products is any professional or commercial activity for the purpose of doing business which consists of the procuring, storing, dispensing or exporting of medicinal products, with the exception of the dispensing of medicinal products to consumers other than physicians, dentists, veterinarians or hospitals.

A clinical trial on human beings is any investigation on human subjects intended to investigate or verify the clinical or pharmacological effects of medicinal products, or to identify side-effects or to study the absorption, distribution, metabolism or excretion, with the aim of ascertaining the safety or efficacy of the medicinal product.

The sponsor is a natural or legal person who assumes responsibility for the commissioning, organisation and financing of a clinical trial on human beings.

The investigator is generally a physician responsible for the conduct of the clinical trial on human beings at a site or, in justified exceptional cases, another person whose profession, owing to the scientific requirements and the experience in the care of patients which it calls for, qualifies him to conduct research on human beings.

A homeopathic medicinal product is any medicinal product prepared in accordance with a homeopathic manufacturing procedure described in the European Pharmacopoeia or, in absence thereof, in the pharmacopoeias currently used officially in the EU Member States. A homeopathic medicinal product can also contain a number of active substances.

Herbal medicinal products are medicinal products which exclusively contain, as active substances, either one or more herbal substances, one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Section 4a: Exceptions to the scope of the present Act

Section 5: Prohibition in respect of unsafe medicinal products: (1) The placing on the market of unsafe medicinal products shall be prohibited.

(2) Medicinal products shall be considered unsafe if, according to the current level of scientific knowledge, there is reason to suspect that, when used in accordance with their intended purpose, they have harmful effects which exceed the limits considered tolerable in the light of current medical knowledge.

Section 6: Empowerment in respect of health protection: The Federal Ministry of Health (the Federal Ministry) is hereby empowered to specify, restrict or prohibit, by ordinance subject to the approval of the Bundesrat, the use of certain substances, preparations from substances or objects in the manufacture of medicinal products and to forbid the marketing and use of medicinal products which have not been manufactured in compliance with these regulations in so far as this is deemed necessary in the interest of risk prevention or in order to prevent medicinal products from posing a direct or indirect hazard to human or animal health.

Section 8: Prohibitions to prevent deception: (1) It shall be prohibited for medicinal products
1. which, by deviating from recognized pharmaceutical principles, are of considerably reduced quality, 
a. which are incorrectly labeled with regard to their identity or origin (counterfeit medicinal products) or 
2. which bear otherwise misleading designations, specifications or presentations to be manufactured or 
   placed on the market. Deception shall be said to exist, in particular, in cases where 
   a) claims are made to the effect that certain medicinal products have a therapeutic efficacy or effects 
      which they do not possess. 
   b) the erroneous impression is given that success can be expected with certainty or that no harmful 
      effects can be expected to occur when the medicinal product is used in accordance with its intended 
      purpose or over a prolonged period. 
   c) designations, specifications or presentations having an influence on the assessment of the 
      medicinal product are employed to mislead others with regard to its quality. 

(2) It shall be prohibited for medicinal products whose expiry date has elapsed to be marketed. 

Section 9: The party responsible for placing on the market: (1) Medicinal products which are 
   placed on the market within the purview of the present Act shall bear the name or the company and the 
   address of the pharmaceutical entrepreneur. This shall not apply to medicinal products intended for 
   use in a clinical trial on human subjects. 

(2) Within the purview of the present Act, medicinal products may only be placed on the market by a 
   pharmaceutical entrepreneur whose registered place of business is situated within the purview of the 
   present Act, in another Member State of the European Union or another State Party to the Agreement 
   on the European Economic Area. If the pharmaceutical entrepreneur appoints a local representative, 
   this shall not release him from his legal responsibility. 

Section 10: Labeling: Finished medicinal products which are medicinal products and are not intended 
   for clinical trials on human beings or exempted from the obligation to obtain a marketing authorisation, 
   may only be marketed within the purview of the present Act provided that the specified particulars are 
   displayed on the containers and, where used, on the outer wrapping in easily legible and indelible 
   characters, in easily comprehensible German. 

In the case of medicinal products included in the Register of Homeopathic Medicinal Products, 
   following particulars should be included: 

1. the nature and quantity of the stocks and the degree of dilution; in this regard, symbols from 
   the pharmacopoeias currently used officially, should be utilised; the scientific name of the 
   stock can be supplemented by an invented name, 
2. name and address of the pharmaceutical entrepreneur and, if available, of his local 
   representative, 
3. method of administration, 
4. expiry date; sub-section 1 sentence 1 no. 9 and sub-section 7 shall apply, 
5. pharmaceutical form, 
6. content by weight, volume or number of items, 
7. information stating that medicinal products should be kept out of the reach of children, other 
   special precautionary measures for storage and warnings, including additional information for 
   safe use if required or if stipulated in sub-section 2, 
8. batch number,
9. registration number abbreviated to 'Reg.-Nr.' and the phrase 'Registered homeopathic medicinal product therefore no therapeutic indication stated';
10. information advising the user to seek medical advice if medical symptoms persist during the use of the medicinal product,
11. for medicinal products to be sold only in pharmacies, the information 'Apothekenpflichtig' (pharmacy-only),
12. for samples, the information 'Unverkäufliches Muster' (sample - not for sale).

In the case of traditional herbal medicinal products the following information shall also be included in addition other specified particulars;

1. the medicinal product is a traditional medicinal product registered for the field of application exclusively based on long-standing use, and
2. if medical symptoms persist, or in the event of side effects other than those referred to in the package leaflet, the user should consult a doctor or other medically qualified person.

MANUFACTURE OF MEDICINAL PRODUCTS

Section 13 Manufacturing authorization: Any person wishing to manufacture medicinal products which are of human, animal or microbia origin or are manufactured using genetic engineering, as well as other substances of human origin intended for the manufacture of medicinal products on a commercial or professional basis for the purpose of dispensing to others, shall require an authorisation by the competent authority. The same shall also apply to legal persons, nonincorporated associations and companies established under civil law which manufacture medicinal products for distribution to their members. Distribution to others, in the meaning of the first sentence, shall exist if the person manufacturing the medicinal product is not the same as the person using it.

The following, among others, shall not require an authorisation:

1. the owner of a pharmacy manufacturing medicinal products within the scope of the normal operation of a pharmacy,
2. the body responsible for a hospital, in so far as it is authorised to distribute medicinal products pursuant to the Law on Pharmacies,
3. the veterinarian operating a veterinary dispensary. 

The decision on the granting of the authorisation shall be reached by the competent authority of the federal Land where the factory site is situated or is to be situated.

Section 14: Decision on the manufacturing authorization: An authorisation may only be refused if:

1. there is not at least one person available with the expertise required i.e qualified person pursuant to Section 14 who is responsible for the activities referred to in Section 19;
2. a Production Manager and a Quality Control Manager with sufficient specialist qualifications and practical experience are not available,
3. the qualified person pursuant to number 1 and the managers pursuant to number 2 are not sufficiently reliable in the performance of their job,
4. the qualified person referred to in number 1 cannot consistently perform the duties incumbent upon him,
5. (deleted)
a) 5a. in enterprises which manufacture medicated feeding stuffs from medicated pre-mixes, the person responsible for supervising the technical side of the manufacturing procedure does not possess sufficient knowledge and experience in the field of mixing technology, or

b) 5b. the physician under whose responsibility pre-treatment of the donor is carried out for the purpose of separating blood stem cells or other blood components, does not possess the expert knowledge required,

c) 5c. contrary to Section 4 sentence 1 no. 2 of the Transfusion Act, no physician in charge has been appointed or said person does not possess the necessary professional knowledge according to the state of the medical art or, contrary to Section 4 sentence 1 no. 3 of the Transfusion Act, no physician is present when the withdrawal procedure is carried out on a human donor,

d) suitable premises and equipment for the intended manufacture, testing and storage of the medicinal products are not available, or

e) 6a. the manufacturer is not in a position to ensure that the manufacture or the testing of the medicinal products is carried out according to the latest standards prevailing in science and technology, and in the procurement of blood and blood components.

Section 15: Expert knowledge: Proof of the required expert knowledge on the part of the qualified person shall be furnished as prescribed.

Section 16: Limitation of the manufacturing authorization: The authorisation shall be issued to the manufacturer for a specific factory site and for particular medicinal products and pharmaceutical forms of medicinal products and, in cases also for a specific factory site of the commissioned company or the other company.

Section 17: Deadlines for the granting of an authorization: The competent authority shall reach a decision on the application for an authorisation within three months. The competent authorities shall enter the data on the authorisation into a database.

If the holder of the authorisation makes an application for the authorisation to be modified in respect of the medicinal products to be manufactured or the premises and equipment, the authority shall reach a decision within one month. In exceptional cases, the deadline shall be extended by a further two months. The applicant shall be notified thereof prior to the expiry of the deadline and shall be informed of the grounds.

If the authority gives the applicant the opportunity to correct the flaws the deadlines shall be interrupted until such flaws have been corrected or until the expiry of the deadline set. The interruption of the deadline shall begin on the day the applicant receives the request to correct the flaws.

Section 18: Withdrawal, revocation, suspension The authorisation shall be withdrawn if it becomes known subsequently that one of the grounds for refusal, existed at the time the authorisation was granted. The authorisation shall be revoked if one of the grounds for refusal subsequently developed; the suspension of the authorisation may be ordered instead of its revocation.

The competent authority may issue a provisional order mandating that the manufacture of a medicinal product be discontinued if the manufacturer fails to furnish the evidence required for manufacture and testing. The provisional order may be restricted to one batch.

Section 19: Areas of responsibility: The qualified person shall be responsible for ensuring that each batch of the medicinal product is manufactured and tested in accordance with the regulations applicable to the trade in medicinal products. He must certify the fulfillment of these provisions for each batch of medicinal products in a serially numbered register or comparable document before it is placed on the market.
Section 20: Obligations to notify: The marketing authorisation holder shall notify the competent authority in advance of any change in the information referred to in Section 14 and submit evidence. Any unforeseen change in the qualified person referred to in Section 14, must be notified immediately.

MARKETING AUTHORISATION FOR MEDICINAL PRODUCTS

Section 21: Obligation to obtain a marketing authorisation

Finished medicinal products which are medicinal products, as defined, may only be placed on the market within the purview of the present Act, if they have been authorised by the competent higher federal authority or if the Commission of the European Communities or the Council of the European Union has granted an authorisation for them to be placed on the market pursuant to Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31st March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. The same shall apply to medicinal products which are not finished medicinal products and which are intended for administration to animals, provided they are not intended for distribution to pharmaceutical entrepreneurs holding an authorisation for the manufacture of medicinal products.

A marketing authorisation (Zulassung) shall not be required for medicinal products of specified categories.

Section 22: Marketing authorisation documents: The applicant shall attach the required specified particulars, written in German, and also certain information, to his application for a marketing authorisation.

Section 24a: Use of a previous applicant’s documents: The applicant can refer to the documents including the expertise report submitted by an earlier applicant (previous applicant), if the previous applicant’s written agreement, including confirmation that the documents referred to meet the requirements of the Guidelines for the Testing of Medicinal Products. The previous applicant shall respond to a request for agreement, within a period of three months.

Section 24b: Authorisation of a generic medicinal product, document protection: In the case of a generic medicinal product, reference can be made, without the previous applicant’s agreement, to the documents including the expert report for the previous applicant’s medicinal product (reference medicinal product), if the reference medicinal product has been authorised for at least eight years or was authorised at least eight years previously; this shall also apply to authorisation in another Member State of the European Union. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed following the first authorisation of the reference medicinal product. The period referred to shall be extended to a maximum of eleven years.

Authorisation as a generic medicinal product shall require that the medicinal product in question has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference medicinal product and that the bioequivalence has been demonstrated in bioavailability studies.

If the reference medicinal product was not authorised by the competent higher federal authority but by the competent authority of another Member State, the applicant shall indicate in the application form, where the reference medicinal product is or has been authorised.
Section 25: Decision on marketing authorization: The marketing authorisation, together with a marketing authorisation number, shall be issued in writing by the competent higher federal authority. The marketing authorisation shall only be applicable to the medicinal product specified in the marketing authorisation notice and, in the case of medicinal products manufactured according to homeopathic manufacturing procedures, it shall also apply to the degree of dilution mentioned in results published and specified in the marketing authorisation notice.

The competent higher federal authority may only refuse to grant the marketing authorisation if certain documents are incomplete and / or lacking in required information.

If an application is submitted for different strengths, pharmaceutical forms, administration routes or presentations of a medicinal product, at the applicant’s request, these can be the subject of a uniform comprehensive marketing authorisation; this shall also apply to subsequent amendments and extensions. This shall require a uniform authorisation number to which further codes must be added to allow differentiation between the different pharmaceutical forms or concentrations.

The marketing authorisation shall be without prejudice to the pharmaceutical entrepreneur’s penal or civil liability.

Section 25b: Mutual-recognition procedure and decentralised procedure: If the applicant is applying for a marketing authorisation or approval in more than one EU Member State, the applicant shall submit an application based on identical documents in these Member States; this can be worded in English.

If the medicinal product has already been approved or given a marketing authorisation in another EU Member State when the application is submitted, this marketing authorisation shall be recognised on the basis of the assessment report sent by this State.

Section 52a: Wholesale trading of medicinal products: Any person who engages in the wholesale trading of medicinal products test sera or test antigens, requires an authorisation to do so. Excepted from this obligation to obtain an authorisation are the finished medicinal products released for trade outside of pharmacies.

In submitting the application, the applicant shall submit required documents and furnish information as per provisions.

The decision on granting the authorisation shall be taken by the competent authority of the Land in which the site is or will be located. The competent authority shall take the decision on the application for authorisation within three months.

The authorisation may only be refused if:

1. the prerequisites pursuant to sub-section 2 are not fulfilled or
2. facts justify the assumption that the applicant or the person responsible pursuant to subsection 2 no. 3 does not possess the necessary reliability to perform the activity.

The authorisation shall be withdrawn if it subsequently becomes known that one of the grounds for refusal existed at the time of issuance. The authorisation is to be revoked if the prerequisites for the granting of an authorisation no longer exist; instead of the revocation, the suspension of the authorisation may also be ordered.
The authorisation holder shall notify the competent authority in advance of any changes in the particulars as well as any fundamental change in the wholesale trading activity, submitting evidence to that effect. In the case of an unforeseen change with respect to the person responsible the notification shall be immediate.

Section 55: Pharmacopoeia: The Pharmacopoeia is a collection of recognized pharmaceutical practice regarding the quality, testing, storage, dispersing and designation of medicinal products and the substances used in their manufacture, published by the Federal Ministry. The Pharmacopoeia also contains requirements regarding the nature of containers and outer packaging.

The rules contained in the Pharmacopoeia are laid down by the German Pharmacopoeia Commission or by the European Pharmacopoeia Commission. Publication of the rules can be refused or annulled for legal or technical reasons.

It is incumbent upon the German Pharmacopoeia Commission to stipulate the rules contained in the Pharmacopoeia and to assist the Federal Ministry with its work within the framework of the Convention on the Elaboration of a European Pharmacopoeia.

Section 55a: Official compilation of test procedures: The competent higher federal authority shall publish an official compilation of test procedures for the sampling and testing of medicinal products and their starting materials. The procedures shall be established in consultation with experts for the field of pharmacovigilance, scientists and pharmaceutical entrepreneurs. The compilation of procedure shall be kept up to date. (http://www.cgerl.org)

3.3 CANADA

Regulated parties that market drugs and medical devices have the primary responsibility for the safety of any product they sell, manufacture, import or distribute to the Canadian public. These regulated parties must comply with all legislative and regulatory requirements.

A manufacturer can put his drug on the market once it has received a Notice of Compliance from Health Canada. The manufacturer must meet a number of obligations, but as long as the drug causes no adverse reactions or the manufacturer does not need to make changes to the drug, it may never be subject to review by Health Canada again. (www.hc-sc.gc.ca/dhp-mps/homologation/licensing/info-renseign_hist_e.html)

The Health Products and Food Branch Inspectorate (Inspectorate) has the legislative/regulatory authority to conduct compliance and enforcement activities including: the delivery of inspections, investigations, most establishment licensing and related laboratory analysis functions for the HPFB. It also has a responsibility to foster partnerships in the regulatory community, including our international, federal and provincial partners.

A drug should be evaluated throughout its life cycle, and not just before it is licensed for release on the market. Hence regulatory decisions regarding a drug would be based on the body of evidence that accumulates throughout the life cycle of the drug. The licensing framework itself must also be subject to evaluation.

Planning throughout the regulatory process could allow for a proactive approach to managing both expected and unexpected issues. Plans for regulatory filing, the assessment of clinical trials, post market activities, and changes in manufacturing are examples of plans that could help to strengthen the licensing system while removing inefficiencies.
The underlying accountability of both Health Canada and drug manufacturers is the ongoing requirement to justify the marketing of a drug. Health Canada is accountable for granting, adjusting, or removing a drug license.

The evaluation of the benefits and risks of a drug are rooted in the scientific evidence of safety (i.e. how well a drug works), and quality (i.e. purity, potency and manufacturing standards), but encompasses a broader range of issues. Such issues include, among others, the availability of other therapies and anticipated manageability of risks.

"Drug" includes any substance or mixture of substances manufactured, sold or represented for use in

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals.
(b) Restoring, correcting or modifying organic functions in human beings or animals, or
(c) Disinfection in premises in which food is manufactured, prepared or kept;

"Sell" includes offer for sale, expose of sale, have in possession for sale and distribute, whether or not the distribution is made for consideration.

Drug GMP Requirements: Drug GMP is that part of quality assurance which ensures that drugs are consistently produced and controlled to the quality standards appropriate to their intended use as required by the marketing authorization.

The Drug GMP requirements under the FDR apply to all drug establishments that fabricate, package, label, distribute, import, wholesale, or test a drug. Establishments exempted are also required to comply with Drug GMPs. Compliance with Drug GMP requirements is assessed by conducting inspections of these establishments pursuant to the powers provided in the Sec. 23 of the Food and Drugs Act (FDA) and complemented by corresponding with regulatory or making specific inquiries. As described these inspections and the determination of compliance with Drug GMP requirements are the basis for the issuance of Establishment Licences (ELs) to domestic sites.

EL Requirements: Important regulatory changes were introduced on January 1st, 1998 to provide for an EL framework the FDR to apply uniform GMPs for all drugs.

These EL requirements apply to all Canadian drug establishments except those exempted. Natural Health Products (NHP) establishments have been exempted. Despite this exemption FDR requires NHP manufacturers and importers to meet GMP requirements.

It should also be noted that an establishment which performs the tests specified in Division 2 must hold a licence as a testing facility. Although licenced fabricators, packagers / labellers, distributors (who holds a DIN), and/or importers who have their own testing laboratory, are not required to hold a licence which specifies testing laboratory, the testing is listed on the EL, thus providing more information on all the activities being carried out at a particular site.

An establishment wishing to obtain an EL must demonstrate that applicable requirements for Drug GMP have been met. To demonstrate Drug GMP compliance, the establishment will need to provide evidence that its buildings, equipment and proposed practices and procedures meet the applicable requirements of the FDR, i.e. the establishment must have been inspected by the Inspectorate and have been subsequently found to comply with Drug GMP requirements and consequently been assigned a C rating. For foreign sites, they must demonstrate Drug GMP compliance by submitting inspection reports as described in the policy document entitled Conditions for
Acceptance of Foreign Inspections Reports for listing foreign sites on Canadian Establishment Licences. These reports are assessed to determine Drug GMP Compliance.

POLICY STATEMENT: An establishment, whether or not it is subject to the Drugs EL requirements, may be found to be non-compliant with Drug GMP requirements. In addition to being noncompliant with Drug GMPs, an establishment whose activities are covered under the Drugs EL Regulations, may not be in possession of a valid EL for the activities it conducts or wishes to conduct, for the following reasons:

• the establishment has not applied for an EL;
• the establishment has not renewed their EL by December 31st;
• the establishment has applied for, but was refused a licence due to a non-compliant (NC) inspection rating;
• the establishment has applied for a licence but certain foreign sites have not been approved for inclusion on the EL;

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• the establishment has applied for an EL amendment or gave notice of a major change, but this request was denied;
• the establishment’s EL’s terms and conditions have been amended or new terms and conditions have been imposed; or
• the establishment’s EL has been suspended.

Consistent with the Inspectorate’s Compliance and Enforcement Policy (POL-0001), appropriate enforcement actions will be considered in these situations, as the Inspectorate will not permit establishments to conduct regulated drug related activities without compliance with Drug GMP and/or EL requirements. These enforcement actions will be coordinated with any other violation discovered, such as Drug Identification Number (DIN) violations. Non-compliance with any other EL regulatory requirement, such as failure to apply for amendments, and failure to notify regarding changes made or proposed, may also result in enforcement action being taken.

Although the Inspectorate will work with drug establishments to help bring their operations into Drug GMP compliance, it will not tolerate chronic non-compliance with the regulations, which are meant to ensure that the health of the consumer is protected through quality and safety standards being met. Appropriate enforcement action must be considered in such situations to prevent further distribution of potentially unsafe drug products.

