CHAPTER III

APPROVAL PROCESS FOR NEW DRUGS
AND
RIGHTS OF THE CLINICAL TRIAL SUBJECTS

There appears to be a constant competition between nature which can be said to be responsible for new ailments on one side and human ingenuity engaged in research to find out new curative process. What is considered to be a best medicine today for treatment of a particular disease becomes out of date and soon go out of the market with the discovery of new drugs. Again what is considered to be incurable at any given point of time becomes subjected to treatment and cure with new medicines. With the onward march of science and complexities of living process hitherto unknown diseases are noticed. AIDS and Cancer still pose great challenge to the researchers in medicine. Major breakthroughs are yet to be made to effectively combat these and other new diseases.

To meet these new challenges, new drugs have to be identified. There is every need to accelerate research and development in the field of medicine and bio-technology. Therefore, the change appears to be the rule in this field. Legal provisions should help the growth of knowledge intended to minimise the human misery caused due to diseases. At the same time, the need to respect the human being as a member of the human species is to be recognised. It is necessary to recognise the importance of the dignity of the human being. We
must be conscious of the probable misuse of biology and medicine and endangering human dignity.

In the process of medical research, human beings should not be used as subject for experimentation without due safeguards. Trading in human tissue is also prevalent, in different parts of the world. There is commercial activity going on in human blood, foetus, organs, embryos, eggs and wombs. The development in medicine has thus made many things today which were impossible previously. Trading, in human tissues is perceived as lucrative business. It also means good money for those who are willing to sell their body in parts one by one for the purpose of transplantation to others who need and can afford to purchase. Thus, the advances in biotechnology has made the body a valuable property. The consequences of such kind were not contemplated before. therefore, the need for concern for human rights in this area.

It is true that humanity, both present and future generation must be allowed to enjoy the benefits of development in biology and medicine and at the same time it must be resolved to take all such measures as are necessary to safeguard human dignity and fundamental freedom of the individual in the application of biology and medicine.

The Supreme Court, by reading Article 21 with Articles 39 and 47 ruled that the right to life would cover amenities ensuring good living which include medical attention, life free from diseases and longivity up to normal
expectations. In *Bandhua Mukti Morcha v. Union of India*¹, the Court aptly observed that it is the fundamental right of everyone in this country, assured under the interpretation given to Article 21 to live with human dignity, free from exploitation.

Several global conventions² were adopted to protect the dignity and identity of all human beings and guarantee every one, without discrimination, respect for their integrity and fundamental freedom with regard to the application of biology and medicine.

The guidelines of the World Health Organisation (herein after referred to as WHO) insists on the protection of the rights and safety of the subjects including patients in the process of investigations directed to the advancement of public health objectives³. The declaration of World Medical Association at Geneva held the view that in research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject and the mission of the physician should always be the health of his patient⁴.

In the background of these guidelines and objectives, it is intended to examine the clinical trial procedures envisaged for the approval of new drug to be marketed in India either by manufacturing in India or by importing into

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India. Identically, the provisions for clinical trial procedure to approval new
drugs in the U.S. are also discussed. It is also proposed to study the provisions
for protection of the subjects of bio-medical research in the light of the
guidliness issued by the Supreme Court of India and international agencies like
World Health Organisation. The European Convention on Human Rights and
Declaration of Helsinki on duties of physicians are also examined.

Approval process for new drug:- The new drugs are very complex and their
discovery and development require costly technology. The regulatory control
has also become very strict. The drug has to pass through more stringent safety
and other tests. Therefore, the introduction of new drugs has been on the
decline. In India number of new drugs declined from 564 in 1953 to 166 in
1962. The number of drugs introduced in the U.S. market declined from early
average of 100 in 1960 to less than 40 in 1980s. Though the discovery rate has
increased due to explosive growth of biomedical knowledge, the number of
new drugs has continued to decline in the 90s because of the strict regulatory
requirements. Only 28 new drugs were approved in the U.S. in 1995 and only
40 new drugs were introduced Worldwide during the same year. The
pharmaceutical industry in India and elsewhere expressed the view that
controls on new drugs are stringent and costly. The procedures stand in the