The Inspectorate may suspend an establishment licence under the authority provided in the Food and Drug Regulations and Medical Device Regulations where there are reasonable grounds to believe that any provisions of the Acts and Regulations have been contravened or that the licence has made a false or misleading statement in its application for an establishment licence. (www.hc-sc.gc.ca)

This Act may be cited as the Food and Drugs Act.

8. No person shall sell any drug that 

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(a) was manufactured, prepared, preserved, packaged or stored under unsanitary conditions; or

(b) is adulterated.

9. (1) No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety. Drugs labelled or packaged in contravention of regulations

(2) A drug that is not labelled or packaged as required by, or is labelled or packaged contrary to, the regulations shall be deemed to be labelled or packaged contrary to subsection (1).

10. (1) Where a standard has been prescribed for a drug, no person shall label, package, sell or advertise any substance in such a manner that it is likely to be mistaken for that drug, unless the substance complies with the prescribed standard.

(2) Where a standard has not been prescribed for a drug, but a standard for the drug is contained in any publication referred to in Schedule B, no person shall label, package, sell or advertise any substance in such a manner that it is likely to be mistaken for that drug, unless the substance complies with the standard.

Where no prescribed or trade standard

(3) Where a standard for a drug has not been prescribed and no standard for the drug is contained in any publication referred to in Schedule B, no person shall sell the drug unless

(a) it is in accordance with the professed standard under which it is sold; and

(b) it does not resemble, in a manner likely to deceive, any drug for which a standard has been prescribed or is contained in any publication referred to in Schedule B.

11. No person shall manufacture, prepare, preserve, package or store for sale any drug under unsanitary conditions.

12. No person shall sell any drug described in Schedule C (Drugs, other than radionuclides, sold or represented for use in the preparation of radiopharmaceuticals) or D unless the Minister has, in prescribed form and manner, indicated that the premises in which the drug was manufactured and the process and conditions of manufacture therein are suitable to ensure that the drug will not be unsafe for use.

13. No person shall sell any drug described in Schedule E (No items mentioned) unless the Minister has, in prescribed form and manner, indicated that the batch from which the drug was taken is not unsafe for use.

14. (1) No person shall distribute or cause to be distributed any drug as a sample.

(2) Subsection (1) does not apply to the distribution, under prescribed conditions, of samples of drugs to physicians, dentists, veterinary surgeons or pharmacists.

15. No person shall sell any drug described in Schedule F (No items mentioned).

22. (1) The Minister may designate any person as an inspector for the purpose of the enforcement of this Act.
23. (1) Subject to subsection (1.1), an inspector may at any reasonable time enter any place where the inspector believes on reasonable grounds any article to which this Act or the regulations apply is manufactured, prepared, preserved, packaged or stored, and may

(a) examine any such article and take samples thereof, and examine anything that the inspector believes on reasonable grounds is used or capable of being used for that manufacture, preparation, preservation, packaging or storing;

(a.1) enter any conveyance that the inspector believes on reasonable grounds is used to carry any article to which section 6 or 6.1 applies and examine any such article found therein and take samples thereof;

(b) open and examine any receptacle or package that the inspector believes on reasonable grounds contains any article to which this Act or the regulations apply;

(c) examine and make copies of, or extracts from, any books, documents or other records found in any place referred to in this subsection that the inspector believes on reasonable grounds contain any information relevant to the enforcement of this Act with respect to any article to which this Act or the regulations apply; and

(d) seize and detain for such time as may be necessary any article by means of or in relation to which the inspector believes on reasonable grounds any provision of this Act or the regulations has been contravened.

(1.1) Where any place mentioned in subsection (1) is a dwelling-house, an inspector may not enter that dwelling-house without the consent of the occupant except under the authority of a warrant issued under subsection (1.2).

(1.2) Where on ex parte application a justice of the peace is satisfied by information on oath

(a) that the conditions for entry described in subsection (1) exist in relation to a dwelling-house,

(b) that entry to the dwelling-house is necessary for any purpose relating to the administration or enforcement of this Act, and

(c) that entry to the dwelling-house has been refused or that there are reasonable grounds for believing that entry thereto will be refused,

the justice of the peace may issue a warrant under his hand authorizing the inspector named therein to enter that dwelling-house subject to such conditions as may be specified in the warrant.

(1.3) In executing a warrant issued under subsection (1.2), the inspector named therein shall not use force unless the inspector is accompanied by a peace officer and the use of force has been specifically authorized in the warrant.

Definition of “article to which this Act or the regulations apply”

(2) In subsection (1), “article to which this Act or the regulations apply” includes

(a) any food, drug, cosmetic or device;

(b) anything used for the manufacture, preparation, preservation, packaging or storing thereof; and

(c) any labelling or advertising material.
(3) The owner or person in charge of a place entered by an inspector pursuant to subsection (1) and every person found therein shall give the inspector all reasonable assistance and furnish the inspector with any information he may reasonably require.

24. (1) No person shall obstruct or hinder, or knowingly make any false or misleading statement either orally or in writing to, an inspector while the inspector is engaged in carrying out his duties or functions under this Act or the regulations.

(2) Except with the authority of an inspector, no person shall remove, alter or interfere in any way with anything seized under this Part.

25. Any article seized under this Part may, at the option of an inspector, be kept or stored in the building or place where it was seized or, at the direction of an inspector, the article may be removed to any other proper place.

26. An inspector who has seized any article under this Part shall release it when he is satisfied that all the provisions of this Act and the regulations with respect thereto have been complied with.

27. (1) Where an inspector has seized an article under this Part and its owner or the person in whose possession the article was at the time of seizure consents to its destruction, the article is forthwith forfeited to Her Majesty and may be destroyed or otherwise disposed of as the Minister or the Minister of Agriculture and Agri-Food may direct.

(2) Where a person has been convicted of a contravention of this Act or the regulations, the court or judge may order that any article by means of or in relation to which the offence was committed, and any thing of a similar nature belonging to or in the possession of the person or found with the article, be forfeited. On the making of the order, the article and thing are forfeited to Her Majesty and may be disposed of as the Minister or the Minister of Agriculture and Agri-Food may direct.

(3) Without prejudice to subsection (2), a judge of a superior court of the province in which any article is seized under this Part may, on the application of an inspector and on such notice to such persons as the judge directs, order that the article and any thing of a similar nature found with it be forfeited to Her Majesty, if the judge finds, after making such inquiry as the judge considers necessary, that the article is one by means of or in relation to which any of the provisions of this Act or the regulations have been contravened. On the making of the order, the article or thing may be disposed of as the Minister or the Minister of Agriculture and Agri-Food may direct.

30. (1) The Governor in Council may make regulations for carrying the purposes and provisions of this Act into effect, and, in particular, but without restricting the generality of the foregoing, may make regulations

(a) declaring that any food or drug or class of food or drugs is adulterated if any prescribed substance or class of substances is present therein or has been added thereto or extracted or omitted therefrom;

(b) respecting

(i) the labelling and packaging and the offering, exposing and advertising for sale of food, drugs, cosmetics and devices,

(ii) the size, dimensions, fill and other specifications of packages of food, drugs, cosmetics and devices,

(iii) the sale or the conditions of sale of any food, drug, cosmetic or device, and
(iv) the use of any substance as an ingredient in any food, drug, cosmetic or device, to prevent the purchaser or consumer thereof from being deceived or misled in respect of the design, construction, performance, intended use, quantity, character, value, composition, merit or safety thereof, or to prevent injury to the health of the purchaser or consumer;

(c) prescribing standards of composition, strength, potency, purity, quality or other property of any article of food, drug, cosmetic or device;

(d) respecting the importation of foods, drugs, cosmetics and devices in order to ensure compliance with this Act and the regulations;

(e) respecting the method of manufacture, preparation, preserving, packing, storing and testing of any food, drug, cosmetic or device in the interest of, or for the prevention of injury to, the health of the purchaser or consumer;

(f) requiring persons who sell food, drugs, cosmetics or devices to maintain such books and records as the Governor in Council considers necessary for the proper enforcement and administration of this Act and the regulations;

(g) respecting the form and manner of the Minister’s indication under section 12, including the fees payable therefor, and prescribing what premises or what processes or conditions of manufacture, including qualifications of technical staff, shall or shall not be deemed to be suitable for the purposes of that section;

(h) requiring manufacturers of any drugs described in Schedule E to submit test portions of any batch of those drugs and respecting the form and manner of the Minister’s indication under section 13, including the fees payable therefor;

(i) respecting the powers and duties of inspectors and analysts and the taking of samples and the seizure, detention, forfeiture and disposition of articles;

(j) exempting any food, drug, cosmetic or device from all or any of the provisions of this Act and prescribing the conditions of the exemption;

(k) prescribing forms for the purposes of this Act and the regulations;

(l) providing for the analysis of food, drugs or cosmetics other than for the purposes of this Act and prescribing a tariff of fees to be paid for that analysis;

(l.l) respecting the assessment of the effect on the environment or on human life and health of the release into the environment of any food, drug, cosmetic or device, and the measures to take before importing or selling any such food, drug, cosmetic or device;

(m) adding anything to any of the schedules, in the interest of, or for the prevention of injury to, the health of the purchaser or consumer, or deleting anything from them;

(n) respecting the distribution or the conditions of distribution of samples of any drug;

(o) respecting
(i) the method of manufacture, preparation, preserving, packing, labelling, storing and testing of any new drug, and

(ii) the sale or the conditions of sale of any new drug,

and defining for the purposes of this Act the expression "new drug";

(p) authorizing the advertising to the general public of contraceptive devices and drugs manufactured, sold or represented for use in the prevention of conception and prescribing the circumstances and conditions under which, and the persons by whom, those devices and drugs may be so advertised;

(q) defining "agricultural chemical", "food additive", "mineral nutrient", "veterinary drug" and "vitamin" for the purposes of this Act; and

(r) respecting interim marketing authorizations, including applications for authorizations.

(2) Without limiting or restricting the authority conferred by any other provisions of this Act or any Part thereof for carrying into effect the purposes and provisions of this Act or any Part thereof, the Governor in Council may make such regulations governing, regulating or prohibiting

(a) the importation into Canada of any drug or class of drugs manufactured outside Canada, or

(b) the distribution or sale in Canada, or the offering, exposing or having in possession for sale in Canada, of any drug or class of drugs manufactured outside Canada,

as the Governor in Council deems necessary for the protection of the public in relation to the safety and quality of any such drug or class of drugs.

(3) Without limiting or restricting the authority conferred by any other provisions of this Act or any Part thereof for carrying into effect the purposes and provisions of this Act or any Part thereof, the Governor in Council may make such regulations as the Governor in Council deems necessary for the purpose of implementing, in relation to drugs, Article 1711 of the North American Free Trade Agreement or paragraph 3 of Article 39 of the Agreement on Trade-related Aspects of Intellectual Property Rights set out in Annex 1C to the WTO Agreement.

(4) In subsection (3),

"North American Free Trade Agreement" has the meaning given to the word "Agreement" by subsection 2(1) of the North American Free Trade Agreement Implementation Act;

"WTO Agreement" has the meaning given to the word "Agreement" by subsection 2(1) of the World Trade Organization Agreement Implementation Act.

(5) Without limiting or restricting the authority conferred by any other provisions of this Act or any of its Parts for carrying into effect the purposes and provisions of this Act or any of its Parts, the Governor in Council may make any regulations that the Governor in Council considers necessary for the purpose of implementing the General Council Decision.

(6) The definitions in this subsection apply in this subsection and in subsection (5).

"General Council" means the General Council of the WTO established by paragraph 2 of Article IV of the Agreement Establishing the World Trade Organization, signed at Marrakesh on April 15, 1994.
"General Council Decision" means the decision of the General Council of August 30, 2003 respecting Article 31 of the TRIPS Agreement, including the interpretation of that decision in the General Council Chairperson’s statement of that date.


3.4 AUSTRALIA

Regulation of Therapeutic Goods in Australia

OVERVIEW: The objective of the "Therapeutic Goods Act 1989" which came into effect on 15 February 1991, is to provide a national framework for the regulation of therapeutic goods in Australia to ensure the quality, safety and efficacy of medicines and ensure the quality, safety and performance of medical devices.

The regulatory framework is based on a risk management approach designed to ensure public health and safety, while at the same time freeing industry from any unnecessary regulatory burden.

Essentially therapeutic goods must be entered on the Australian Register of Therapeutic Goods (ARTG) (www.tga.gov.au/docs.htm1/artg.htm) before they can be supplied in Australia. The ARTG is a computer database of information about therapeutic goods for human use approved for supply in, or exported from, Australia.

The Therapeutic Goods Administration (TGA) is a unit of the Australian Government Department of Health and Ageing and is responsible for the administering the provisions of the legislation.

The TGA carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard. At the same time, the TGA aims to ensure that the Australian Community has access, within a reasonable time, to therapeutic advances.

Overall control of the supply of therapeutic goods is exercised through three main processes:

* Auditing and assessment of the quality of their manufacture
* Pre-market assessment of the goods
* Post marketing monitoring of compliance with standards once the goods are supplied on the market.

REGULATING MEDICINES: Australian manufacturers of all medicines must be licenced under part 4 of the "Therapeutic Goods Act 1989" and their manufacturing processes must comply with the principles of GMP.

Medicines assessed as having a higher level of risk (prescription medicines, some non-prescription medicines) are evaluated for quality, safety and efficacy and are registered on the ARTG. Medicines having a lower risk (consumer medicines purchased over the counter such as complimentary medicines including vitamins) are assessed for quality and safety. In assessing
the level of risk, factors such as the strength of the product, side effects, potential harm through prolonged use, toxicity and the seriousness of the medical condition for which the product is intended to be used, are all taken into account.

Once approved for marketing in Australia, medicines are included in the ARTG and can be identified by the AUST R number (for registered medicines) or an AUST L number (Listed medicines) that appears on the packaging of the medicine.

**MANUFACTURING PRINCIPLES:** (1) The minister may, from time to time, determine written principles to be observed in the manufacture of therapeutic goods for use in humans.

(2) The manufacturing principles may relate to:

(a) the standards to be maintained, and the equipment to be used, at premises used for the manufacturing of therapeutic goods for use in humans; or

(b) procedures for quality assurance and quality control to be employed in the manufacturing of therapeutic goods for use in humans; or

(c) the qualifications and experience required of persons employed in the manufacture of therapeutic goods for use in humans; or

(d) the manufacturing practices to be employed in the manufacturing of therapeutic goods for use in humans; or

(e) other matters relevant to the quality, safety and efficacy of therapeutic goods for use in humans that are manufactured in Australia; and may include codes of good manufacturing practice:

The Minister may, before taking action under sub section (1) in relation to the manufacturing principles, obtain advice from a committee established by the regulations on the action that should be taken under that subsection as to the principles to be observed in the manufacture of therapeutic goods for use in humans.

**APPLICATION FOR LICENCE:** (1) An application for a licence must:

(a) Be made in writing in accordance with a form approved by the Secretary; and

(b) Identify the therapeutic goods or classes of therapeutic goods that the applicant proposes to manufacture; and

(c) Identify the manufacturing premises that will be used in the manufacture of those goods; and

(d) Identify the steps in the manufacture of those goods that the applicant proposes to carry out under the licence; and

(da) if the applicant proposes to carry out steps in the manufacture of blood or blood components under the licence contain information relating to those steps set out in regulations made for the purposes of this paragraph; and

(a) state the names, qualifications and experience of the persons who are to have control of the production of the goods and of quality control measures that are to be employed; and
(b) be delivered to an office of the Department specified in the form; and
(c) be accompanied by the prescribed application fee.

(2) The Secretary may, by notice in writing given to an applicant for a licence, requires the applicant:

(a) to give to the Secretary, within such reasonable time as is specified in the notice, such further information concerning the application as is specified in the notice; or
(b) to allow an authorized person, at any reasonable time specified in the notice, to inspect the premises, equipment, processes and facilities that will be used in the manufacture of the goods, or other goods on those premises.

**GRANT OF LICENCE:** 1. Where:

(a) a person has made an application to carry out steps in the manufacture of therapeutic goods at particular manufacturing premises; and

(b) the prescribed application and inspection fee has been paid; and

(c) the applicant has complied with any requirements made by the Secretary under sub section 37(2) in relation to the application; the Secretary must grant the applicant a licence to carry out those steps at those premises unless the Secretary is satisfied that:

(d) the applicant will be unable to comply with the manufacturing principles; or

(e) the premises are not satisfactory for the manufacture of the goods; or

(f) the applicant is not a fit and proper person to hold a licence; or

(g) a person who is participating in, or is likely to participate in, managing the applicant’s affairs is not a fit and proper person to participate in the management of the affairs of a holder of a licence; or

(h) a person who has, or is likely to have, effective control over the applicant is not a fit and proper person to have effective control over a holder of a licence.

(i) Without limiting the matters to which the Secretary may have regard in considering whether the applicant or person is not a fit and proper person for the purposes of above paragraph the Secretary must have regard to:

"a suspension or revocation of a manufacturing licence granted"

Where the Secretary grants or refuses to grant a licence to an applicant, the Secretary must:

(a) give the applicant written notice of the decision; and

(b) in the case of a refusal – include in the notice the reasons for the refusal.

Where the Secretary grants a licence, the Secretary must cause particulars of the decision to be published in the “Gazette” as soon as practicable after the decision is made.

**TERM OF LICENCE:** A licence commences on the day specified in the licence and remains in force until it is revoked or suspended.
CONDITIONS OF LICENCES: (1) A licence may be granted subject to such conditions relating to the manufacture of the goods as the Secretary thinks appropriate.

(2) The Secretary may, by notice in writing given to the holder of a licence, impose new conditions on the licence or vary or remove existing conditions.

(3) The imposition or variation of a condition under subsection (2) takes effect:

(a) if the notice states that the action is necessary to prevent imminent risk of death, serious illness or serious injury—on the day on which the notice is given to the person; or

(b) in any other case—on the day specified for the purpose in the notice, being a day not earlier than 28 days after the notice is given to the person.

(4) In addition to any conditions imposed under subsection (1) or (2), each licence is except as otherwise specified in the licence, subject to the conditions that the holder of the licence will:

(a) ensure that:

(i) the goods conform to any standard applicable to the goods; and

(ii) the holder of the licence observes the manufacturing principles in carrying out any steps in the manufacture of the goods under the licence.

SECTION 41 REVOCATION AND SUSPENSION OF LICENCES
SECTION 41 A PUBLICATION OF LIST OF MANUFACTURERS ETC.

3.5 INDIA

Chapter IV of Drugs And Cosmetics Act 1940 deals with “Manufacture, Sale And Distribution of Drugs And Cosmetics

Section 16: Standards of quality

Section 17, 17A, 17B, 17C and 17D: Definitions of Misbranded, Adulterated, Spurious Drugs & Misbranded and Spurious Cosmetics respectively

Section 18: Prohibition of Manufacture and sale of certain drugs and cosmetics

DRUGS AND COSMETICS RULES 1945

PART VII OF THE ‘RULES’ ” MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF DRUGS OTHER THAN HOMOEOPATHIC MEDICINES” (GSR 785 (E) 10th Oct. 1985)

Rule 68: Manufacture on more than one set of premises: If drugs are manufactured on more than one set of premises a separate application shall be made and a separate licence shall be issued in respect of each such set of premises.

Rule 68-A: Grant or Renewal of Licences by the Central Licence Approving Authority: Notwithstanding any thing contained in this Part, on and from the commencement of the Drugs And Cosmetics (9th Amendment) Rules 1992, a licence for the manufacture for sale or distribution of drugs as specified from time to time by the Central Government by notification in the Official Gazette, for the
purpose of this Rule, shall be granted or renewed, as the case may be, by the Central Licence Approving Authority (appointed by the Central Government) (GSR 923 (E) 14th December 1992)

**PROVIDED** that the application for grant or renewal of such licence shall be made to the licensing authority.

On receipt of the application the licensing authority shall verify the statement made in the application, cause the manufacturing and testing establishment to be inspected in accordance with the provisions of Rules. And if the licensing authority is satisfied he shall forward the application and his report to the Central Licence Approving Authority for grant or renewal of licence as the case may be.

**PROVIDED** that if the licensing authority is of the opinion that the applicant is not in a position to fulfill the requirements laid down in these rules, he may, by order, for reasons to be recorded in writing, refuse to grant or renew the licence as the case may be.

The Central Licence Approving Authority on being satisfied may grant or renew the licence, as the case may be:

**PROVIDED** that if the Central Licence Approving Authority is of the opinion that the applicant is not in a position to fulfill the requirements laid down in these rules, he may, notwithstanding the report to the licensing authority, by order, for reasons to be recorded in writing, reject the application for grant or renewal of licence as the case may be.

**Rule 68-B**  Delegation of Powers by the Central Licence Approving Authority.

**Rule 69:** Application for licence to manufacture drugs other than those specified in Schedules C and C(1) of the Drugs And Cosmetics Rules: Application for grant or renewal of licence of manufacture for sale (or for distribution) of drugs, other than those specified in Schedules C and C(1) shall be made to the licensing authority appointed by the State Government for the purpose of this Part (hereinafter in this part referred to as the licensing authority) and shall be made on prescribed forms and on deposition of necessary fee as prescribed under these rules.

Where an application under this Rule is for the manufacture of drug formulations falling under the purview of new drug as defined in rule 122-E, such application shall also be accompanied with approval, in writing, in favour of the applicant, from the Central Licensing Authority (GSR 311 (E) dated 1.5.2002 w.e.f. 1.5.2002)

**Rule 69-A:** Loan Licences: (1) application for the grant or renewal of loan licences to manufacture for sale or for distribution of drugs other than those specified in schedule C, Schedule C(1) and Schedule X and shall be made in prescribed form accompanied by a licence and inspection fee to the licensing authority. The rule also provices to apply for renewal of a licence after its expiry but within six months of such expiry, with late fee. (Notification No. F.1-16/57-D dated 15th June 1957)

**Explanation**- For the purpose of this rule a loan licence means, licence which a licensing authority may issue to an applicant who does not have his own arrangements for manufacture but who intends to avail himself of the manufacturing facilities owned by a licensee.

**Rule 70:** Form of Licence to Repack or Manufacture Drugs other than those specified in Schedule C and C(1)

**Rule 70-A** Form of loan licence to manufacture for sale (or for distribution) of drugs other than those specified in Schedules C, C(1) and X : (GOI F.1-16/57-D dated 15th June 1957)

**Rule 71** Conditions for grant or renewal of a Licence in Form 25 (or FORM 25-F): Before a licence in form 25 (other than schedule C and C1 drugs i.e. Non-biological drugs (or form 25-F i.e. Narcotics) is granted or renewed the following conditions shall be complied with by the applicant:
(1) The manufacture shall be conducted under the active direction and personal supervision of competent technical staff consisting at least of one person who is a whole time employee and who possesses prescribed qualification and experience.

PROVIDED that the licensing authority may, in the matter of manufacture of disinfectant fluids, insecticides, liquid paraffin, medicinal gases, non-chemical contraceptives, plaster of Paris and surgical dressings, permit manufacture of the substance under the active direction and personal supervision of the competent technical staff, who, although not having any of the qualifications included in this rule, has, in the opinion of the Licensing Authority, adequate experience in the manufacture of such substance.

(2) The factory premises shall comply with conditions prescribed and shall provide adequate space, plant and equipment for the manufacturing operations, the space, plant and equipment recommended for various operations as given in Schedule M.

(3) The applicant shall provide and maintain adequate staff, premises and laboratory equipment for carrying out tests of the strength, quality and purity of the substances at the testing unit, which shall be separate from the manufacturing unit and head of the testing unit, possesses prescribed qualification, shall be independent of the head of the manufacturing unit.

(4) The applicant shall make adequate arrangements for the storage of drugs manufactured by him.

(5) The applicant shall, while applying for a licence to manufacture patent or proprietary medicines, (other than Pharmacopoeial or Generic drugs), furnish to the licensing authority evidence and data justifying that the patent or proprietary medicines-

(i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;

(ii) are safe for use in the context of the vehicles, excipients and additives and pharmaceutical aids used in the formulation and under the conditions in which the formulations for administration and use are recommended;

(iii) are stable under the conditions of storage recommended; and

(iv) contain such ingredients and in such quantities for which there is therapeutic justification.

(v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in rule 122-E, from the licensing authority as defined in clause (b) of rule 21.

(6) The licensee shall comply with the requirements of "Good Manufacturing Practices" as laid down in Schedule M. [GSR 894 (E) 11th December 2001 effective from 1st July 2005 for existing licencees]

Rule 71-A Conditions for the Grant or Renewal of a Licence in Form 25-B (for Repacking of Drugs)

Rule 71-B Conditions for the Grant or Renewal of a Licence in FORM 25-A (Loan licence for drugs other than Schedule C and C1 drugs).

Rule 72 Duration of Licence: An original licence or a renewed licence in form 25 [form 25-B or form 25-F] unless sooner suspended or cancelled shall be (valid for a period of five years on and from the date on which) it is granted or renewed.

PROVIDED that if the application for the renewal of a licence is made before its expiry, or if the application is made within six months of its expiry, after payment of additional fee, the licence shall continue to be in force until orders are passed on the application and the licence shall be deemed to have expired if the application for its renewal is made NOT within six months of its expiry.
Rule 73 CERTIFICATE OF RENEWAL

Rule 73-A CERTIFICATE OF RENEWAL OF LOAN LICENCE

Rule 73-AA DURATION OF LOAN LICENCE

Rule 73-B CERTIFICATE RENEWAL OF LICENCE IN FORM 25-B

Rule 74 Conditions of Licence in Form 25 and 25-F: A licence in form 25 and 25-F shall be subject to conditions stated therein and to the following further conditions namely:

(a) the licensee shall provide and maintain staff, premises and equipment as specified in Rule 71;

(b) the licensee shall comply with the provisions of the Act and of these rules and with further such requirements, if any, as may be specified in any rules subsequently made under Chapter IV of the Act, provided that where such further requirements are specified in the rules, these would come into force, four months after publication in the Official Gazette;

(c) the licensee shall either in his own laboratory or in any other laboratory approved by the licensing authority [under Part XV-A of these Rules] test each or lot of the raw material used by him for the manufacture of his products and also each batch of the final product and shall maintain records or registers showing the particulars in respect of such tests as specified in Schedule U. The records or registers shall be retained for a period of five years from the date of the manufacture;

(d) the licensee shall keep records of the details of manufacture as per particulars given in Schedule U of each batch of the drugs manufactured by him and such records shall be retained for a period of five years;

(e) the licensee shall allow an [inspector authorized by the Act] to enter, with or without prior notice, any premises and to inspect the plant and the process of manufacture and the means employed in standardizing and testing the drugs;

(f) the licensee shall allow an [inspector authorized by the Act] to inspect all registers and records maintained under these rules and to take samples of the manufactured drugs and shall supply to such Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and the Rules thereunder have been observed;

(g) the licensee shall, from time to time, report to the licensing authority any changes in the expert staff responsible for the manufacture or testing of the drugs and any material alterations in the premises or plant used for the purpose which have been made since the date of the last inspection made on behalf of the licensing authority;

(h) the licensee shall, on request, furnish to the licensing authority, the controlling authority or to such authorities as the licensing authority or the controlling authority may direct, from every batch or batches of the drugs as the licensing authority or the controlling authority may from time to time specify, a sample of such quantity as may be considered adequate by such authority for any examination and, if so required, also furnish full protocols or tests which have been applied;

(i) if the licensing authority [or the controlling authority] so directs and if requested by the licensee who had also furnished prima facie reasons for such directions, the licensee shall not sell or offer for sale any batch in respect of which a sample is or protocols are furnished under clause (h) until a certificate authorizing the sale of the batch has been issued to him by or on behalf of the licensing authority [or the controlling authority];

(j) Licensee shall on being informed by the licensing authority [or the controlling authority] that any part of any batch of the drug has been found by the licensing authority [or the controlling authority] not to conform with the standards of strength, quality or purity specified in these rules and on being directed
so to do, withdraw the remainder of the batch from sale, and, so far as may in the particular circumstances of the case be practicable, recall all issues already made from the batch;

(k) The licensee shall maintain an Inspection Book in form 35 to enable an Inspector to record his impressions and the defects noticed;

(l) The licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the label, the reference samples shall be maintained for a period of three months beyond the date of expiry of potency. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture;

(m) The licensee, who has been granted a licence in form 25-F, (Narcotics) shall-

(i) forward to the licensing authority of the concerned States of manufacture and supply of drugs a statement of the sales effected to the manufacturers, wholesalers, retailers, hospitals, dispensaries and nursing homes and Registered Medical Practitioners every three months.

(ii) maintain accounts of all transactions giving details as required in a register bound and serially page numbered and such records shall be retained for a period of five years or one year after the expiry of potency.

(n) The licensee shall store drugs specified in Schedule X in bulk form and when any of such drug is required for manufacture in a place other than its place of storage it shall be kept in separate place under the direct custody of a responsible person.

(o) The licensee shall comply, with the requirements of ‘Good Manufacturing Practices’ as laid down in Schedule M.

Rule 74-A CONDITIONS FOR LICENCE IN FORM 25-B i.e. Repacking of drugs

Rule 74-B CONDITIONS OF LICENCE IN FORM 25-A i.e. Loan Licence

Rule 75 Forms of application for Licence to manufacture for sale or distribution of drugs specified in schedules C and C(1) (Excluding those specified in part X-B and schedule X):

(1) applications for the grant or renewal of licence to manufacture for sale or distribution of drugs specified in Schedule C and C (1) (excluding those specified in Part X-B and Schedule X), shall be made to the licensing authority in prescribed form and shall be accompanied by appropriate licence fee for every inspection or for the purpose of renewal of licences.

(2) Application for grant or renewal of licence to manufacture for sale or distribution of drugs specified in Schedules C, C (1) and X shall be made to the licensing authority in prescribed form and shall be accompanied by appropriate licence fee for every inspection or for the purpose of renewal of licences.

PROVIDED that the applicant shall posses a licence in form 28, i.e. Schedule C and C1 drugs, to manufacture such drugs:

(3) The application for grant or renewal of licences to manufacture for sale or distribution of drugs in ‘Large Volume Parenteral’ and ‘Sera and Vaccines’ shall be made to the licensing authority appointed under this Part in prescribed form and shall be accompanied by appropriate licence fee for every inspection or for the purposes of renewal of licences.

(4) Where an application under this rule is for the manufacture of drug formulations falling under the purview of new drug as defined in rule 122-E, such application shall also be accompanied with approval, in writing, in favour of the applicant, from the Central Licensing Authority.

Rule 75-A LOAN LICENCES: Provisions and procedure for grant or renewal of loan licences.
Rule 76 Forms of Licences to manufacture drugs specified in schedules C and C(1), excluding those specified in [part X-B i.e. Blood Products and ] schedule X i.e. Narcotics, or drugs specified in schedules C and C(1) and X. (Narcotics) The Conditions for the Grant or Renewal of such Licences:

A licence to manufacture for sale or for distribution of drugs specified in Schedules C and C(1) other than Large Volume Parenterals, Sera and Vaccines, drugs specified in Part X-B and Schedule X shall be issued in form 28 and a licence to manufacture for sale or distribution of drugs specified under Schedules C and C(1) (other than Large Volume Parenterals, Sera and Vaccines, drugs specified in Part X-B) and Schedule X shall be issued in form 28-B. A licence to manufacture for sale or for distribution of Large Volume Parenterals, Sera and Vaccines shall be issue in form 28-D. Before a licence in form 28, or form 28-B or form 28-D is granted or renewed, the following conditions, among others, shall be complied with by the applicant, (Substituted GSR 119 (E) 11th March 1996 licence for Large Volume Parenterals, Sera and Vaccines by Central Licensing Authority in form 28-D)

1. The manufacture will be conducted under the active direction and personal supervision of competent technical staff consisting at least of one person who is a whole time employee and who possesses prescribed qualification and experience.

2. The factory premises shall comply with the conditions prescribed and shall provide adequate space, plant and equipment for any or all the manufacturing operations; the space, plant and equipment recommended for various operations are given in Schedule M.

3. The applicant shall provide and maintain adequate staff, premises and laboratory equipment for carrying out such tests of the strength, quality and purity of the substances as may be required to be carried out by him under the provisions of Part X of these rules including proper housing for animals used for the purposes of such tests, the testing unit being separate from the manufacturing unit and the head of the testing unit being separate from the manufacturing unit possessing prescribed qualification & experience and being independent of the head of the manufacturing unit.

4. The applicant shall make adequate arrangements for the storage of drugs manufactured by him.

5. The applicant shall furnish to the Licensing Authority, if required to do so, data on the stability of drugs which are likely to deteriorate for fixing the date of expiry which shall be printed on the labels of such drugs on the basis of the data so furnished.

6. The applicant shall, while applying for a licence to manufacture patent or Proprietary medicines, furnish to the Licensing Authority evidence and data justifying that the Patent or Proprietary medicines-

   (i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in in relation to the claims or conditions for which medicines are recommended for use or claimed to be useful;

   (ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in formulations, and under the conditions in which the formulations for administration and use are recommended;

   (iii) are stable under the conditions of storage recommended; and

   (iv) contain such ingredients and in such quantities for which there is therapeutic justification;

   (v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in rule 122-E, from the licensing authority as defined in clause (b) of rule 21.

7. The licensee shall comply, with the requirements of ‘Good Manufacturing Practices’ as laid down in Schedule M. (GSR 894 (E) dated 11.12.2001 effective from 1st July 2005)
Explanation: For the purpose of this rule, “Large Volume Parenterals” shall mean the sterile solutions intended for parental administration with a volume of 100 ml. or more (and shall include anti-coagulant solutions) in one container of the finished dosage form intended for single use.

Rule 76-A: FORM OF LOAN LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF DRUGS SPECIFIED IN SCHEDULES C AND C (1) [EXCLUDING THE DRUGS SPECIFIED IN SCHEDULE X] AND CONDITIONS FOR THE GRANT OR RENEWAL OF SUCH LICENCE: Provision and procedure for grant or renewal of loan licence in form 28-A

Rule 77 Duration of Licence: An original licence in [ Form 28, Form 28-B and Form 28-D or renewal licence in Form 26, 26-F and Form 26-H], unless sooner suspended or cancelled shall be [valid for a period of five years on and from the date on which it is granted or renewed.

Rule 78 Conditions of Licence: A licence in [ Form 28, Form 28-B or Form 28-D] shall be subject to the special conditions, if any, set out in Schedule F or Schedule F(1), as the case may be, which relate to the substance in respect of which the licence is granted and to the following general conditions:

(a) (i) The licensee shall provide and maintain an adequate staff and adequate premises and plant for the proper manufacture and storage of the substances in respect of which the licence is issued.

(ii) Without prejudice to the generality of the foregoing requirement, every holder of a licence who for any purpose engaged in the culture or manipulation of pathogenic spore-bearing micro-organisms shall provide to the satisfaction of the licensing authority separate laboratories and utensils and apparatus required for the culture or manipulation of such micro-organisms, the laboratories, utensils and apparatus so provided not being used for the manufacture of any other substance.

(b) The licensee shall provide and maintain staff, premises and equipment as specified in Rule 76.

(c)(i) The licensee shall maintain records of manufacture as per particulars given in Schedule U.

(ii) The licensee shall either in his own laboratory or in any laboratory approved by the Licensing Authority test each batch or lot of the raw material used by him for the manufacture of his product and also each batch of the final product and shall maintain records or registers showing the particulars in respect of such tests as specified in Schedule U. The records or registers shall be retained in the case of a substance for which a potency date is fixed for a period of two years from the expiry of such date, and in the case of other substances for a period of five years from the date of manufacture.

(d) The licensee shall allow an Inspector appointed under the Act, to enter, with or without prior notice, any premises where the manufacture is carried on and to inspect the premises, and in the case of substances specified in Schedules C and C(1), to inspect the plant and process of manufacture and the means employed for standardizing and testing the substance.

(e) The licensee shall allow an Inspector appointed under the Act, to inspect all registers and records maintained under these rules and to take samples of the manufactured product and shall supply to such Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Act and Rules thereunder have been observed.

(f) The licensee shall from time to time report to the Licensing Authority any changes in the staff responsible for the manufacture and testing of the substance and any material alterations in the premises or plant used for that purpose which have been made since the last date of inspection made on behalf of the Licensing Authority before the issue of the licence.

(g) The licensee shall on request furnish to the Licensing Authority, controlling authority or to such authorities as the Licensing Authority or the controlling authority may direct, from every batch of the drugs as the Licensing Authority or the controlling authority may from time to time specify, a sample of such quantity as may be considered adequate by such authority for any examination and, if so required, also furnish full protocols of the tests which have been applied.
(h) If the Licensing Authority or the controlling authority so directs, the licensee shall not sell or offer for sale any batch in respect of which a sample is, or protocols are furnished under the last preceding sub-paragraph until a certificate authorizing the sale of the batch has been issued to him by or on behalf of the Licensing Authority or controlling authority.

(i) The licensee shall on being informed by the Licensing Authority or the controlling authority that any part of any batch of the substance has been found by the Licensing Authority or the controlling authority not to conform with the standards of strength, quality or purity specified in these Rules and on being directed so to do, withdraw the remainder of that batch from sale and so far as may in the particular circumstances of the case be practicable recall all issues already made from that batch.

(j) No drug manufactured under the licence shall be sold unless the precautions necessary for preserving its properties have been observed throughout the period after manufacture.

(k) The licensee shall comply with the provisions of the Act and of these rules and with such further requirements, if any, as may be specified in any rules subsequently made under Chapter IV of the Act, provided that where such further requirements are specified in the rules, these would come into force four months after publication in the Official Gazette.

(l) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and defects noticed.

(m) The licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drugs required to conduct all the tests performed on the batch. In case of drugs bearing any expiry date on the label of the reference samples shall be maintained for a period of three months beyond the date of expiry. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture.

(n) The licensee, who has been granted a licence in Form 28-B i.e. Schedule C & C1 and Schedule X Drugs, shall:

(i) forward to the Licensing Authority of the concerned States of manufacture and supply of drug a statement of the sales effected to the manufacturers, wholesalers, retailers, hospitals, dispensaries, Nursing Homes and Registered Medical Practitioners every three months;

(ii) maintain accounts of all transactions giving details required in a register bound and serially page numbered, and such record shall be retained for a period of five years or one year after the date of expiry of potency, whichever is later.

(o) The licensee shall store drugs specified in Schedule X in bulk form and when any such drug is required for manufacture it shall be kept in a separate place under direct custody of a responsible person.

(p) The licensee shall comply with the requirements of “Good Manufacturing Practices” as laid down in Schedule M. (GSR 894 (E) 11th December 2001 effective from 1st July 2005)

Rule 78-A Conditions of Licence in Form- 28 A: i.e. loan licences

Rule 79 Inspection before Grant or Renewal of Licence:

Before a licence under this part is granted or renewed the Licensing Authority or Central Licence Approving Authority, as the case may be, shall cause the establishment in which the manufacture is proposed to be conducted or being conducted to be inspected by one or more Inspectors appointed under the Act with or without an expert in the field concerned. The Inspector or Inspectors shall examine and verify the statements made in the application regard to their correctness, and the capability of the applicant to comply with the requirements of competent technical staff, manufacturing plants, testing equipments and the requirements of ‘Good Manufacturing Practices’ and the

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Requirements of Plant and Equipment as laid down in Schedule M read with the Requirements of maintenance of records as laid down in Schedule U.

Rule 80 Report by Inspector: The Inspector shall forward a detailed descriptive report giving his findings on each aspect of inspection along with his recommendations after completion of his inspection in accordance with the provisions of Rule 79, to the Licensing Authority or Central Licence Approving Authority, as the case may be.

Rule 81 Procedure of Licencing Authority: (1) If the Licensing Authority (or Central Licence Approving Authority as the case may be) after such further enquiry, if any, as he may consider necessary, is satisfied that the requirements of the Rules under the Act have been complied with and that the conditions of the licence and the Rules under the Act will be observed, he shall issue a licence.

(2) If the Licensing Authority (or the Central Licence Approving Authority as the case may be) is not so satisfied, he shall reject the application and shall inform the applicant of the reasons of such rejection and of the conditions which must be satisfied before a licence can be granted and shall supply the applicant with a copy of the inspection report.

Rule 82 Further Application after Rejection: If within a period of six months from the rejection of an application for a licence the applicant informs the Licensing Authority (or Central Licence Approving Authority as the case may be) that the conditions laid down have been satisfied and deposits an inspection fee the Licensing Authority (or Central Licence Approving Authority as the case may be) may, after causing a further inspection to be made, he is satisfied that the conditions for the grant of a licence have been complied with, [in respect of drugs notified under Rule 68-A-Amended w.e.f. 14th December 1992] issue a licence in Form 28 [or Form 28-B-Amended w.e.f. 22nd June 1982].

Rule 83 RENEWAL: On application being made for renewal, the licensing authority may cause an inspection to be made and, if satisfied that the condition of the licence and the rules under the Act are, and will continue to be observed [he shall prepare a report to that effect in respect of those drugs which have been notified by the Central Government under Rule 68-A and forward it along with the application to the Central Licence Approving Authority], and shall issue a certificate of renewal.

Rule 84 The provisions of this Part shall apply to the manufacture of drugs for sale notwithstanding that such drugs are manufactured for sale outside India.

Rule 84-A Provisions for Appeal of The State Government or Central Government by party whose Licence has not been granted or renewed: Any person who is aggrieved by the order passed by the Licensing Authority or the Central Licence Approving Authority, as the case may be, refusing to grant or renew a licence, may within thirty days from the date of receipt of such order, appeal to the State Government or Central Government, as the case may be, and the State Government or the Central Government, after such enquiry into the matter, as is considered necessary and after giving the said person an opportunity for representing his views, may pass such order in relation thereto as it thinks fit.

Rule 85 Cancellation and Suspension of Licences: (1) The Central Licence Approving Authority may, after giving the licensee an opportunity to show cause, why such an order should not be passed by an order in writing stating the reasons there for, cancel a licence issued under this Part, or suspend it for such period as he thinks fit either wholly or in respect of any of the drugs to which it relates [or direct the licensee to stop manufacture, sale or distribution of the said drugs and ] thereupon order the destruction of drugs and ] the stock thereof in the presence of an inspector, if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act or rules made there under.