5 See Keayla, "TRIPS agreement on patent laws: Impact on pharmaceuticals and health for all" a
paper presented at International Conference as Global Health Law organised by the Indian Law
Institute in collaboration with World Health Organisation during December 5-7, 1997 at p.12.
6 Id. at p.13.
7 F. Steward & G. Wibberly, "Drug innovation - what is slowing it down?" (1980) 284 Nature 118 at
p.120; Also see K. Hartley and Maynard, "The cost and benefits of regulating new product
development in the U.K. Pharmaceutical Industry", (1982), a study produced for the Pharmaceutical
way of innovations and prevent the availability of new therapies quickly. It is
necessary to reconcile the conflicting interests of the pharmaceutical industry
and the requirements of the needy patients in the process of approval of new
drugs. The role of the authorities in this context is not only to ensure that
innovative drugs are marketed at the earliest but also to protect the public from
unsafe drugs.

**Definition of new drug**

A new drug according to the provisions of the Act is a drug, the
composition of which is such that the drug is not generally recognised among
experts as safe for use. It includes a drug which may have been found safe for
use under investigational conditions but which has not been used for any
appreciable length of time under the said conditions. Thus a new drug would
cover drugs under the following categories.

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8 Drugs and Cosmetics Rules 1945, Explanation to Rule 30A. These rules were framed in exercise of
the powers conferred by Sections 6(2), 12, and 33 of the Drugs and Cosmetics Act 1940.

It reads: “30-A. Explanation :- For the purpose of this rule, “new drug” means a drug the
composition of which is such that the drug is not generally recognised among experts as safe for use
under the conditions recommended or suggested in the label thereof and includes any drug the
composition of which is such that the drug as a result of investigations for determining its safety for
use under such conditions, is so recognised, but which has not otherwise than during the course of
such investigations, been used to any large extent or for any appreciable length of time under the said
conditions”.

(i) a new therapeutic discovery,

(ii) a new therapeutic use for an established drug for another disease,

(iii) a drug recommended for administration by a new route,

(iv) combination of established drugs for new indications or when claims are made that the combination contribute an improvement in therapy as compared to the individual components when used separately.

With a view to ensure uniform yardstick in clearance of new drugs, authority to clear new drugs has been vested with Drugs Controller of India. No new drug can be manufactured or imported into the country without his approval. Procedure for importing of new drugs are also prescribed. For clearance of import or manufacture of a new drug, a person is required to produce before the Drugs Controller of India detailed particulars regarding

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10 *Id.*, Rule 21(b) and 22 read:

"21. licensing authority" means the authority appointed by the Central Government to perform the duties of the licensing authority under these Rules and includes any person to whom the powers of a licensing authority may be delegated under Rule 22".

11 *Id.*, Rule 30 (A) reads:

"30-A (1) No new drug shall be imported except under and in accordance with the permission in writing of the licensing authority.

(2) The importer of a new drug when applying for permission shall provide before the licensing authority all documentary and other evidence, relating to its standards of quality, purity and strength and such other information as may be required by the licensing authority including the results of therapeutic trials carried out with it"
toxicological, pharmacological, bio-chemical and teratogenic studies carried out with drug and clinical trial reports. the manufacturer or importer has to produce before the licensing authority all the documentary and other evidence relating to the standards of quality, purity and strength and any other information required by the licensing authority. This information may include therapeutic trials carried out with such drugs. For obtaining licence to manufacture new drug, the manufacturer has to produce evidence that the drug for the manufacture of which application is made has already been approved. The clinical data furnished by the applicant would be screened by experts. Some drugs may be new to India but they may have history of use and clinical test in other countries. The reports of clinical tests made in other countries must be submitted with the application. In practice, this foreign test data, if extensive and accepted in many countries, may be sufficient to support approval of the drug in India. There appears to be similarities in the approach of new drug regulation in most part of the world.