(2) The Licensing Authority may, for such licences granted or renewed by him, after giving the licensee an opportunity to show cause why such an order should not be passed, by an order in writing
stating the reasons there for, cancel a licence issued under this Part or suspend it for such period as he thinks fit either wholly or in respect of any of the drugs to which it relates, or direct the licensee to stop manufacture, sale or distribution of the said drugs and therewith order the destruction of drugs and the stocks thereof in the presence of an Inspector, if in his opinion, the licensee had failed to comply with any of the conditions of the licence or with any provisions of the Act or rules made there under.

(3) A licensee whose licence has been suspended or cancelled by the Central Licence Approving Authority or Licensing Authority Sub-rule (1) or Sub-rule (2), as the case may be, may, within ninety days of the receipt of a copy of the order by him prefer an appeal to the Central Government or the State Government, as the case may be, and the Central Government or the State Government may after giving the licensee an opportunity of being heard, confirm, reverse or modify such order.

PART VII: A MANUFACTURE FOR SALE [OR DISTRIBUTION] OF HOMOEOPATHIC MEDICINES

Rule 85 A to 85-I (Added by Notification F. 1-35/64-D dated 18th August 1964)


Rule 85E (2) Schedule M-I - GMP for Homoeopathic medicines inserted vide GSR 507 (E) dated 12.6.1987, and requirement to mention Expiry date was inserted in the year 2006.

Rule 86 to 93: PART VIII Manufacture for Examination, Test or Analysis

PART IX Labelling and packing of Drugs other than Homoeopathic Drugs

Rule 94 Exemption of certain drugs from certain provisions of this part: (1) labels on packages or containers of drugs for export shall be adopted to meet the specific requirements of the law of the country to which the drug is to be exported but the following particulars shall appear in a conspicuous position on the innermost container in which the drugs is packed and every other covering in which that container is packed-

(a) name of the drug
(b) the name, address of the manufacturer and the number of the licence under which the drug has been manufactured
(c) batch or lot number
(d) date of expiry, if any.

PROVIDED that where a drug, not classified under Schedule F, Schedule F(1) and Schedule X, blood products, Narcotic and Psychotropic substances is required by the consignee to be not labeled with the name and address of the manufacturer the labels on packages or containers shall bear a code number as approved by the Central Licensing Authority.

(2) The provisions of Rule 96 to 1CL inclusive, shall not apply to a medicine made up ready for treatment, whether after or without dilution, which is supplied on the prescription of a registered medical practitioner provided that-

(i) the medicine is labeled with the following particulars-
(a) the name and address of the supplier;
(b) the name of the patient and the quantity of the medicine
(c) the number representing serial number of the entry in the prescription register;
(d) the dose, if the medicine is for internal use;

(e) the words 'For External Use only' shall be printed on the label if the medicine is for external application.

(ii) Condition (3) of the conditions in Rule 65 is satisfied.

**Rule 95 Prohibition of Sale or Distribution unless labelled:** Subject to the other provisions of these Rules, no person shall sell or distribute any drug (including a patent or proprietary medicine) unless it is labeled in accordance with these Rules.

**Rule 96 Manner of Labelling:** (1) Subject to the other provisions of these Rules, the following particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any drug and on every other covering in which the container is packed, namely-

(i) The name of the drug:

(A) For this purpose, the proper name of the drug shall be printed or written in a more conspicuous manner than the trade name, if any which shall be shown immediately after or under the proper name and shall be –

(a) for drugs included in Schedule F or Schedule F(1), the name given therein;

(b) or drugs included in the Indian Pharmacopoeia or the official Pharmacopoeias and official compendia of drug standards prescribed in Rule 124, the name or synonym specified in the respective official Pharmacopoeias and official compendia of drug standards followed by the letters 'I.P.' or, as the case may be, by the recognized abbreviations or the respective official pharmacopoeia and official compendia of drug standards;

(c) for drugs included in the National Formulary of India, the name or synonym specified therein followed by the letters 'N.F.I.'

(d) for other drugs, the international non-proprietary name, if any, published by the World Health Organisation or where an international non-proprietary name is not published the name descriptive of the true nature or origin of the substance.

(ii) A correct statement of the net contents in terms of weight, measure, volume, number of units of contents, number of units of activities, as the case may be, and weight, measure, and volume shall be expressed in Metric system.

(iii) The content of active ingredients - This shall be expressed -

(a) for oral liquid preparations in terms of content per single dose, the dose being indicated in 5 milliliters.

**PROVIDED** that where the dose is below 5 ml. the contents of active ingredients may be expressed in terms one ml. [or fraction thereof]

**PROVIDED FURTHER** that where the single dose is more than 5 ml., the content of active ingredients shall be expressed in terms of minimum single dose as approved by the Licensing Authority.

(b) for liquid parenteral preparations ready for administration, in terms of 1 ml. or percentage by volume or per dose in the case of a single dose container.

**PROVIDED** that if the preparation is contained in an ampoule it will be enough if the composition is shown on the label or wrapper affixed to any package in which such ampoule is issued for sale;

(c) for drugs in solid form intended for parenteral administration in terms of units or weight per milligrams or gram;
(d) for tablets, capsules, pills and the like, in terms of the content in each tablet, capsule, pill or other unit, as the case may be;

(e) for other preparations, in terms of percentage by weight or volume or in terms of unit per gram or ml. as the case may be;

Provided that clause (iii) shall not apply to a pharmacopoeial preparation where the composition of such preparation is specified in the respective pharmacopoeia and to a preparation included in the National Formulary of India;

(iv) the name of the manufacturer and the address of the premises of the manufacturer where the drug has been manufactured

(v) a distinctive batch number, that is to say, the number by reference to which details of manufacture of the particular batch from which the substance in the container is taken are recorded and are available for inspection, the figure representing the batch number being preceded by the words ‘Batch No.’ or ‘B.No.’ or ‘Batch’ or ‘Lot No.’ or ‘Lot’

(vi) every drug manufactured in India shall bear on its label the number of the licence under which the drug is manufactured, the figure representing the manufacturing licence number being preceded by the words ‘Manufacturing Licence Number’ or ‘Mfg. Lic. No.’ or ‘M.L.’

(vii) drugs specified in schedule P and their preparations including combinations with other drugs shall bear on their labels the date of manufacture and the date of expiry of potency, and the period between the date of manufacture and the date of expiry shall not exceed that laid down in the said schedule (under the conditions of storage specified therein). Drugs and their preparations not included in schedule P, shall bear on their labels the date of their manufacture and also the date of their expiry which shall not exceed sixty months from the date of manufacture.

Provided that this period may be extended by the Licensing Authority specified in clause (b) or Rule 21 in respect of any specified drugs if satisfactory evidence is produced by the manufacturer to justify such an extension.

(viii) drugs specified in schedule C(1) and their preparations including combinations with other drugs shall bear on the labels (a) the date of manufacture, (b) the date of expiry of potency fixed by the manufacturer, and (c) where such drugs are imported, also the number of licence under which the drug is imported, preceded by the words ‘Import Licence’.

Provided that drugs in bulk form included in schedule C(1) which are not ready for use and not included in schedule P need not bear on the label the date of expiry of potency.

Provided further that no reference shall be made to any other licence number granted by any authority outside India on any label or container or in any covering in which the container is packed or in any other matter or advertisement enclosed therewith.

(ix) every drug intended for distribution to the medical profession as free sample shall, while complying with the labeling provisions under clauses (i) to (viii), further bear on the label of the container the words ‘Physician sample-Not to be sold’ which shall be overprinted.

(x) if any preparation contains not less than 3 percent by volume of alcohol the quantity of alcohol shall be stated in terms of the average percentage by volume of absolute alcohol in the finished products.

(xi) in addition to the other particulars which are required to be printed or written under these Rules, the label of innermost container of the following categories of drugs and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which should not be less than 0.5 mm in width and without disturbing the other conditions printed on the label under these rules, name-y-
Narcotic analgesics, hypnotics, sedatives tranquillisers, corticosteroids, hormones, hypoglycemic, antimicrobials, anti-epileptic, antidepressants, anticoagulants, anti-cancer drugs and other drugs falling under Schedule 'G', 'H', and 'X' whether covered or not in the above list.

PROVIDED that the provisions of this clause shall not apply to-
(a) preparations intended for animal treatment;
(b) preparations intended for external use;
(c) Ophthalmic preparations and ear drops; and
(d) sterile preparations such as sutures, surgical dressings and preparations intended for parenteral use.

(2) (i) The particulars to be printed or written on the label of a mechanical contraceptive shall be as specified in Schedule R.

(ii) The following particulars, in addition to those specified under sub-rule (1) shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container and on every other covering in which the container of a contraceptive, other than a mechanical contraceptive, is packed, namely-
(a) date of manufacture
(b) the date up to which contraceptive is expected to retain its properties;
(c) the storage conditions necessary for preserving the properties of the contraceptive up to the date indicated in sub-clause (b)

PROVIDED that for oral contraceptives it shall be sufficient to display on the label of the container the date of manufacture only.

(3) (i) The particulars prescribed in sub-rule (1) shall be printed or written in indelible ink either on the label borne by a container or vaccine lymph or on a label or wrapper affixed to any package in which the container is issued for sale. The said particulars shall be indelibly marked on the sealed container of surgical ligature or suture or printed or written in indelible ink on a label enclosed therein.

(ii) Nothing in these Rules shall be deemed to require the labeling of any transparent cover or any wrapper, case or other covering used solely for purpose of packing, transport or delivery.

(4) Where by any provision of these rules any particulars are required to be displayed on a label on the container such particulars may, instead of being displayed on a label, be etched, painted or otherwise indelibly marked on the container.

PROVIDED that, except where the otherwise provided in these rules, the name of the drug or any distinctive letters intended to refer to the drug shall not be etched, painted or otherwise indelibly marked on any glass container other than ampoules.

Explanation- For the purpose of this rule, the date of expiry shall be in terms of month and year and it shall mean that the drug is recommended till the last day of the month. The date of expiry shall be preceded by the words 'Expiry date'.

Rule 97 Labelling of Medicines: (1) The container of a medicine for internal use shall-
(a) If it contains a substance specified in Schedule G, be labeled with the words 'Caution- it is dangerous to take this preparation except under medical supervision' - conspicuously printed and surrounded by a line within which there shall be no other words;
(b) If it contains a substance specified in Schedule H be labeled with the symbol Rx and conspicuously displayed on the left top corner of the label and be also labeled with the following words:
'Schedule H drug - Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only'

(c) if it contains a substance specified in Schedule H and comes within the purview of the Narcotics Drugs and Psychotropic Substances Act, 1985 be labeled with the symbol NRx which shall be in red and conspicuously displayed on the left top corner of the label, and be also labeled with the following words:

'Schedule H drug-Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only'

(d) if it contains a substance specified in Schedule X, be labeled with the symbol XRx which shall be in red conspicuously displayed on the left top corner of the label, and be also labeled with the following words:

'Schedule X drug-Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only'

(2) The container of an embrocation, liniment, lotion, ointment, antiseptic cream or other liquid medicine for external application shall be labeled with the words in capital "For External use only"

(3) The container of a medicine made up ready only for treatment of an animal shall be labeled conspicuously with the words ‘Not for human use: for animal treatment only’, and shall bear a symbol depicting the head of a domestic animal.

(4) The container of a medicine prepared for treatment of human ailments shall if the medicine contains industrial methylated spirit, incitate this fact on the label and be labeled with the words “FOR EXTERNAL USE ONLY”

(5) Substances specified in Schedule X in bulk form shall bear a label wherein the symbol as specified in sub-rule (1) shall be given conspicuously in red letters.

Rule 98 to 101. Omitted in the year 1982

Rule 102 NOT-STERILE SURGICAL LIGATURE AND SUTURE

Rule 103 (1).... Omitted 15.6.1957

(2) The name and address of the manufacturer shall be printed on the label of the container of a patent or proprietary medicine.

(3) The true formula or list of ingredients shall be printed or written in indelible ink on the outer label of every package containing patent or proprietary medicine.

Rule 104 Use of Letters I.P. ETC: The letters ‘I.P.’ and recognized abbreviations of pharmacopoeias and official compendia of drug standards prescribed under these Rules shall be entered on the label of the drug only for the purpose of indicating that the drug is in accordance with standards set out in the Indian Pharmacopoeia or any such Pharmacopoeia or official compendium of drug standards recognized under the Rules

Rule 104-A Prohibition against altering inscriptions on containers labels or wrappers of drugs: No person shall alter, obliterate or deface any inscription or mark made or recorded by the manufacturer on the container, label, or wrapper of any drug:

PROVIDED that nothing in this rule shall apply to any alteration, any inscription or mark made on the container, label or wrapper of any drug at the instance or direction or with the permission of the Licensing Authority.
Rule 105 Packing of drugs:

(1) The pack sizes of drugs meant for retail sale shall be as prescribed in Schedule P-1 to these rules.

(2) The pack sizes of drugs not covered by the Schedule P-1 shall be as given below:

   Unless specified otherwise in Schedule P-1,

(i) The pack sizes of tablets, capsules shall be-

Where the number of tablets (coated or uncoated)/ capsules (hard or soft gelatin) is less than 10, such packing shall be made by the integral number. For numbers above 10, the pack sizes of tablets/capsules shall contain multiples of 5.

(ii) The pack sizes for liquid oral preparations shall be 30 ml. (pediatric only) 60 ml. / 100 ml. / 200 ml. / 450 ml.

(iii) The pack sizes for pediatric Oral Drops shall be 5ml/10ml/ 15 ml.

(iv) The pack sizes for Eye/Ear/Nasal Drops shall be 3ml/5ml/10ml

(v) The pack sizes for Eye ointment shall be 3 gm/ 5gm/ 10 gm.

PROVIDED that the provisions of the pack sizes covered under this rule shall not apply to:

1. Pack sizes or dosage forms not covered by the foregoing provisions of this rule,
2. The imported formulations in finished form.
4. Preparations intended for veterinary use.
5. Vitamins/Tonics/Cough preparations/Antacids/Laxatives in Liquid oral form, Unit dose (including applicaps)
6. Pack sizes of dosage meant for retail sale to Hospitals, Registered Medical Practitioners, Nursing Homes.
7. Physician’s Samples.
8. Pack sizes of Large Volume Intravenous Fluids.

PROVIDED ALSO that pack sizes of any of the new drug as and when approved by the Licensing Authority appointed under Rule 21 and if not covered under this rule, shall be examined for the purpose of approval with specific justification by the said Licensing Authority.

Rule 105-A Packing of drugs specified in schedule X: The drugs specified in Schedule X shall be marked in packings not exceeding:

(i) 100 unit doses in the case of tablets/capsules;
(ii) 300 ml. In the case of oral liquid preparation;
(iii) and ml. In the case of injections.

PROVIDED that nothing in this rule shall apply to packings meant for use of a Hospital or a Dispensary subject to the conditions that:

(i) such supplies are made by the manufacturers or distributors direct to the hospitals/ dispensaries; and
hospital packs shall not be supplied to a retail dealer or to a Registered Medical Practitioner.

Rule 106 Diseases which a drug may not purport to prevent or cure:

(1) No drugs may purport or claim to prevent or cure or may convey to the intending user thereof any idea that it may prevent or cure, one or more the diseases or ailments specified in Schedule J

(2) No drug may purport or claim to procure or assist to procure, or may convey to the intending user thereof any idea that it may procure or assist to procure, miscarriage in women.

PART IX-A LABELLING AND PACKING OF HOMOEOPATHIC MEDICINES

PART X SPECIAL PROVISIONS RELATING TO BIOLOGICAL AND OTHER SURGICAL PRODUCTS

PART X-A IMPORT OR MANUFACTURE OF NEW DRUG FOR CLINICAL TRIALS OR MARKETING

Rule 122-A APPLICATION FOR PERMISSION TO IMPORT NEW DRUG

Rule 122-B Application for approval to manufacture NEW DRUG other than the drugs classifiable under schedules C and C(1):

(1) (a) No New drug shall be manufactured for sale unless it is approved by the Central Licensing Authority.

(b) An application for grant of approval to manufacture the new drug and its formulations shall be made to the Central Licensing Authority and shall be accompanied by prescribed fee.

(2) A manufacturer of a new drug under sub-rule (1) when applying for approval to the Central Licensing Authority mentioned in sub-rule (1) shall submit data including the results of clinical trials carried out in the country on the prescribed format.

(2A) The Central Licensing Authority after being satisfied that the drug if approved to be manufactured as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in country, shall issue approval subject to the conditions stated therein.

PROVIDED that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission could be considered.

Rule 122-D Permission to Import or Manufacture Fixed dose combination:

(1) An application for permission to import or manufacture fixed dose combination of two or more drugs as defined shall be made to the Central Licensing Authority accompanied by prescribed fee and shall be accompanied by such information and data as is prescribed.

(2) The Licensing Authority after being satisfied that the fixed dose combination, if approved to be imported or manufactured as finished formulation shall be effective and safe for the use in the country, shall issue permission subject to the conditions stated therein.

PROVIDED that the Licensing Authority shall where the data provided or generated on the fixed dose combination is inadequate, intimate the applicant in writing, and the conditions which shall be satisfied before grant of approval / permission could be considered.

Rule 122-DA APPLICATION FOR PERMISSION TO CONDUCT CLINIC TRIALS FOR NEW DRUG/INVESTIGATIONAL NEW DRUG

Rule 122-DB SUSPENSION OR CANCELLATION OF PERMISSION/APPROVAL

Rule 122-DC APPEAL

Rule 122-E Definition of New Drug: For the purpose of this Par., new drug shall mean and include-
(a) A drug, as defined in the Act including bulk drug substance which has not been used in the
country to any significant extent under the conditions prescribed, recommended or suggested in the
labeling thereof has not been recognized as effective and safe by the licensing authority mentioned
under rule 21 for the proposed claims:

PROVIDED that the limited use, if any, has been with the permission of the licensing authority.

(b) A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims,
which is now proposed to be marketed with modified or new claims, namely, indications, dosage,
dosage form (including sustained release dosage form) and route of administration.

(c) A fixed dose combination of two or more drugs, individually approved earlier for certain claims,
which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in
an already marketed combination is proposed to be changed, with certain claims, viz. indications,
dosage, dosage form (including sustain release dosage form); and route of administration.

Explanation – For the purpose of this rule-

(i) all vaccines shall be new drugs unless certified otherwise by the Central Licensing Authority under
Rule 21;

(ii) a new drug shall continue to be considered as new drug for a period of four years from the date of
its first approval or its inclusion in the Indian Pharmacopoeia whichever is earlier.

REQUIREMENTS FOR THE COLLECTION, STORAGE, PROCESSING AND DISTRIBUTION OF
WHOLE HUMAN BLOOD, HUMAN BLOOD COMPONENTS BY BLOOD BANKS AND
MANUFACTURE OF BLOOD PRODUCTS

Rule 122 EA to 122-P

Rule 123 The drugs specified in Schedule K shall be exempted from the provisions of Chapter
IV of the Act and Rules made there under to the extent and subject to the conditions specified
in that Schedule.

Rule 124 Standards of Drugs:

(1) For drugs included in the Indian Pharmacopoeia-

(a) The standards for identity, purity and strength shall be those as may be specified in the edition of
the Indian Pharmacopoeia for the time being in force.

(b) In case the standards of identity, purity and strength for drugs are not specified in the edition of of
the Indian Pharmacopoeia for the time being in force but are specified in the edition of the Indian
Pharmacopoeia immediately preceding, the standards for identity, purity and strength shall be those
occurring in such immediately preceding edition of the Indian Pharmacopoeia.

(2) For other drugs:

(a) The standards of identity, purity and strength shall be those as may be specified in the edition of
the official pharmacopoeia, for the time being in force, of any country to which the drug claims to
comply with.

(b) In case the standards for identity, purity and strength for drugs are not specified in the edition of such
official pharmacopoeia, for the time being in force, but are specified in the edition immediately
preceding, the standards for identity, purity and strength shall be those occurring in such immediately
preceding edition of such official pharmacopoeia to which the drug claims to comply with.

(c) For drugs for which standards are not included in the edition of the official pharmacopoeia, for
the time being in force, of any country or in its edition immediately preceding but included in the official
compendia of drugs standards, namely, the British Pharmaceutical Codex or the National Formulary of the United States, for the time being in force, to which the drug claims to comply with.

Rule 124-A  STANDARDS FOR VETERINARY DRUGS

Rule 124-B Standards for Patent or Proprietary Medicines: The standards for Patent or Proprietary medicines shall be those laid down in Schedule V and such medicines shall also comply with the standards laid down in the Second Schedule of the Act.