12 Id., Rule 69-B. The Rule reads, "Applications to manufacture 'new drugs' other than the drugs classifiable under schedules C and C(1) products:- Subject to other provisions of these Rules:-

(i) no 'new drug' shall be manufactured unless it is previously approved by the licensing authority mentioned in Rule 21;

(ii) the manufacturer of a 'new drug' when applying for approval to the licensing authority in sub-rule (i) shall produce all documentary and other evidence relating to its standards of quality, purity and strength and such other information as may be required including the results of therapeutic trials carried out with it;

(iii) while applying for a licence to manufacture a 'new drug' or its preparation an applicant shall produce along with his application evidence that the drug for the manufacture of which application is made has already been approved". See also Rule 75(B), which reads:

"75-B Applications to manufacture 'new drugs' classifiable under Schedules C and C(1) ..."
In European countries, authorisation for putting a new product on the market are granted by national authorities. The U.S. law requires pre-market approval of all new drugs. Approval is based on controlled clinical tests showing safety and efficacy of the drug. The FDA also accepts foreign data and clinical studies in support of a new drug approval when satisfied about relevance of the testing to the U.S. population.

In China the law establishes a pre-market licensing system for new drugs not previously sold in that country. Controlled clinical tests are also required for certain categories of drugs. In China, as in the U.S., full clinical tests are not necessarily required for "generic" drugs that are identical to or similar to an approved pioneer drug. Bio-availability test can be sufficient as the basis of approval for a generic drug when the authority is satisfied about similarity and bio-availability of the drug.

When the conditions for authorisation of new medicinal products are identical, when the same tests are carried out, the same test animals are used and the same documents are forwarded to the authorities, it appears, the only decision left to the individual countries is the evaluation of the documents.

(Please note that the rest of this rule reads same as 69-B (i) (ii) (iii))


15 21 C.F.R. 114 106


received. When all national decisions regarding the authorisation of pharmaceutical production are based on the same factual considerations which are harmonised, it is difficult to conceive that a product which is considered safe and has consequently been granted approval in one country, could be considered unsafe in other countries. The legal principle underlying this idea is that a product deemed reasonable in a given country should be reasonable in all the countries.

But due to some peculiar conditions prevailing in India, every new drug is required to undergo clinical trial before they are permitted to be marketed.\textsuperscript{18} The physiological norms like height and weight of people in this country differ from those in developed countries from where new drug normally emanates. The nutritional status of people of India is low when compared to that of the developed countries with the result that dosage patterns which are considered safe enough in developed countries may not be applicable in India. A substantial portion of the population suffers from chronic diseases such as amoebic infection or malaria and this could affect the function of the liver and spleen. Since most drugs are metabolised through liver, there is a possibility that efficacy, including side effects of these drugs in the Indian population may be different. Genetic or racial factors may also affect response to a drug.

While primary considerations for granting permission for a new drug is safety and efficacy, clinical superiority over existing drugs is to be taken into

\textsuperscript{18} See V C. Sane, “Drug Control: India”, World Congress on Law and Medicine, New Delhi, Feb 23. 1985 at p. 3.
consideration while clearing new drug application, as India cannot afford the luxury of permitting introduction of a new drug, which does not show any clinical superiority over an existing drug\textsuperscript{19}.

The analysis of the above provisions reveal that the legal provisions to monitor the procedure followed during the clinical trials when the drug was experimented on animals and human beings before an application for approval to manufacture is completely absent and hence there is no means to protect the rights of persons who are called trial subjects during the trial of the drug since these clinical trials are not controlled. The procedure envisaged under law only intends to verify the documents relating to test carried out in clinical trials. In addition to this the demands of some new diseases like AIDS have refocussed the whole issue about development process of new drugs in the world. Because of this reason, the authorities appeared to have shown considerable urgency to allow the drug to be marketed than it was in the past.\textsuperscript{20}

\textbf{Clinical trial procedures of the U.S.A.}

It is not out of context here to analyse briefly the procedure followed in clinical trials in the U.S. since it is considered as the standard procedure accepted by most of the countries.\textsuperscript{21} This procedure must not only serve the interest of those who are actively involved in the research process but also

\textsuperscript{19} Ibid.


protect the rights and safety of the subjects apart from advancing public health objectives.