Rule 124-C  STANDARDS FOR SURGICAL DRESSINGS

Rule 124-D  STANDARDS FOR STERILIZED UMBILICAL TAPES

Rule 125  STANDARDS FOR SUBSTANCES (OTHER THAN FOOD) INTENDED TO AFFECT THE STRUCTURE OR ANY FUNCTION OF HUMAN BODY- CONTRACEPTIVES

Rule 125-A  STANDARDS FOR MEDICAL DEVICES

Rule 126 Standards for substances intended to be used for the destruction of vermin or insects which cause disease in human beings or animals

Rule 126-A  STANDARDS FOR OPHTHALMIC PREPARATIONS (INCLUDING HOMOEOPATHIC OPHTHALMIC PREPARATIONS)

Rule 127 LIST OF DRUGS PERMITTED TO BE USED IN DRUGS

PART XVI  MANUFACTURE FOR SALE OF AYURVEDIC (INCLUDING SIDDHA) OR UNANI DRUGS

PART XVI A  APPROVAL OF INSTITUTIONS FOR CARRYING OUT TESTS ON AYURVEDIC, SIDDHA AND UNANI DRUGS AND RAW MATERIALS USED IN THEIR MANUFACTURE ON BEHALF OF LICENSEES FOR MANUFACTURE FOR SALE OF AYURVEDIC, SIDDHA AND UNANI DRUGS

PART XVII  LABELLING, PACKING AND LIMIT OF ALCOHOL IN AYURVEDIC (INCLUDING SIDDHA) OR UNANI DRUGS

PART XVIII GOVERNMENT ANALYSTS AND INSPECTORS FOR AYURVEDIC (INCLUDING SIDDHA) OR UNANI DRUGS

PART XIX STANDARDS FOR AYURVEDIC, SIDDHA AND UNANI DRUGS

(www.cdsco.nic.in)

3.6 THAILAND

The regulation of pharmaceutical products on Thailand began in 1909 where adulteration of drug products and narcotic substances was prohibited. There has been practically no control of drugs before 1909. The first legislation passed in 1922 was the Harmful and habit-forming Drugs Act. However, the drug manufacturing and dispensing medicines were not assigned to pharmaceuticals till 1929.

The control of production and registration of pharmaceutical products as well as the standard requirements of drug were included in the Act and came into force in 1951. After several years of endeavor, the Drugs Act 1967 was promulgated thereafter Drug Act 1987, which has major features follows:

1. Medicines are classified into two major groups:

MODERN DRUGS: are further divided into four categories, namely
1) household remedies whose sales require no licence;
2) ready-packed drugs that are sold in drug stores by nurses or other medical professionals;
3) Dangerous drugs and
4) specially controlled drugs.

**TRADITIONAL DRUGS** are those intended to be used in indigenous or traditional medical care as monographed in the official pharmacopoeia of traditional medicines or those declared by the Minister of Public Health as traditional medicines or those permitted to be registered as traditional medicines. Control and registration of drugs in this group are less stringent than the modern drugs.

2. The Ministry of Public Health is authorized to publish in the Government Gazette a list of specially-controlled products, a list of dangerous drugs, the list of particular drugs requiring additional labeling (e.g. expiration, warning etc.)

3. Licensing for manufacture, importation and sale of pharmaceutical products required by law. Applications for licences are to be conducted in accordance with the rules, measures and conditions prescribed in the Ministerial Regulations.

4. Duties of licensees and pharmacists at the place of production, importation and sale are also described. For instance, a licensee who manufactures medicines must have finished products of each batch analyzed for quantities of the constituents before the products are released to the market.

5. Licensees must register their products before manufacture or import. Details of the products and their formulas, as being registered, cannot be sold without prior approval or permission from the authorities.

6. The Minister of Public Health is empowered to either suspend or revoke licence from violating or non-compliance licensees.

**PRE-MARKETING CONTROL: LICENSING**

Applications for licences must be submitted to the licensing authority, buildings and facilities will then be inspected. A licence will be issued after inspection has confirmed that the applicant has adequate capabilities of such business, and he/she can secure appropriate facilities and personnel for the purpose.

Licences are issued, according to the business of the applicant, in nine categories:
- Licence to manufacture modern medicines
- Licence to import modern medicines
- Licence to sell modern medicines
- Licence as a wholesaler of modern medicines
- Licence to sell modern medicines in sealed packages which are claimed neither dangerous nor specially-controlled medicines
- Licence to sell modern veterinary medicines in sealed packages
- Licence to manufacture traditional medicines
- Licence to import traditional medicines

**DRUG REGISTRATION:** The registration process is necessary to ensure quality, safety and efficacy of drugs being marketed in the country. Only authorized licensees are qualified to apply for product registration. Manufacturing plants, in which drugs products are manufactured, are **subject to inspection for GMP compliance.** According to the new Drug Act a product registration is valid for five
years as from the date of issuance of process of drug registration will be carried out in 2 channels, which differ in degree of control and dossier submission:

1. Registration of general medicines
2. Registration of Thai traditional medicines

Due to some differences in the requirements for dossiers to be submitted for product approvals, the general medicines will have to be further defined:

**GENERICS** whose registration require only dossiers on product manufacturing and quality control along with product information.

**NEW MEDICINES** whose registrations require a complete set of dossiers;

**NEW GENERICS** whose registrations require dossiers of bioequivalence studies in addition to the required dossiers for generics submissions.

Generics mean pharmaceutical products with the same active ingredients same dosage forms as those of the original products, but manufactured by different manufacturers.

New medicines include products of new chemicals, new indications, new combinations or new delivery systems and new dosage forms.

New generics are medicines with the same active ingredients, doses and forms as those of the new compounds registered after 1992.

The amended registration procedure for new drug products, adopted in 1989, involves a two year period of safety monitoring program. Thus new drugs will be firstly approved for use only in hospitals or clinics at least two years. Then safety reports must be submitted for consideration whether general marketing should be allowed. Meanwhile, new generics have to pass bioequivalence studies to assure completely therapeutic outcomes. The bioequivalance data must be submitted to the authority with proofs of the product bioavailability along with the product information (www.fda.moph.go.th)

### 3.7 CHINA

**DRUG ADMINISTRATION LAW OF THE PEOPLE’S REPUBLIC OF CHINA**

**CHAPTER (1) One**

**GENERAL PROVISIONS**

**Article 2** All institutions and individuals engaged in research, production, distribution, use, or drug administration in the People’s Republic of China shall abide by this Law.

**Article 5** The drug regulatory department under the State Council shall be responsible for the drug administration nationwide. The drug regulatory departments of the People’s government of provinces, autonomous regions, and municipalities directly under the Central Government shall be responsible for drug regulation in their administrative areas.

Devi Ahilya Vishwavidyalaya Indore
CONTROL OVER DRUG MANUFACTURERS

Article 7 The establishment of a drug manufacturer shall be subject to approval by the local drug regulatory department of the People's government of the province, autonomous region or municipality directly under the Central Government and be granted the Drug Manufacturing Certificate, and, with this certificate, the manufacturer shall be registered with the administrative department for industry and commerce. No one may manufacture drugs without the certificate.

The valid term and the scope of manufacturing shall be indicated in the Drug Manufacturing Certificate. For renewal of the certificate on expiration, reexamination is required. When giving approval to the establishment of a new manufacturer, the drug regulatory department shall see to it that, apart from the requirements specified by the provisions in Article 8 of this Law that should be met.

Article 8 A drug manufacturer to be established shall meet the following requirements:

(1) having legally qualified pharmaceutical and engineering professionals, and the necessary technical workers;

(2) having the premises, facilities, and hygienic environment required for drug manufacturing;

(3) having the institutions and personnel capable of quality control and testing for drugs to be produced and the necessary instruments and equipment; and

(4) having rules and regulations to ensure the quality of drugs.

Article 9 The drug regulatory department shall inspect a drug manufacturer as to its compliance with the GMP requirements and issue a certificate to the manufacturer passing the inspection. The specific measures and schedule for implementing the GMP shall be formulated by the drug regulatory department under the State Council.

Article 10 With the exception of the processing of prepared slices of Chinese crude drugs, a drug shall be produced in conformity with the National Drug Standard and with the production processes approved by the drug regulatory department under the State Council, and the production record shall be complete and accurate. When drug manufacturers make any change in the production process that may affect the drug quality, they shall submit the matter for examination and approval to the original approval authority.

Article 12 Drug manufacturers shall perform quality test of the drug produced, each drug should meet the national drug standards.

Article 13 A drug manufacturer may accept contract production of drugs upon approval by the drug regulatory department under the State Council, or by the drug regulatory department of the people's government of a province, autonomous region, municipality directly under the Central Government authorized by the drug regulatory department under the State Council.

Article 48 Production and distribution of counterfeit drugs are prohibited

A drug is a counterfeit drug in any of the following cases:

(1) the ingredients in the drug are different from those specified by the national drug standards; or
(2) A non-drug substance is simulated as a drug or one drug is simulated as another.

A drug shall be treated as a counterfeit drug in any of the following cases:

(1) Its sale is prohibited by the regulations of the drug regulatory department under the State Council;

(2) It is produced or imported without approval, or marketing without being tested, as required by this Law;

(3) It is deteriorated;

(4) It is contaminated;

(5) It is produced by using drug substances without approval number as required by this Law;

(6) the indications or functions indicated are beyond the specified scope.

Article 49 Production and distribution of substandard drugs are prohibited. A drug with content not up to the national drug standards is a substandard drug. A drug shall also be treated as substandard drug in any of the following cases:

(1) the date of expiry is not indicated or is altered;

(2) the batch number is not indicated or altered;

(3) it is beyond the date of expiry;

(4) no approval is obtained for the immediate packaging material or container;

(5) colorants, preservatives, spices, flavorings or other excipients are added without authorization; or

(6) other cases where the drug standard are not conformed.

Article 50 A drug name listed in the national drug standard is an adopted name in China, Such an adopted name may not be used as a trademark.

Article 52 No drug manufacturers may use immediate packaging materials and containers for which no approval obtained. If the immediate packaging materials and containers are not up to the standard, the drug regulatory department shall give orders stopping the use of such materials and containers.

Article 53 Drug packaging shall conform to drug quality requirements and be convenient for storage, transportation and medical use.

Article 54 A label shall be printed or stuck on the drug package together with an inert sheet, as required by regulations. In the label or insert sheet shall be indicated the adopted name of the drug in China, its ingredients, strength, manufacturer, approval number, product batch number, production date, date of expiry, indications or functions, usage, dosage, contraindications, adverse drug reactions, and precautions.

CHAPTER VIII (Eight)

INSPECTION OF DRUGS

Article 64 Drug regulatory departments shall have the power to supervise and inspect, according to drug and administrative regulations, matters related to drug research and development, which it has
given approval, to drug production and distribution, and to the use of drugs by medical institutions. No institutions or individuals concerned may resist the supervision and inspection or conceal any facts.

Article 65 Drug regulatory departments may conduct selective testing of drug quality in light of the supervision and inspection, sampling for selective testing shall be carried out according to relevant regulations, and no fees whatever may be charged for sampling or testing.

The drug regulatory department shall take administrative enforcement measures to seal or seize the drugs and related materials that are proved to be potentially harmful to human health and shall, within seven days, make an administrative decision on the matter in question. Where it is necessary to test drugs, it shall, within fifteen days from the date the testing report is issued, make the administrative decision.

Article 67 Where the party has objection to the results of testing conducted by the drug testing institution, it may, within seven days from the date it receives the testing results, apply for retesting to the said drug testing institution, or to such an institution established or designated by the drug regulatory department at the next higher level, and it may also directly apply to the drug testing institution established or designated by the drug regulatory department under the State Council. The drug testing institution that accepts the application shall, within the time limit specified by the drug regulatory department under the State Council, draw a conclusion from the re-test. (www.sfda.gov.cn)

3.8 JAPAN

Pharmaceutical and Food Safety Bureau The work of this Bureau involves controlling the production and sales of drugs, quasi-drugs, cosmetics and medical devices, and collecting/offering information on adverse reactions from products in order to ensure effectiveness and safety.

Organization and Function of the Ministry of Health, Labour and Welfare:

The Ministry of Health, Labor, and Welfare (MHLW) (Koseirodosho in Japanese) was established by a merger of the Ministry of Health and Welfare (MHW) and the Ministry of Labor, on January 6, 2001 as part of the Government program for reorganizing Government Ministries. The MHLW, which was originally established in 1938, has been in charge of the improvement and promotion of social welfare, social security and public health, and the new organization has the same tasks.

The MHLW is in charge of pharmaceutical regulatory affairs in Japan, and the Pharmaceutical and Food Safety Bureau (PFSB) undertakes main duties and functions of the Ministry: it handles clinical studies, approval reviews and post-marketing safety measures, i.e., approvals and licensing.

Pharmaceutical Laws and Regulations

1. PHARMACEUTICAL LAWS:

Pharmaceutical administration in Japan is based on various laws and regulations, consisting mainly of: (1) the Pharmaceutical Affairs Law, (2) Pharmacists Law, (3) Law Concerning the establishment for Pharmaceuticals and Medical Devices Organization, (4) Law Concerning Securing a Stable Supply of Blood Products, (5) Poisonous and Deleterious Substances Control Law, (6) Narcotics and Psychotropic Drugs Control Law, (7) Cannabis Control Law, (8) Opium Law, and (9) Stimulants Control Law.

For the enforcement and management of these laws, detailed regulations are prepared by the government in the form of ministerial ordinances and notices, such as the Enforcement Ordinance and...
the Enforcement Regulations of the Pharmaceutical Affairs Law, and notifications issued by the Director General of the bureau.

2. PHARMACEUTICAL AFFAIRS LAW:

The objective of the Pharmaceutical Affairs Law is to improve public health through regulations required to assure the quality, efficacy, and safety of drugs, quasi-drugs, cosmetics and medical devices, and through measures to promote R&D of drugs and medical devices that are especially essential for health care.

The Pharmaceutical Affairs Law has 11 chapters as under and 91 articles:

Chapter 2: Prefectural Pharmaceutical Affairs Councils (Article 3)
Chapter 3: Pharmacies (Article 4 - Article 11)
Chapter 4: Manufacturers/Distributors and Manufacturers (Article 12 - Article 23)
Chapter 5: Retail Sellers of Drugs and Retail Sellers of Medical Devices
Chapter 6: Standards and Government Certification for Drugs (Article 41 - Article 43) (Japanese Pharmacopoeia and other standards, etc.)
Chapter 7: Handling of Drugs
Chapter 8: Advertising of Drugs (Article 68-2 - Article 68-11) (False advertising, restrictions on advertising of drugs for designated diseases, prohibition of advertising of drugs before approval, etc.)
Chapter 8-2: Exceptions for Biological Products (Article 69 - Article 77)
Chapter 9: Supervision (Article 69 - Article 77) (On-site inspections, on-site inspections by PMDA,
Chapter 9-2: Designation of Orphan Drugs and Orphan Medical Devices (Article 77-2 - Article 77-2-6)
Chapter 11: Penal Provisions (Article 83-6 - Article 91)

3. OUTLINE OF PHARMACEUTICAL REGULATIONS:

Various regulations apply to the development, manufacture, import, marketing, and proper use of drugs and medical devices in the form of the Pharmaceutical Affairs Law, cabinet orders, MHLW ordinances, etc. An outline of the main regulations affecting pharmaceuticals is presented here.

3.1 Definition of Drugs: The term "drug" refers to the following substances.

1) Substances listed in the Japanese Pharmacopoeia.

2) Substances (other than quasi-drugs), including dental materials, medical supplies and sanitary materials, which are intended for use in the diagnosis, treatment or prevention of disease in humans or animals, and which are not equipment or instruments.

3) Substances (other than quasi-drugs or cosmetics) which are intended to affect the structure or functions of the body of humans or animals, and which are not equipment or instruments.

3.2 Classification of Drugs: Drugs can be classified as follows based on the regulatory provisions in the Pharmaceutical Affairs Law, etc.

1) Prescription drugs: Drugs intended for use by a physician or dentist or under the prescription or instructions of a physician or a dentist

2) Non-prescription (OTC) drugs: Drugs other than prescription drugs that are intended for use at the discretion of general consumers by direct purchase in a pharmacy or drug store
The Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 69, enforcement expected in 2009) announced on June 14, 2006 to define non-prescription (OTC) drugs as the drugs not having pronouncedly strong intended actions (indications) in humans and those to be selected by users based on information provided by pharmacist or other medical personnel and to classify them in three types based on the degree of risk: Type 1 (highly risky), Type 2 (moderately risky) and Type 3 (relative low risky).

3.3 Licenses for Marketing Businesses and Manufacturing Businesses:

1) Licenses for marketing businesses

Persons wishing to start marketing business for drugs, quasi-drugs, cosmetics or medical devices must obtain a marketing business license depending on the type of business. These licenses are of the following types.

(1) Type 1 drug marketing business license: marketing of prescription drugs
(2) Type 2 drug marketing business license: marketing of drugs other than prescription drugs
(3) Quasi-drug drug marketing business license: marketing of quasi-drugs
(4) Cosmetic drug marketing business license: marketing of cosmetics
(5) Type 1 medical device marketing business license: marketing of specially controlled medical devices
(6) Type 2 medical device marketing business license: marketing of controlled medical devices
(7) Type 3 medical device marketing business license: marketing of general medical devices
(8) Marketing of drugs manufactured in pharmacies

The licensing requirements for drug marketing businesses include the appointment of a general marketing compliance officer who is a pharmacist, and compliance with Good Quality Practice (GQP) and Good Vigilance Practice (GVP).

The general marketing compliance officer, the quality assurance supervisor of the quality assurance unit in charge of GQP and the safety management supervisor of the general safety management division in charge of GVP are known as the "manufacturing/marketing triumvirate" and are at the center of the marketing system.

2) Manufacturing business licenses

Persons wishing to establish a business for the manufacture of drugs, quasi-drugs, cosmetics or medical devices must obtain a manufacturing business license in accordance with the manufacturing category as specified by MHLW ordinance.

3.4 Marketing Approvals:

Devi Ahilya Vishwavidyalaya Indore
Formal approvals and licenses are required in order to marketing drugs in Japan, and formal approval and/or licenses must first be obtained from the Minister of the MHLW or prefectural governor.

The approval and licensing system has been revised in the amended Law and manufacturing (import) approvals became marketing approvals from April 2005. Product licenses have been abolished and GMP compliance for each product has been specified as an approval condition.

Marketing approvals require a review to determine whether or not the product in the application is suitable as a drug to be marketed by a person who has obtained a marketing business license (marketing authorization holder) for the type of drug concerned and confirmation that the product has been manufactured in a plant compliant with GMP.

3.5 Good Manufacturing Practice (GMP):

GMP specifies that compliance with the Regulations for Buildings and Equipment of Pharmacies, etc. that specify standards for structures and equipment in manufacturing plants for each manufacturing category without relation to the products manufactured is a requirement for a manufacturing business license. Compliance with the GMP ordinance that specifies standards for structures and equipment required for the product concerned as well as standards for manufacturing control and quality control for each manufactured product is a condition for approval of the drug concerned.

3.6 Drug Master File (MF):

The drug master file system aims at protecting intellectual property of relevant information and facilitating review work by allowing a registrant (master file registrant) other than an applicant to separately submit information on quality and the manufacturing method at the time of approval reviews of drug substances to be used in drug products.

When the registered contents of the drug master file (MF) are changed, an application to change the MF or a slight modification notification must be submitted.

3.7 Accreditation of Overseas Manufacturers:

Persons wishing to manufacture drugs, quasi-drugs, cosmetics or medical devices exported to Japan from overseas (overseas manufacturers) must receive accreditation from the Minister (enforced from April 1, 2005).

The specifications for accreditation are the same as those for manufacturing licenses for domestic manufacturers.

3.8 Drug Retail Seller Licensing:

A license must be obtained from the Prefectural Governor, etc. in order to sell or supply drugs. Licenses of drug retail selling businesses are divided into the following four types:

(1) First-class seller of drugs
(2) Second-class seller of drugs
(3) Seller of drugs by household distribution
(4) Third-class seller of drugs
* In the revised Pharmaceutical Affairs Law announced on June 14, 2009, the types of drug retail business licenses have been amended to three types: retail store sellers, home distribution sellers and wholesale sellers of drugs.

3.9 Quality Standards and Government Certification:

The Japanese Pharmacopoeia, Japanese Pharmaceutical Codex, Japanese Pharmaceutical Excipients, and other similar standards have been specified as quality standards. Certain specified drugs such as biological products must not be marketed or supplied without government certification based on batch tests.

3.10 Labeling and Package Inserts:

Specified items must be entered on the immediate container of drugs. The package inserts must contain indications, dosage and administration, precautions and precautions for handling.

All ingredients used as excipients must be included in the package inserts of prescription and non-prescription drugs.

3.14 Good Post-Marketing Study Practice (GPSP):

GPSP specified the system and scope of activities to be conducted by companies to assure proper implementation of post-marketing surveillance and the reliability of the data obtained.

3.15 Reexamination and Reevaluation:

Marketers must perform post-marketing surveys on new drugs so that efficacy and safety can be reconfirmed by reexamination by the MHLW for a specified period after marketing approval.

4. Requirements for drug manufacturing and marketing approvals and manufacturing business licenses

Proper control at the stage of drug manufacture is essential so that drugs can be supplied to patients with good quality. This means that the manufacturers and the buildings and facilities in the manufacturing plants must be appropriate so that drugs based on the approvals can be produced. The manufacturing process as a whole must be controlled on the basis of scientific principles, and it is also necessary to assure the quality of drugs manufactured by taking measures to prevent errors during processing.

1) Required Documentation:

According to the Regulations for Manufacturing Control and Quality Control of Drugs, all of the operations in the plants must be divided into operations for manufacturing control and those for quality control, and various types of documentation are required, including standard operating procedures for standardization of all work conditions (drug product standards, manufacturing control standards, manufacturing hygiene control standards and quality control standards), documentation required for actual operation procedures based on these standards (manufacturing instructions and test and self-inspection protocols), records of the results of all of these operating procedures (records related to manufacture, records of manufacturing hygiene control, and records of tests and self-inspections), and records of storage and distribution. Additional documents should be compiled if they are considered necessary for proper manufacturing control and quality control. These documents must be retained for designated time periods from the date of preparation.
When damage to the health of patients or other users of biological products (biotechnological technology-derived and of biological origin) occurs, records must be retained for the period required to clarify the cause of this damage.

2) Personnel Organization:

The final responsibility for deciding whether or not drugs should be shipped and that for solving problems related to overall manufacturing control and quality control in the plant lies with the drug manufacturing control manager designated in each plant under the Pharmaceutical Affairs Law.

The control regulations specifies that the plant must be organized so that there is a quality control unit independent of the manufacturing unit. Appropriate personnel with the ability to supervise the work so that it is performed correctly and smoothly must be appointed in accordance with the organization of the plant, and the scale and types of work involved.

3) Manufacturing Control:

The manufacturer, etc. must assure that the duties set forth are carried out appropriately by the manufacturing department in compliance with standard operating procedures.

4) Quality Control:

The manufacturer, etc. must assure that the duties set forth are carried out systematically and appropriately by the quality department in compliance with standard operating procedures.

5) Documents Concerning Procedures for Validation, etc.:

The manufacturer must prepare written procedures for validation change control, deviation control, complaints, recalls, self-inspections, training and education for each plant so that these procedures can be performed appropriately.

6) Validation:

The manufacturer, etc. must ensure that the following obligations are fulfilled by a person designated beforehand in compliance with the standard operating procedures:

- The validation plan and results must be reported in writing to the quality control unit.
- The document prepared based on the validation must be retained for 3 years from the date of preparation (when the drugs concerned are cell or tissue-derived drugs, the period until the expiration date plus 10 years).

The manufacturer, etc. must take appropriate measures when improvements are required in manufacturing control or quality control based on the results of the validation. Records of the measures taken must be prepared and retained.

7) Change Control:

When manufacturers, etc. implement changes with respect to manufacturing procedures, etc. that might affect the quality of the product, they must assure that a previously designated person carries out the duties set forth in compliance the standard operating procedures:
8) Deviation Control:

When a deviation from the manufacturing procedures occurs, the manufacturer, etc. must assure that a previously designated person carries out the duties set forth in compliance with the standard operating procedures.

9) Information Related to Quality and Handling Quality Defects:

When the manufacturer, etc. acquires information relating to the quality, etc. of a drug, he must, except in cases in which it is clear that the items relating to the quality information are not attributable to the manufacturing plant concerned, assure that a previously designated person carries out the duties set forth, in compliance with the standard operating procedures.

10) Product Recalls:

When manufacturers decide to recall drugs for reasons related to quality, etc., they must assure that a previously designated person carries out the duties set forth in compliance with the standard operating procedures.

11) Self-inspections:

The manufacturer, etc. must have the obligations fulfilled by a person designated beforehand in compliance with the standard operating procedures.

12) Education and Training:

The manufacturer must have the following obligations fulfilled by a person designated beforehand in compliance with the standard operating procedures.

4.1 GMP Compliance Reviews:

When an application is submitted for a new drug manufacturing and marketing approval, the plant must be inspected by the authorities to determine if it actually complies with the GMP standards. Evaluation Rank Criteria

A: (Compliance): Manufacturing is performed properly.

B: (Slightly defective): There is little effect on drug quality but improvement necessary for complete compliance with control regulations.

C: (Moderately defective): Effect on drug quality can not be ruled out and improvement necessary for compliance with control regulations.

D: (Seriously defective): Clear violation of control regulations

First, a review is conducted for each product using the following criteria for GMP compliance as to each article in the control regulations and building and facility regulations. Next, a review is undertaken for each product using the following criteria on the basis of the results of the review of GMP compliance for each article in the control regulations and building and facility regulations:

• Compliance: Cases of A only.
• General compliance: Cases of A and B or B only.

• Improvement required: Cases of C evaluated for half or less of all items and no D, unless categorized "Compliance" or "General compliance."

• Non-compliance: Cases not corresponding to any of the above.

When GMP compliance by product is determined as "General compliance" or "Improvement required," an order for improvement(s) for the item(s) rated as B is issued in writing.

In such cases, the applicant must submit a concrete plan of improvements. When improvements are completed, a report on the improvement must be submitted. When the improvements have been confirmed, the rating of the corresponding item is changed to "Compliance."

The results of reviews or assessments at each of the above stages are compiled, and a report of the GMP compliance review is prepared for the plant in the application concerned. When the initial GMP compliance review results of a product correspond to "General compliance" or "Improvement required," the subsequent course is entered in the GMP compliance review report.

4.2 Mutual Recognition of GMP:

Japan has concluded mutual agreements for GMP approvals with countries with equivalent levels of GMP. These agreements are meant to assure the quality of drugs imported into Japan through mutual acceptance of GMP inspection results and exchange of information on drugs distributed in the two countries. These mutual agreements have been concluded with Germany, Sweden, Switzerland and Australia. Mutual recognition of drug GMP with the EU countries had been limited to Germany and Sweden, but the agreement has been expanded to include the 15 EU countries (Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Austria, Portugal, Finland, Sweden and the United Kingdom) as well as 10 new EU countries (Poland, Hungary, Czech Republic, Slovakia, Slovenia, Estonia, Latvia, Lithuania, Cyprus and Malta) for 25 countries in total since May 29, 2003 (Notification No. 0528001 of the Compliance and Narcotics Division, PFSB dated May 28, 2004, Notification No. 0528004 of PFSB dated May 28, 2004, and Notification No. 0428001 of PFSB dated April 28, 2004).

4.3 Regulations for Imported Drug Management and Quality Control:

Since it is very important to assure the quality of imported drugs in the same way as drugs manufactured in Japan, items related to manufacturing control and quality control when importers and markets import drugs were specified in Import Control and Quality Control of Drugs and Quasi-drugs were specified (MHW Ordinance No.62, June 2, 1999) and enacted on August 1, 1999, but since the import business license has been including in the manufacturing/distribution business license, this was abolished on March 31, 2005. Instead, from April 1, 2005, import certificate needs to be submitted for custom clearance prior to the import of products when the manufacturer/distributor or manufacturer import drugs for business.

These regulations included matters to be agreed upon with the manufacturer in the exporting country by the importer in accordance with the agreement. The importer must confirm that the drug to be imported is manufactured under appropriate manufacturing control and quality control, and must import, store and distribute drugs and conduct testing in accordance with standards, etc.
When a mutual agreement for GMP approvals has been concluded between the exporting country and Japan, part of the quality control work may be omitted if the following two conditions are met. One is that it is confirmed by the government organization in the exporting country, that the plant where the imported drug was manufactured complies with the GMP in the country. The other is that the records of tests performed by the manufacturer of the drug are provided to the importer in Japan. (www.mhlw.go.jp)

3.9 NEW ZEALAND

New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods

Introduction

The Medicines Act 1981 defines the parameters and requirements for the sale, manufacture and supply of medicines in New Zealand. Section 30 of this Act describes the process that a study sponsor or manufacturer must follow to obtain an exemption from Section 20 and Section 24 of the Act for medicines required for use in clinical studies. Section 30 also describes the obligations of the sponsor for reporting adverse effects and progress to the Ministry of Health during the course of the study.

Manufacture, in relation to a medicine, includes any process carried out in the course of making the medicine; but does not include—

Dissolving or dispersing the medicine in, or diluting or mixing it with, some other substance used as a medium for the purpose of administering the medicine to a particular person.

licensing authority—(a) means the Director-General; and

(b) to avoid doubt, includes any person or persons acting as the Director-General's delegate as a consequence of a delegation.

qualifying new medicine means a new medicine that—

a) is or contains a new organism; and

(b) meets the criteria set out in section 38(3) of the Hazardous Substances and New Organisms Act 1996

Responsible person, in relation to a licensee corporation, means an agent or employee of that corporation who is a pharmacist or a person approved by the licensing authority as a responsible person for the purposes of the licence

Sell includes—

(a) Barter; and

(b) Offering or attempting to sell, or having in possession for sale, or exposing for sale, or sending or delivering for sale, or causing or allowing to be sold, or offered or exposed for sale; and

(c) Supplying by way of gift or sample for the purpose of promoting a sale;—and sale has a corresponding meaning
Selling by wholesale, selling by retail, and selling in circumstances corresponding to retail sale have the meanings assigned to those terms by section 5 of this Act.

3. **Meaning of medicine, new medicine, prescription medicine, and restricted medicine**

(1) The term **medicine** means any substance or article, other than a medical device, that is manufactured, imported, sold, or supplied wholly or principally—

(a) For administering to one or more human beings for a therapeutic purpose; or

(b) For use as an ingredient in the preparation of any substance or article that is to be administered to one or more human beings for a therapeutic purpose, where it is so used—

(i) In a pharmacy or a hospital; or

(ii) By a practitioner, or registered midwife, or designated prescriber, or in accordance with a standing order; or

(iii) In the course of any business that consists of or includes the retail sale, or the supply in circumstances corresponding to retail sale, of herbal remedies; or

(c) For use as a pregnancy test.

(2) In this Act, unless the context otherwise requires, the term **medicine** does not include—

(a) Substances used in dental surgery for filling dental cavities; or

(b) Bandages and other surgical dressings, except medicated dressings where the medication has a curative function that is not limited to sterilising the dressing; or

(c) Any radioactive material within the meaning of section 2(1) of the Radiation Protection Act 1965; or

(d) Any animal food in which a medicine is incorporated; or

(e) Any animal remedy; or

(f) Any other substance or article of a kind or belonging to a class that is declared by regulations made under this Act to be a kind or class of substance or article that is not a medicine for the purposes of this Act.

(3) In this Act, unless the context otherwise requires.

**New medicine** means—

(a) Any medicine that has not been generally available in New Zealand—

(i) Before the commencement of this Act; or

(ii) At any time during the period of 5 years immediately preceding the date on which it is proposed to become so available:

(b) Any medicine that, immediately before the commencement of this Act, was a therapeutic drug to which the Food and Drug Act 1969 applied, and in respect of the sale or distribution of which the Minister had not given his consent under that section:
(c) Any medicine that becomes a medicine within the meaning of this Act for the first time after the commencement of this Act:

(d) Any medicine that is referred to the Minister under this Act:

**Pharmacy-only Medicine**, as from 22.10.2003, means a medicine that is declared by regulations made under this Act to be one that, except as may be permitted by the regulations, may be—

sold by retail only—in a pharmacy or hospital

**Prescription Medicine**, as from 15.10.1999, means a medicine that is declared by regulations made under this Act to be one that, except as may be permitted by regulations made under this Act, may be—

Sold by retail only under a prescription given by a practitioner, registered midwife, veterinarian, or a designated prescriber; and

Administered only in accordance with—A prescription given by a practitioner, registered midwife, veterinarian, or a designated prescriber.

**Restricted Medicine**, as from 22.10.2003, means a medicine that is declared by regulations made under this Act to be one that, except as may be permitted by the regulations, may be—

(a) sold by retail only by a pharmacist in a pharmacy or hospital; or

(b) supplied in circumstances corresponding to retail sale only—

(i) by a pharmacist in a pharmacy or hospital; or

(ii) in accordance with a standing order.

**Meaning of therapeutic purpose**

**Meaning of selling by wholesale, selling by retail, and selling in circumstances corresponding to retail sale**

**Principals and agents:** (1) For the purposes of this Act, but subject to subsection (2) of this section, every person shall be deemed to manufacture, sell, supply, pack, or label any medicine whether he does so on his own account or as the agent or employee of any other person.

(2) For the purposes of this Act, if a person who is authorised by or under this Act to manufacture, sell, supply, pack, or label a medicine does so, in accordance with that authority, as the agent or employee of another person who is not so authorised, that other person shall not be held to have manufactured, sold, supplied, packed, or labelled that medicine.

(3) For the purposes of this Act, while a person who is authorised by or under this Act to manufacture, sell, supply, pack, or label a medicine has that medicine in his custody or under his control as the agent or employee of another person who is not so authorised, that other person shall not be held to be in possession of that medicine.

(4) For the purposes of this Act, any natural person who manufactures, sells, supplies, packs, or labels a medicine while working under the supervision and control of a responsible person or of another
natural person authorised by or under this Act, otherwise than by section 32 of this Act, to manufacture, sell, supply, pack, or label that medicine, shall be deemed to be the agent or employee of the responsible person or the person so authorised, and in any such case the responsible person or person so authorised shall be deemed to be the principal or employer of the first-mentioned person, without prejudice to the liability of any other person, under this Act.

Manufacturers, wholesalers, packers of medicines, and operators of pharmacies to be licensed

(1) Except as provided in this Act, or as may be permitted by regulations made under this Act, no person shall, in the course of any business carried on by that person,—

(a) Manufacture any medicine; or
(b) Sell any medicine by wholesale; or
(c) pack or label any medicine; or
(d) operate any pharmacy—otherwise than in accordance with a licence issued under this Act.

(2) Every person who contravenes subsection (1) commits an offence and is liable on summary conviction to a fine not exceeding $40,000.

Sale of medicines by retail

Except as provided in this Act, or as may be permitted by regulations made under this Act, no person shall, in the course of any business carried on by that person, sell by retail, or supply in circumstances corresponding to retail sale, or distribute by way of gift or loan or sample or in any other way,—

"any prescription medicine with specified exemptions"

Every person who sells or supplies or distributes a prescription medicine in contravention of above provision commits an offence and is liable to imprisonment for a term not exceeding 6 months or a fine not exceeding $40,000.

Restrictions on sale or supply of new medicines

(1) Except as provided in this Act, this section applies to new medicines.

(2) No person shall—

Sell; or Distribute by way of gift or loan or sample or in any other way; or Advertise the availability of— any medicine to which this section applies before the consent or provisional consent of the Minister to the distribution of the medicine has been notified in the Gazette, or otherwise than in accordance with such conditions as may be imposed by the Minister on giving his consent or provisional consent and notified in the Gazette.

(3) No consent given under this section shall be deemed to warrant the safety or efficacy of the medicine to which the consent relates.

(4) A person who contravenes subsection (2) commits an offence, and is liable on conviction—

(a) In the case of an individual, to imprisonment for a term not exceeding 6 months or a fine not exceeding $20,000;
(b) In the case of a body corporate, to a fine not exceeding $100,000.
Applications for Minister's consent: Every application for the Minister's consent under above section of this Act shall—Be made in the true name of the manufacturer or importer or proprietor, or the proposed manufacturer or importer or proprietor, in New Zealand of the medicine, by that person or by his duly authorised agent and be addressed to the Director-General with the prescribed fee and state, or be accompanied by a statement of, the particulars specified.

Procedure in respect of applications for Minister's consent: The procedure for consent to the distribution of a medicine may or may not be accorded by the Minister after considering all the particulars and information submitted. In case of consent is refused and on an objection by the applicant, the matter shall be referred to Medicine Review Committee whose recommendation shall form the basis of final decision by the Minister.

Minister may give provisional consent: The Minister may, by notice in the Gazette, in accordance with this section, give his provisional consent to the sale or supply or use of a new medicine where he is of the opinion that it is desirable that the medicine be sold, supplied, or used on a restricted basis for the treatment of a limited number of patients.

Procedure if Director-General declines to grant approval: The Director-General may decline to grant an approval because the new organism is not a qualifying new medicine.

Exemptions for practitioners and others: An authorised prescriber may manufacture, pack, and label a medicine that is specially prepared for, or intended for administration to a particular patient of that authorised prescriber.

Exemptions in respect of herbal remedies: Any person may, in the course of a business carried on by that person, manufacture, pack, and label, or sell or supply, any herbal remedy for administration to a particular person after being requested by or on behalf of that person to use his own judgment as to the treatment required.

Exemption for medicine required by medical practitioner: The Act does not prevent the supply by any person to any medical practitioner, on the medical practitioner's request, of any medicine required by that medical practitioner for the treatment of a particular patient currently under that medical practitioner's care.

Exemption for clinical trial: The importer or manufacturer in New Zealand of any medicine may distribute it for the sole purpose of obtaining clinical and scientific information with respect to its safety and efficacy, if the clinical trial, and the persons (in this section called the investigators) who will conduct the trial, have been approved by the Director-General on the recommendation of the Health Research Council of New Zealand.

Exemptions in respect of importation by the Crown: The Crown may, in respect of any medicine approved by the Director-General for the purposes of this section: Import the medicine into New Zealand; and Sell the medicine, or distribute it by way of gift or loan or sample or in any other way, or advertise it for sale, or advertise the availability of it—in doing any of those things, it shall not be necessary for the Crown to comply with any of the provisions of this Act.

Exemption for sale by wholesale of medicines that are not prescription, restricted, or pharmacy-only medicines: This Act does not apply in respect of the sale by wholesale of a medicine that is not a prescription medicine or a restricted medicine or a pharmacy-only medicine.
Revocation and suspension of consents: The Minister may at any time, by notice in the Gazette, revoke, or suspend for such period as he may determine, any consent given under section 20 or section 23 of this Act, if he is of the opinion that—

Compliance with standards: If a standard is prescribed in respect of a medicine, or a medical device, or the ingredient of a medicine, no person shall, in the course of any business, sell or supply any substance or article unless the substance or article, or the ingredient of the substance or article, complies with the standard.

Every person commits an offence against this Act who contravenes subsection (1) of this section.

Duty of importer or manufacturer to report untoward effects of medicines: If at any time the importer or manufacturer in New Zealand of any medicine has reason to believe that any substantial untoward effects have arisen from the use of the medicine the importer or manufacturer shall forthwith notify the Director-General of the nature of those effects and the circumstances in which they have arisen, so far as they are known to him.

Every person commits an offence against this Act and is liable to a fine not exceeding $1,000 who fails to comply with as above.

Duty of importer and manufacturer to have and produce specifications of medicines: No importer or manufacturer shall sell, or distribute by way of gift or loan or sample or in any other way, or advertise for sale, or advertise the availability of, any medicine other than a herbal remedy unless he is in possession of—

(a) Details of the specifications for testing the quality of that medicine; and
(b) A certificate of the results of testing in respect of every batch of that medicine distributed or to be distributed in New Zealand.

A person who contravenes this section commits an offence, and is liable on conviction—

(a) In the case of an individual, to imprisonment for a term not exceeding 3 months or a fine not exceeding $10,000:
(b) In the case of a body corporate, to a fine not exceeding $100,000.

Containers and packages of medicines: (1) Except as may be permitted by regulations made under this Act, no person shall, in the course of any business, pack, store, sell, supply, or cause to be transported any medicine, unless—

(a) The medicine is in a container that—

(i) Is impervious to the medicine; and
(ii) Is so constructed that it can be readily and effectively resealed after any portion of the contents has been used; and
(iii) Is of the prescribed character or type; and
(iv) Is labelled in the prescribed manner; and

(b) If the container is enclosed in a package that is required to be of a prescribed character or type, or to be labelled in a prescribed manner, the package is of that character or type, or is labelled in that manner.

(2) Notwithstanding subsection (1)(a)(i) of this section, where—
(a) The container bears a label with directions to the effect that the whole of the contents must be used immediately on opening; and

(b) The quantity and nature of the contents are such that it is unlikely that less than the whole of the contents will be used on any one occasion—the container need not be of a type that can be readily and effectively resealed.

(3) Every person commits an offence against this Act who contravenes subsection (1) of this section.

Records: Every person who, in the course of any business, manufactures, packs, or sells, or supplies in circumstances corresponding to retail sale, any medicine shall keep, in some place of security at his place of business, such records as may be prescribed and shall retain them for such period as may be prescribed.

Applications for licences: Every application for a licence must be made in the prescribed form, accompanied by such particulars, information, documents, samples and other material as may be prescribed, and shall be accompanied by the prescribed fee, to the Director-General or to any person designated for the purpose by the Director-General by notice in the Gazette.

Grant of licences: (1) On receiving an application, the licensing authority shall issue a licence, in accordance with regulations made under this Act, to the applicant if he is satisfied in respect of all the following matters:

(a) That the requirements of this Act have been complied with:

(2) Except as may be permitted by regulations made under this Act, the licensing authority shall not issue a licence to sell medicines by retail in respect of any premises other than a shop that is open to the public and is situated at least 10 kilometres by the most practicable route from a pharmacy in respect of which a licence to operate has been, or is deemed to have been, issued.

(3) The licensing authority shall not decline an application for a licence under this section without first giving the applicant a reasonable opportunity to be heard

(4) A licence shall be in the prescribed form and shall be subject to such conditions (if any) as may be imposed on the issue of the licence or at any time thereafter, by or pursuant to regulations made under this Act.

(5) A licence to sell a medicine may be combined with a licence to pack that medicine.

(6) If in any case the licensing authority is satisfied that the holder of a licence has failed or is failing to comply with any conditions attaching to the licence, he may—

(a) Suspend the licence for such reasonable period as may be required to enable the licensing authority to consider the case; or

(b) After giving the licensee a reasonable opportunity to be heard and considering any evidence adduced or submission made by the licensee, cancel the licence.

(6A) If the licensing authority is satisfied that the holder of a licence to operate a pharmacy has failed to comply with any conditions affecting the licence, the licensing authority may, instead of or as well as exercising the powers conferred by subsection (6),—
Drugs may be licenced to:
(a) Manufacture medicines
(b) Pack medicines
(c) Sell medicines by wholesale
(d) Sell medicines by retail
(e) Operate a pharmacy

Effect of Licences:

Licence to manufacture medicines shall authorise the manufacture, packing and labelling, and sale by wholesale, of the medicines described in the licence.

Licence to pack medicines shall authorise the packing and labelling, and the sale by wholesale of the medicines described in the licence.

Licence to sell medicines by wholesale shall authorise the sale by wholesale of the medicines described in the licence.

Licence to sell medicines by retail shall authorise the sale by retail, and the supply in circumstances corresponding to retail sale, of the medicines described in the licence.

Licence to operate a pharmacy authorises the establishment of the pharmacy and the carrying on of pharmacy practice in the pharmacy.

Duration of Licences:

Every licence, unless sooner cancelled, continues in force for a period of 1 year and then expires.

Any licence issued within the period of 2 months preceding the date of expiration of an existing licence that it is intended to supersede shall continue in force for a period of 1 year beginning on that date.

If a licensee applies for a new licence not more than 3 months and not less than 1 month before the date of expiration of an existing licence that the new licence is intended to supersede, and the application is not disposed of before that date, the existing licence shall continue in force until the application is disposed of.
Display of licences: Every licensee shall cause his current licence to be permanently exhibited in some conspicuous place where it can be readily seen by all persons having access to the premises to which the licence relates.

Powers of officers: An officer, and any other person assisting him and acting under his direct supervision, may at any reasonable time—Enter and inspect any premises or vehicle, examine books, documents etc., Examine any package or container, Examine any process of manufacture or packing of any article, Purchase or take samples of any medicine or cosmetic, Any advertising material or labelling material, Seize and detain any article, not being equipment, Take photographs of any premises or vehicle, or any article,

Procuring samples for analysis: When an officer intends to procure a sample of a substance or article for the purposes of analysis, he shall—

(a) Pay or tender the current market value of the sample to the owner thereof or the person from whom the sample is to be obtained:

(b) Before or forthwith after obtaining the sample, inform the owner of the sample or the person from whom the sample is obtained of his intention to submit the sample to an analyst.

Cancellation of licence: (1) In any case where a licensee is convicted of an offence against this Act, or against any regulations made under this Act, the Court may, in addition to or instead of imposing any other penalty,—

(a) Cancel the licence, either forthwith or with effect from such future date as may be specified by the Court:

(b) Disqualify the licensee from obtaining any new licence for such period as the Court may specify:

(c) Cause particulars of the conviction, and of any order made under paragraph (a) or paragraph (b) of this subsection to be endorsed on the licence.

(2) When a Court cancels a licence pursuant to subsection (1) of this section, the licence shall cease to have effect either forthwith or on the date specified by the Court, as the case may require.

(3) Any licence cancelled or required by the Court for endorsement under this section shall be produced by the licensee in such manner and within such time as the Court directs.

(4) For the purposes of this Act the cancellation or endorsement of a licence, or a disqualification, under this section shall be deemed to be a sentence or part of a sentence, as the case may be.

Refusal of licensing authority to grant licence: Any person who is aggrieved by a decision—Of the Director-General or the licensing authority made under this Act may appeal against that decision to the Medicines Review Committee and thereafter before the High Court. Subject to this section, on any appeal, the Court may—

(a) By interim order, suspend the operation of the decision to which the appeal relates until the final determination of the proceedings:

(b) Dismiss the appeal, or make such modifications in the decision to which the appeal relates as it thinks fit, or quash the decision with or without substituting a new decision in its place.
3.10 KOREA

FOOD AND DRUG ADMINISTRATION

Article 26 (licensing etc. of manufacturing)

(1) Any one who intends to manufacture drugs shall get a licence from the Commissioner of the Korea Food and Drug Administration for each product and each product shall be approved or notified. If the manufacturer intends to change the approved or notified label as designated by the Ministry of Health and Welfare, the application of the change shall be submitted in accordance with an ordinance of the Ministry of Health and Welfare. (amended on January 12, 2000)

2. Any one who intends to get an approval from or notify the Commissioner under the provision of paragraph (1), shall establish the necessary facilities in accordance with the standards of facilities as provided by the Presidential Decree (amended on December 31, 1991)

ENFORCEMENT RULE OF PHARMACEUTICAL AFFAIRS ACT

Article 23 (licensing application of manufactured and imported items)

(1) Anyone who intends to get an item licence for drugs in accordance with paragraph 1 of Article 26 shall submit application form according to No. 12 form together with documents by the classification of the following each item to the Commissioner of the KFDA (amended on March 3, 2000, June 16, 2000, January 12, 2002 and November 5, 2002)

DRUGS. SANITARY PRODUCTS: A. Less than two years of notification of safety and efficacy review approval in accordance with the provision of Article 27 or data required for the safety and efficacy review. However, they are not submitted for items that come under one of the following:

(1) Items suitable for standard manufacturing criteria notified by the Commissioner of the KFDA who standardize the types, norms and contents of components and prescription.

(2) Items listed in Korea Pharmacopoeia (KP)

(3) Items which are listed in antibiotic monograph under the provisions of Article 44 of Pharmaceutical Affairs Act (PAA) or items not listed in KP which are listed in Herb monograph (hereinafter referred to as "Herb Monograph")

(4) DNA recombinant drugs, cell culture products, biological products, cell therapy products, gene therapy products and similar items with same final bulk as that of items already locally approved.

(5) Items listed in pharmacopoeia recognized by the Commissioner KFDA or drug formulary.

(6) Items whose specifications and test methods are separately notified by the Commissioner of the KFDA.

(7) Besides, items that the Commissioner of the KFDA judges relevant data do not need to be submitted.
B. Less than 2 years of notification of specifications and test methods review approval in accordance with the provision of paragraph 2, Article 27 or data on specifications and test methods. However, they are not submitted for items that come under one of the followings:

(1) items that come under (2),(3),(5) and (6) of A section
(2) items that are listed in biologics monograph under the provision of Article 44 and can be proved to be same as other items already locally approved.
(3) Drugs that should be urgently introduced due to no appropriate substitutional and are orphan drugs decided by the Commissioner of the KFDA (hereinafter referred to as “orphan drugs”)

C-G OMITTED

H. In case of items using drug substances (including drug substances for biological products, herein after referred to as “drug substances that should be registered”) in accordance with subsection 6, paragraph 1 of Article 24, application for drug substance registration and required data in accordance with paragraph 3 of Article 24 are submitted. However, they are not submitted for drug substances already registered in accordance with paragraph 3 of Article 24.

Article 24 REGISTRATION OF MANUFACTURED AND IMPORTED ITEMS

(1) drugs that should be registered in accordance with paragraph 1 of Article 26 or paragraph 1 of Article 34 of PAA are as follows:

Provided, items whose licensing of manufacturing and import is restricted under the provisions of Article 21, safety and efficacy should be reviewed according to paragraph 1 of Article 27, biological products, radiopharmaceuticals, DNA recombinant drugs, cell culture products, gene therapy products and cell therapy products are excluded. And in case items that come under Subsection 1 to 4 are drug substances that should be registered, the Subsections 1 to 4 are not applied. (amended on March 3, 2000, June 16, 2000 and January 12, 2002)

(2) items listed in the Korea Pharmacopoeia or Herb Monograph

(3) items listed in the pharmacopoeia recognized by the Commissioner of the KFDA or drug formulary. However, items not locally approved are excluded.

(4) items suitable for the criteria for standard manufacturing of drugs standardized and notified by the Commissioner of the KFDA.

(5) Drugs are sanitary products whose specifications and test methods are notified by the KFDA Commissioner.

(6) Omitted (June 16, 2000)

(7) Drugs etc. notified by KFDA Commissioner as items that should be registered.

(8) Anyone who intends to register the manufacturing and import drug substances that should be registered shall submit the application form for drug substance registration of Form No. 2 of Annex No. 15 attached by data for the following each item to the Commissioner of the KFDA. When data need to be protected, supplier of drug substances can directly submit data for following each item to the KFDA Commissioner. How to prepare the data, the requirements of the data to be submitted, the extent of exemption from submission, the standards for processing the application are decided and notified by the KFDA Commissioner. (Newly established on January 12, 2002)
1. Data on the facilities as necessary for production and quality control under the provisions of Paragraph 2 of Article 26 of the Act.

2. Data on physicochemical properties and stability.

3. Data on the manufacturing process, packaging containers, cautions in handling, etc.

4. Data evidencing that production of each drug substance is in conformity with the Korea Good Manufacturing Practice (KGMP), Annex 4 of the Enforcement Rule or any thing equivalent there to or higher.

5. Data on batch analysis for drug substances, analytical procedures, the solvents used, etc.

6. Sample drug substances as necessary for the quality test.

(www.ktda.go.kr)

3.11 NIGERIA

NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION CONTROL (NAFDAC)

Year 1987 to present is the era with six main ownership structures. 5 Indigenous manufacturers control 56% of manufacturing, Asian companies control 18%, Anglo American owned companies has 14%, the government companies' control 5% and others control 5%. From this structure it is clear that indigenous ownership in the country is on the increase.

GUIDELINES FOR DRUG REGISTRATION IN NIGERIA

A. GENERAL

1. THESE GUIDELINES ARE FOR THE INTEREST OF THE GENERAL PUBLIC AND IN PARTICULAR, PHARMACEUTICAL INDUSTRIES IN NIGERIA.

2. IT IS NECESSARY TO EMPHASIZE THAT, NO DRUG SHALL BE MANUFACTURED, IMPORTED, EXPORTED, ADVERTISED, SOLD OR DISTRIBUTED IN NIGERIA UNLESS IT HAS BEEN REGISTERED IN ACCORDANCE WITH THE PROVISIONS OF DECEASE 19 OF 1993 AND THE ACCOMPANYING GUIDELINES.

B. APPLICATIONS/ MANUFACTURER

1. (a) An application for registration of a drug product shall be made by the manufacturer.

(b) In case of a manufacturer outside Nigeria such shall be represented in Nigeria by a duly registered pharmaceutical company.

(c) An applicant for a manufacturer outside Nigeria, must file an evidence of POWER OF ATTORNEY from the manufacturer which authorizes him to speak for his principal on all matters relating to the latter’s specialties. The original to Attorney is to be notarized and submitted to NAFDAC.

A separate application form shall be submitted for each drug product. In this context, a drug product means a separate drug formulation. However the application for registration of one dosage form with different strengths may be made on a different application form.

C. PRODUCT: (1) A drug product shall not be manufactured in Nigeria, unless the factory is inspected and Certificate of Recognition is issued by NAGFDAC.

1. In case of imported products:-
(a). There must be evidence of registration of such product by the competent Health Authority of the
country of manufacturer i.e. product licence/Certificate of Registration.

(b). There must be evidence from the competent health Authority, that the sale of the product does
not constitute a contravention of Drug Laws of that country i.e. Certificate of Pharmaceutical Product
(COPP) that conforms to WHO format.

(c). The documents in respect of (a) and (b) shall be authenticated by the Nigerian Mission in that
country.

2. In the case of an imported new drug substance, there must be evidence that limited local clinical
trials have been undertaken, and that such product is registered in the country of origin and also, in at
least 2 or more developed countries.

(2). No combination product shall be registered or considered for registration unless there is proven
evidence that such a product has clinical advantage over the single drug available from the same
indication(s).

1. Identification mark must be embossed on all tablets and capsule shell.

2. The application should indicate the class or type of registration required—whether it is a prescription
only product.

3. Product found to be of doubtful, little or no therapeutic value and those which are sometimes rather
harmful and subject to misuse shall not be considered for registration.

(3). An applicant shall not be allowed to register a formulation in more than one brand name even
where different doses of the active ingredient(s) are used.

(4). The product information must be in 2 copies with hard covers per product (dossiers) made out in
accordance with application format (the content of the dossier must be in compliance with the items on
the format)

(5). All dosage forms of a particular brand name must contain the same active ingredient(s) or at
least the major active ingredient(s) e.g.

A Cream - Betamethasone 10 mg
A soap - Betamethasone 20 mg

(6) Evidence of Trade Mark Approval from Federal Ministry of Commerce in Nigeria.

(7). Notarized declaration to be notarized by a Notary Public.

(8). Comprehensive Certificate of analysis of the batch of product to be registered.

(9). Current premises licence.

(10). Annual licence for the Superintendent Pharmacist.

(11). Certificate of Incorporation of the applicant.

D. LABELLING

1. Labeling shall be informative and accurate.

2. Minimum requirements on the package label:

(a). Name of product—brand name and generic, name where applicable. The generic name must be in
similar characters with the brand name.

(b). Location address of the manufacturer
(c) Provision for NAFDAC Registration Number on product label
(d) Batch No. Manufacturing date and Expiry date
(e) Dosage regimen on the package
(f) Leaflet insert, if prescription product and hospital packs
(g) Indications, frequency, route and conditions of administration.
(h) Quantitative listing of all the active ingredients per unit dose.
(i) Adequate warnings where necessary.

3. Where a brand name is used, there MUST be generic name which should be conspicuous in character, written directly under the brand name e.g.

VENTOLIN
“SALBUTAMOL”

4. Any drug product whose name, package or label bears close resemblance to an already registered product or is likely to be mistaken for such registered product, shall not be considered for registration.

5. Any drug product which is labeled in a foreign language shall NOT be considered for registration unless an English translation is included on the label and package insert (where applicable)

6. Information on indication carried on packages and leaflet insert of imported drug product shall not differ from that in other countries, and in particular the country of origin of the product.

7. Failure to comply with these requirements may result in the disqualification of the application or lead to considerable delays in processing of registration.

8. A successful application attracts a Certification of Registration with a validity period of 5 (five) years.

N.B.

(i) Registration of a product does not automatically confer Advertising permit. A separate approval by the Agency shall be required if the product is to be advertised.

(ii) NAFDAC may withdraw the certificate of Registration in the event that the product is advertised without express approval from Agency.

(iii) NAFDAC reserves the right to revoke, suspend or vary the certificate during its validity period.

(iv) FILLING AN APPLICATION FORM OR PAYING FOR AN APPLICATION FORM DOES NOT CONFIR REGISTRATION STATUS.

(v) FAILURE TO RESPONDE PROMPTLY TO QUERIES ON ENQUIRIES RAISED BY NAFDAC ON THE APPLICATION, WILL AUTOMATICALLY LEAD TO SUSPENSION OF FURTHER PROCESSING OF THE APPLICATION. (www.nafdacnigeria.org)

3.12 MALAYSIA

Interpretation

Authority means the Drug Control Authority established under regulation 3;
Contract manufacturer means any person who manufactures any product on the order of another person to whom a manufacturer’s licence has been issued under these Regulations;

Drug has the meaning assigned to it in the Ordinance but does not include a herbal remedy.

licence means any of the licences under regulations 12;

licenced manufacturer means a person to whom a manufacturer’s licence has been issued under these regulations;

manufacture, in relation to any product includes;

(a) the making or assembling of the product;

(b) the enclosing or packing of the product in any container in a form suitable for administration or application, and the labeling of the container; and

(c) the carrying out of any process in the course of any of the foregoing activities;

Establishment and membership of the Authority

(1) An authority to be called the Drug Control Authority is established for the purposes of these Regulations.

(2) The Authority shall consist of the following members:

(a) the Director General of Health;
(b) the Director of Pharmaceutical Services;
(c) the Director of the National Pharmaceutical Control Laboratory; and
(d) seven other members to be appointed by the Minister.

Control of manufacture, sale, supply and importation:

(1) Except as otherwise provided in these Regulations, no person shall manufacture, sell, supply, import, possess for sale any product unless-

(a) the product is a registered product; and
(b) the person holds the appropriate licence required and issued under these Regulations.

(2) The requirement of sub regulation (1) (b) does not apply to the sale or supply of any product by a retailer.

(3) The Authority may, subject to the provisions of these Regulations, issue any of the following licences subject to such conditions as it may impose;

(a) a manufacturer’s licence in form 2 in the Schedule, authorizing the licensee to manufacture the registered products in the premises specified in the licence and to sell by wholesale or supply the products;

(b) a wholesaler’s licence in form 3 in the Schedule, authorizing the licensee to sell by wholesale or supply the registered products from the address of the business premises specified in the licence.
(c) A clinical trial import licence in form 4 in the Schedule, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product;

(d) An import licence in form 5 in the Schedule, authorizing the licensee to import and sell by wholesale or supply the registered products from the address of the premises specified in the licence.

(4) Provided that drugs and cosmetics are not included together in one licence, any number of registered products may be included in any licence other than a clinical trial import licence, which shall include only one product.

(5) Subject to sub-regulation (2), the Authority may, on application by the licensee, add to the registered products included in any licence other than a clinical trial import licence, and make such addition or amendment to the conditions of the licence as are rendered necessary by the addition of the other registered products.

(6) Subject to regulation 17, a licence issued under these regulations, other than a clinical trial import licence, shall be valid for one year.

(7) Subject to regulation 17, a clinical trial import licence shall be valid for such period, not exceeding three years from the date of issue of the licence, as may be specified in the licence.

(8) Every licence shall be personal to the licensee named in the licence and shall not be transferable to another person.

Application for licence:

An application for licence under these Regulations shall be made in such manner or form as the Authority may require and shall be accompanied with processing fee of RM1000 in the case of an application for a manufacturer’s licence and RM500 in the case of application for any other licence and shall furnish such documents, particulars or information as the Authority may require.

Any person who knowingly supplies any false or misleading information to the Authority in connection with his application for a licence commits an offence.

Refusal of application for licence: The Authority may, if it thinks fit and without assigning any reason, refuse any application for a licence.

Exemptions and Savings: 1. Any person who wishes to import any product for the purpose of research in a school of pharmacy or a research or training institution or in order to obtain samples for purposes of registration may on application be exempted by the Authority from the provisions or regulation 7(1).

2. Any requirement of regulation 7(1) as regards a licence to supply or manufacture does not apply to the dispensing, or the doing of an act falling within the definition of "manufacture" which is necessary for the dispensing, of any drug for the purpose of its being used for medical treatment by the following persons and in the following circumstances:

(a) a pharmacist or a person working under the immediate personal supervision of a pharmacist in a retail pharmacy;

(b) a person acting in the course of his duties who is employed in a hospital or dispensary maintained by the Federal or any State Government or out of the public funds or by a charity approved for the
purposes of section 9 (1) (b) of the Poisons Ordinance 1952 or in an estate hospital and who is authorized in writing as provided in that section;

(c) a fully registered medical practitioner or a dental practitioner or a person working under the immediate personal supervision of such a practitioner if the drug in question is for the use of such practitioner or of his patients.

3. Regulation 7(1)(a) shall not apply to any drug manufactured by persons and in the circumstances described in sub regulation (2) if the drug is manufactured for the purpose of dispensing.

4. A school of pharmacy or any research or training institution which wishes to manufacture any product for teaching and research purposes may on application be exempted by the Authority from the provisions of regulation 7(1).

5. Any person who wishes to manufacture any product solely for the purpose of producing samples for clinical trials or for registration under these Regulations may on application be exempted by the Authority from the provisions of regulation 7(1).

6. Any person who wishes to import or manufacture any product solely for the purpose of treatment of any person suffering from a life threatening illness may on application be exempted by the Authority from the provisions of regulation 7(1) subject to such conditions or restrictions as it may impose in such exemption.

Certification: The Authority may issue such certification on payment of RM 50 on any matter relating to any product where such certification is required by any country importing such product.

Suspension or cancellation of registration and revocation of licence: (1) The Authority may, at any time and without assigning any reason, suspend or cancel the registration of any product or revoke any licence issued under these regulations and may amend the conditions to which such licence or registration is subject.

(2) Subject to sub regulation (3), any suspension or cancellation of the registration of any product under sub regulation (1) shall similarly and at the same time affect any licence issued under these regulations relating to that product.

(3) Notwithstanding sub regulation (2), where a licence issued under these Regulations relates to several registered products the suspension or cancellation of the registration of any product under sub-regulation (1) shall not affect the position of other registered products listed in the licence.

Appeal: Any person aggrieved by any decision of the Authority under these Regulations may make a written appeal to the Minister within fourteen days from the date the decision is made known to him and any decision of the Minister made on an appeal shall be final.

MANUFACTURE OF REGISTERED PRODUCTS

Personnel: A licenced manufacturer shall ensure that all personnel employed at all levels of manufacture

(a) possess suitable qualifications required for their job;
(b) have adequate experience and technically competent;
(c) are regularly trained during their employment for the purposes of keeping up to date with any advances or changes; and

Devi Ahilya Vishwavidyalaya Indore
(d) are medically examined regularly

Premises: Registered products shall be manufactured, processed, packed, labeled and tested in the premises which are in accordance with the standards set by the Authority.

Equipments: Manufacturing and testing equipments shall be designed, placed and maintained as prescribes.

Manufacturing Operations: Manufacturing operations shall be carried out in accordance such requirements as may be determined by the Authority.

Quality control department: A licenced manufacturer shall establish a quality control department under the supervision of a suitable qualified person.

Inspections: For the purposes of this Part, a licenced manufacturer shall conduct regular inspections of his manufacturing and quality control activities.

Distribution records: A licenced manufacturer shall maintain proper records of every batch of finished registered products distributed to enable the complete and rapid recall of the registered product if necessary.

3.13 SOUTH AFRICA

MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT NO. 101 OF 1965), AS AMENDED. GENERAL REGULATIONS

SCHEDULE DEFINITIONS

**Adulterated medicine** means a medicine that consists in whole or in part of any substance that is poisonous, harmful, toxic or the medicine's physical attributes are not the same as those approved by the Council during registration of such medicine;

**Adverse drug reaction** means a response to a medicine which is noxious and which occurs at any dosage and can also result from lack of efficacy of a medicine, off-label use of a medicine, overdose, misuse or abuse of a medicine.

**Counterfeit medicine** means a medicine in respect of which a false representation has been made with regard to its contents, identity or source by means which include its labeling and packaging;

**Holder of a certificate of registration** means a person who holds a registration certificate authorising the registration and marketing of a medicine.

**LABELLING OF MEDICINES INTENDED FOR ADMINISTRATION TO HUMANS**

8. (1) Save as provided in sub-regulations (2), (3) and (4), the immediate container of every medicine in which medicine intended for administration to humans is sold shall have a label attached to it on which only the following particulars shall appear in clearly legible indelible letters in English and in at least one other official language:

a. a distinct boxed signal word indicating the Schedule number;
b. the proprietary name of the medicine;
c. the registration number of the medicine allocated in terms of section 15(6) of the Act;
d. the dosage form of the medicine;
e. the approved name of each active ingredient of the medicine and the quantity thereof contained in a dosage unit, or per suitable mass or volume or unit, starting with an active ingredient of a high Schedule, in lettering which has minimum legibility;
f. the name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicine as a preservative;
g. the approved name of any anti-oxidant contained in the medicine;
h. in the case of a medicine for oral or parental administration, the quantity of sugar or ethyl alcohol contained in the medicine, expressed as a percentage of the total volume of the medicine, if such quantity exceeds two per cent by volume;
i. the content of the medicine package expressed in the appropriate unit or volume of the medicine;
j. the indications for use of the medicine;
k. the recommended dosage of the medicine;
l. where applicable, the instruction ‘Shake the bottle before use’;
m. in the case of a medicine intended for injection by a particular route of administration only, that route of administration by means of suitable words or abbreviations;
n. in the case of a medicine listed in any Schedule made in terms of the Act, the letter ‘S’ followed by the number of the relevant Schedule, in a prominent type size and face and surrounded by a square border, immediately preceding the proprietary name of such medicine;
o. the lot number of the medicine;
p. the expiry date of the medicine;
q. the name of the applicant for registration of the said medicine;
r. the requirements regarding the manner in which the medicine shall be stored with specific reference to the applicable storage temperature and other precautions required for the preservation of the medicine;
s. where applicable, the statement: ‘For external use only’;
t. the warning: ‘Keep out of reach of children’;
u. in the case of a medicine intended for oral or parental administration which contains aspirin or paracetamol the warning: ‘Do not use continuously for more than 10 days without consulting your doctor’;
v. in the case of a medicine for oral administration which contains fluorides, the warning: ‘Contains fluoride’
w. in the case of a medicine for oral administration which contains an antihistamine, the warning: ‘This medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressant agents’;
x. in the case of eye drops or artificial tear solutions in respect of which evidence concerning the self-sterilising ability of the medicine has not been approved by the Council, the warning ‘Do not use more than 30 days after opening’;
y. any specified warning required in terms of section 15(7) to be given on the label of the medicine as a condition of registration thereof.
z. the case of a medicine that contains TARTRAZINE, the warning: ‘Contains TARTRAZINE.’

(2) If the medicine package bears both an immediate container label and an outer label, the requirements of sub-regulation (1) shall apply to the outer label as well: Provided that it
shall be sufficient to give on the immediate container label:

a. in the case of medicines intended for administration by injection and having a total volume not exceeding 5 ml, the details prescribed in paragraphs (b), (e), (m), (o), (p) and (q) of sub-regulation (1);
b. in the case of an ointment, cream, gel or powder having a net mass not exceeding 10 grams, the details prescribed in paragraphs (b), (c), (e), (f), (o), (p), (q) and (u) of sub-regulation (1);
c. in the case of liquid, solution or suspension having a total volume of more than 1 ml, but not exceeding 15 ml, the details prescribed in paragraphs (b), (c), (d), (e), (n), (o), (p), (q) and (y) of sub-regulation (1);
d. in the case of a liquid, solution or suspension having a total volume not exceeding 1 ml, the details prescribed in paragraphs (a) and (o) of sub-regulation (1);
e. in the case of a medicine packed in blister or similar packaging, the details prescribed in paragraphs (b), (o), (p) and (q) of sub-regulation (1), repeated as frequently as its practicable.

(3) The Council may authorise the inclusion on the label of a medicine of any special information that is not required by this regulation to be so included.

(4) The requirements of sub-regulation (1) shall not apply to –

a. any medicine sold in accordance with section 14(2) of the Act;
b. any medicine sold by a person authorised to prescribe or a pharmacist in the course of his or her professional activities for the treatment of a particular patient; or
c. any medicine sold by a pharmacist, a person authorised to compound and dispense, or in a hospital pharmacy in accordance with a prescription issued by a medical practitioner or dentist for the treatment of a particular patient: Provided that such medicine shall be sold in a package to which is attached a label containing the following information:

i. the name of the medicine or the name of each active ingredient or constituent medicine;
ii. the name of the person for whose treatment such medicine is sold;
iii. the directions (if any) in regard to the manner in which such medicine should be used;
iv. the name and business address of the medical practitioner, dentist, pharmacist, pharmacy or hospital selling such medicine;
v. date of dispensing;
vi. reference number.

PACKAGE INSERTS FOR MEDICINES FOR HUMANS: Each package of a medicine shall be accompanied by a package insert, either as a separate entity or as an integral part of the package, on which are printed in English and at least one other official language and in type having a minimum legibility under the headings and in the format specified in this regulation, and which shall contain other specified particulars.

PATIENT INFORMATION LEAFLET: Each package of a medicine shall have a patient information leaflet that must contain the following information with regard to the medicine in English and at least in one other official language:

a. Scheduling status;
b. proprietary name and dosage form;
c. what the medicine contains, which includes-

i. the approved name of each active ingredient and the quantity thereof contained in each dosage unit or per suitable mass or volume or unit of the medicine; and
ii. all inactive ingredients that must be listed qualitatively;

d. the approved indications and use;

e. instructions before taking the medicine, which include –

i. contra-indications;
ii. precautions;
iii. warnings e.g. concerning sedative properties of the medicine or risks involved with sudden withdrawal of the medicine;
iv. interactions;
v. the following general statements:

"If you are taking medicines on a regular basis, using the medicine at the same time with another medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice."

"If you are pregnant or breast feeding your baby while taking this medicine please consult your doctor, pharmacist or other health care professional for advice."

f. how to take the medicine, including the following statements:

"Do not share medicines prescribed for you with other persons."

"In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre;"

g. side effects, including the following general statement:

"Not all side-effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice;"

h. storage and disposal information, including the following general statement:

"store all medicines out of reach of children."

i. presentation, which includes the number, volume or mass per package unit and a description of the packaging material, e.g. bottle, blister pack, etc;

j. identification of the medicine, i.e. the description of its physical appearance as tablet, capsule, etc;

k. registration number of the medicine;

l. the name, business and telephone number of the holder of the certificate of registration; and

m. the date of publication of the patient information leaflet;
The Council may authorise a deviation from sub-regulation

**LICENCE TO MANUFACTURE, ACT AS A WHOLESALER OR DISTRIBUTE MEDICINES:**

(1) A person desiring to manufacture medicines, act as a wholesaler or distributor of medicines shall apply to the Council for a licence to manufacture, act as a wholesaler or distributor of medicines.

(2) An application referred to in sub regulation (1) shall be accompanied by an application fee as determined by the Council.

(3) The application shall contain at least the following information:

a. the name and address (both physical and postal) of the applicant;

b. the exact location of the premises where the manufacturing, wholesale or from which the distribution will be carried out;

d. the name of the responsible pharmacist who will be responsible for managing the pharmaceutical aspects of the applicant;

e. in the case of a manufacturer or importer authorised to import medicines in terms of section 15C of the Act, the physical address of the quality assurance laboratory to be used by the applicant;

f. registration number of the applicant, in the case of-

i. a natural person, with a statutory body;

ii. a juristic person, with the relevant registering authority;

f. In the case of a juristic person, the name and title of the person responsible for the application; and

h. any other information that the Council may deem necessary.

(4) A person issued with a licence in terms of this regulation shall:

a. comply with the requirements and guidelines as determined in the latest edition of the South African Guide to Good Manufacturing Practice or any other guide as determined by the Council;

b. in the case of the wholesaler or distributor, purchase Scheduled substances from a licensed pharmaceutical manufacturer or a licensed importer only;

c. keep a record of medicines recalled or withdrawn;

d. store medicines under their recommended storage conditions;

e. employ only properly trained employees;

f. have a system in place for detecting expired medicines from the wholesaler's shelves and such medicines shall be removed from the shelves;

h. keep a secured area for Schedules 5 and 6 substances;

i. have a pest and rodent control system in place;

j. keep the premises clean, dust free, insect-free and in a bird-free condition;

k. have a decontamination procedure for spillages of hazardous substances;

l. keep the premises in a secure condition; and

m. have in place a disposal system for unwanted and expired medicines.

The person issued with a licence shall inform the Council of any changes with regard to information furnished in terms of sub regulation (3).

**PERIOD OF VALIDITY OF A LICENCE ISSUED IN TERMS OF REGULATIONS 18 AND 19 AND RENEWAL OF LICENCES:**
(1) A licence issued in terms of these regulations shall be valid for a period of 3 years from the date of issue.

(2) A licence referred to in sub regulation (1) and which has expired may be renewed upon application to the Director-General or the Council, as the case may be.

(3) An application referred to in sub regulation (2) shall –

   a. contain at least the information referred to in these regulations as the case may be;
   b. be accompanied by a fee as determined from time to time by notice in the Gazette by the Director-General or the Council, as the case may be; and
   c. be made 90 days before the expiry of the existing licence.

APPEAL AGAINST THE DECISION OF THE DIRECTOR-GENERAL OR THE COUNCIL: An appeal in terms of the Act shall be lodged within 21 days from the date on which the decision appealed against was communicated to the appellant.

The appeal committee shall consider the appeal and make a decision in regard thereto within a period of one month from the date

i. on which it was appointed; or,
ii. when the appeal hearing was completed; whichever is the later.

APPLICATION FOR THE REGISTRATION OF A MEDICINE:

(1) Any person residing and doing business in the Republic may make an application for the registration of a medicine.

(2) In case the person referred to in sub regulation (1) is not a pharmacist or veterinarian, the application must be co-signed by a responsible pharmacist or veterinarian, as the case may be.

(3) An application referred to in sub regulation (1) shall be made on the appropriate form obtainable from the Registrar and shall be accompanied by:

   a. a properly completed screening form obtainable from the Registrar;
   b. a proposed label for use on the medicine;
   c. where applicable, a copy of the latest inspection report that is not more than two (2) years old, from the regulatory authority of the medicine's country of origin;
   d. in the case of Schedules 6 and 7 substances, a copy of a permit to manufacture such substances;
   e. all relevant data on the medicine, whether positive or negative;
   f. proof of the existence of a manufacturing site; and
   g. any other information as the Council may from time to time, by guidelines for the registration of medicines, determine.

INFORMATION THAT MUST APPEAR IN THE REGISTER FOR MEDICINES:

A register of medicines must, in respect of any registered medicine, contain the following information:

a. the name of the medicine approved by the Council, which must be the proprietary
name;
b. the registration number allocated to the medicine;
c. the approved name of each active ingredient of the medicine and the quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine;
d. the dosage form of the medicine, where applicable;
e. the name of the holder of the certificate of registration;
f. the name and address of the manufacturer(s);
g. in the case of a medicine, the name of the packer(s);
h. in the case of a medicine, the name of the final product release control (FPRC);
i. in the case of a medicine, the name of the final product release responsibility (FPRR);
j. the date of registration of the medicine;
k. the conditions of sale of the medicine determined in terms of section 15(7) of the Act

APPLICATION FOR AN AMENDMENT TO A MEDICINE REGISTRATION:

A holder of a certificate or registration may submit to the Registrar an application on a form as determined by Council to amend an entry made into the register of medicines with regard to a particular medicine.

CATEGORIES AND CLASSIFICATION OF MEDICINES:

(1) The following are the basic categories of medicines:

a. Category A = Medicines which are intended for use in humans and which are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine.
b. Category B = Medicines which cannot normally be administered without further manipulation;
c. Category C = Medicines intended for veterinary use which are, without further manipulation, ready for administration, including packaged preparations where only vehicle is added to the effective medicine; and
d. Category D = Medicines which are Complementary Medicines of the various categories

(2) Medicines in category A are further subdivided as per its pharmacological actions:

REGISTRATION CERTIFICATE: A certificate of registration in the form shown below shall be issued by the Registrar after a medicine has been registered.

MEDICINES AND RELATED SUBSTANCES CONTROL ACT 1965 (ACT 101 OF 1965) MEDICINE REGISTRATION CERTIFICATE

It is hereby certified that registration of the medicine described below has been approved by the Medicines Control Council in terms of Section 15(3)(a) of the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965), subject to the conditions indicated.

1. Registered name ............................................................

2. Registration number ............................................................

3. Approved name of every active ingredient and quantities thereof per dosage unit or per suitable mass or volume or unit of the medicine ............................................................

4. Dosage form ............................................................

5. Conditions under which the medicine is registered ............................................................

6. Registered in the name of (applicant) ............................................................

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METHOD OF TAKING SAMPLES DURING AN INVESTIGATION, THE CERTIFICATE TO BE ISSUED AND THE REPORTING OF ANALYSIS RESULTS:

(1) An inspector designated in terms of the Act may take a sample or any quantity of samples of a medicine or Scheduled substance for purposes of testing, examination or analysis in terms of the Act by a person designated as an analyst, pharmacologist or pathologist.

(2) The sample contemplated in sub-regulation (1) must—

a. be taken in the presence of the person who is in charge of such medicine or substance, or in the absence of such person, in the presence of any witness present;

b. be taken and stored in such a manner as to ensure its integrity during the entire examination process of the sample;

c. be packed and sealed and suitably labeled or marked in such a manner as its nature may permit and must be transmitted by any suitable means to an analyst, pharmacologist or pathologist together with the certificate signed by the inspector, a copy of which must be issued to the person in charge by the inspector at the earliest possible time;

(3) An analyst, pharmacologist or pathologist referred to in sub-regulation (1) must as soon as possible after receipt of the sample, test, examine or analyse the sample and report the results thereof.

(4) An inspector referred to in sub-regulation (1) may take a sample during a routine inspection from a manufacturer, a wholesaler or retailer for testing, examination or analysis in terms of these regulations.

(5) Certificates or reports issued in terms of this regulation must be submitted by their authors to the Council within 7 days from the date of issue.

SEIZURE OF MEDICINES:

(1) A medicine may be seized if it—

a. is unregistered and sold in contravention of the Act;

b. is suspected counterfeit;

c. is misbranded;

d. is adulterated;

e. is suspected stolen;

f. is Scheduled and is possessed by an unauthorised person or by an authorised person but in unauthorised quantities;

g. has been declared undesirable in terms of the Act;

h. belongs to the State and is found in possession by an unauthorised person; or

i. is used in unauthorised clinical trial.

PRE-PACKING OF MEDICINES INTO PATIENT READY PACKS: The pre-packing of medicines into patient ready packs must—
a. be carried out by a pharmacist or a veterinarian or under the supervision of a pharmacist or veterinarian;
b. have a batch numbering system which contains all the information relating to the ingredients and the procedures used in preparing the patient ready pack;
c. be carried out under the required temperature and humidity conditions;
d. be carried out in an area of the premises specially used for pre-packing only; and
e. be carried out in accordance with any requirements as determined by the Council.

INVESTIGATIONS: The Council may conduct an investigation with regard to a medicine if-

a. such a medicine is recalled in South Africa or any other country;
b. adverse reaction is reported;
c. the medicine is suspected or found not to comply with the requirements of the Act;
d. there is an international alert with regard to such a medicine; or
e. for any other reason, the Council deems it fit to conduct an investigation on the Medicine

COMPLIANCE WITH REQUIREMENTS:

(1) Every medicine shall comply with the standards and specifications which were furnished to the Council on the form prescribed by Regulation and which have been accepted by the Council with regard to such medicine.

(2) Any proposed deviation from accepted standards and specifications as intended in regulation shall be submitted to the Council for prior approval and such deviation shall not be introduced before the said approval has been granted.

SAMPLES WITH APPLICATION FOR REGISTRATION: The council may, with regard to the registration of biological medicines, require, in terms of the Act, that six samples of every lot, together with six copies of the protocols of testing of the bulk lot and filling lot and six copies of the certificate of release issued by the competent authority in the country in which the product was manufactured, be submitted to the council as a lot release condition


3.14 WORLD HEALTH ORGANISATION

Challenges

The increasing globalization of commerce and trade and the merging of pharmaceutical companies, are internationalizing pharmaceutical production. International pharmaceutical norms and standards are thus more important than ever before since they serve as global tools aiming to ensure safety and quality of medicines. One of WHO's roles is to continue to develop such international norms and standards, and to help countries implementing them.

Safety and quality of pharmaceuticals are also being promoted through regional and international efforts to harmonize drug regulation, such as those led by, ASEAN (Association of South-East Asian Nations), CAN (Andean Community), CADREAC (The Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries), the European Union, Gulf Cooperation Council (GCC), the International Conference on Harmonisation (ICH), MERCOSUR (Southern Common Market) the Pan American Network on Drug Regulatory Harmonization (PANDRH) and the Southern African Development Community (SADC). These efforts are to be welcomed since international consensus on quality, safety and efficacy standards can speed up access to medicines.
Important key elements are quality assurance guidance texts in the areas of production, testing, and distribution of medicines. These include guidance on: good manufacturing practices; quality assurance for regulatory approval; prequalification of medicines, laboratories, and supply agencies; model certificates for quality assurance-related activities; quality control testing; new specifications for inclusion in the Basic Tests series and the International Pharmacopoeia; and International Chemical Reference Standards; the programme on International Nonproprietary Names (INN) which is used to identify each pharmaceutical substance or active ingredient by a unique and universally accessible name. All these elements are intended for use by national regulatory authorities, manufacturers, and other interested parties. The need to scale up access to affordable quality medicines for HIV/AIDS, TB, and malaria in developing countries has raised many challenges within the pharmaceutical world. These challenges come on top of the reality that among national regulatory authorities there is a variable capacity to interpret and apply existing norms and standards and guidelines on regulation, quality control, nomenclature, and classification of pharmaceuticals. WHO will work to strengthen and promote global norms, standards, and guidelines for the quality, safety, and efficacy of medicine. That said, quality assurance levels differ from country to country; not all countries have the same capacity and resources for implementing agreements on drug regulation harmonization. Drug regulation experts accordingly recommend a step-wise approach for achieving the highest level of medicines safety, regulation and quality assurance in each country. WHO's role is to identify areas in which further guidance needs to be developed for preliminary and intermediate steps. Simple screening tests for detecting substandard and counterfeit drugs are just one example.

More generally, WHO's task is to help countries consider the implications of the relevant harmonization agreements. This is particularly true with regard to ICH, which currently does not include representatives from all developing countries. WHO needs to evaluate the impact of ICH guidelines, and advise non-ICH Member States on how to adapt existing guidelines to their own needs and conditions.

At the same time WHO must ensure that its own normative guidelines, such as its guidelines on good manufacturing practice (GMP), are maintained and updated. The GMP guidelines aim to provide globally accepted and applicable standards for ensuring that products are consistently produced and controlled according to quality standards.

Rapidly evolving science and technology are likewise creating problems for regulatory authorities everywhere. Training and specialization requirements for dealing with the ever-increasing complexity of assessing technologically advanced products can be especially burdensome. But by developing norms and standards for use in new areas of health technology and product development, WHO can reduce this problem, while at the same time helping to minimize unnecessary duplication of scientific expertise and effort.

Globalization of the pharmaceutical industry is also bringing other safety issues to the fore. For example, non-prescription medicines are becoming increasingly available to the general public in all countries, including through such channels as the Internet. Yet resources for monitoring their safety and quality are often lacking. (http://www.who.int/medicines/areas/quality_safety/challenges/en/)

End of Chapter 03