The analysis of the clinical trial procedure of the U.S. is also important in the light of the fact that there are no strict rules available in India to monitor the ongoing clinical trials where drugs are put to test on human beings. The procedure existing in India under the rules only intends to verify whether the new drug is effective and qualitative as per the standards prescribed before it is marketed. A study of the procedure for approval of new drug application in the U.S. will disclose the need for the similar or improved provisions in India to monitor the ongoing clinical trials. To expedite the procedure for approval of new drug, there appears to be an immense pressure on the authorities in the U.S. to slacken its stringent attitude. This may lead to violation of some safety standards. Analysis would bring to light certain issues regarding rights of the subject involved in these trials and correlative obligation of sponsors and investigators.

First, the drug must be tested for safety in animals before clinical trials in human beings may begin. The clinical testing is performed under an investigational new drug application which must be reviewed by the

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22 See Supra nn. 8-12.

23 Clinical Trial means any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to ascertain their efficacy and safety. It is not possible to draw distinct lines between the various phases of these trials. There are also divergent opinions about details and methodology adopted in each of these phases.

24 Investigational product means any pharmaceutical product or placebo being tested or used as a reference in a clinical trial. See Jonathan S. Khan, Esq. And David T. Read, esq., "Exepedid..."
regulating authority. Clinical trials may continue for 2 to 10 years before new drugs application (NDA) may be submitted for marketing approval.

The lengthy clinical testing period is divided into three phases. Phase 1 is designed to determine the metabolism and pharmacological action of the drug in human beings, the side effects associated with increasing doses and to gain, if possible, easily evidence of effectiveness. Phase 2 involves limited controlled studies in which safety and effectiveness for particular indications are studied; Phase 3 consists of expanded controlled and uncontrolled trials in which the effects of the drug on large population are observed and dosages are adjusted.

**Procedure for ‘Treatment use’ of Investigational New Drug (IND)**

Ordinarily, a new drug is not available to patients other than those enrolled in clinical studies until phase 3 is completed and an NDA is approved. However, new rules are framed for “treatment use” of investigational new drugs (IND). These regulations allow patients to use an experimental drug if the drug is being studied for use against a serious or life threatening disease. This treatment use will be granted if certain conditions are met. For instance where (1) there is no satisfactory alternative drug or other therapy available to treat the same stage of the particular disease in the intended patient population (2) controlled clinical trials under an approved IND are underway or have been

completed, and (3) the sponsor is pursuing ultimate market approval actively and with due diligence, the treatment use can be granted.

'Treatment use' may be requested either by the sponsor or by the physician treating the patient. A drug sponsor\textsuperscript{25} may submit a treatment protocol\textsuperscript{26}. It contains, among other things, (1) a description of the intended use of the drug, (2) an explanation of the rationale for use of the drug, (3) a description of the criteria for patient selection, (4) an informational brochure to be supplied to each treating physician and (5) a commitment that all participating investigators will comply with informed consent\textsuperscript{27} requirements. Alternatively an individual physician may submit a request for treatment through IND if the sponsor agrees to provide him with the experimental drug. The request for treatment through IND must contain information similar to that in the treatment protocol.

\textsuperscript{25} Sponsor is an individual, a company or a research organisation which takes responsibility for the initiation, management and financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, then the investigator also assumes the role of the sponsor.

\textsuperscript{26} Protocol means a document which states the background, rationale and objectives of the trial. It describes the design and methodology to be adopted in the trial. It also includes statistical considerations and conditions under which the clinical trial is to be conducted. It can also function as a contract between the sponsor and investigator.

\textsuperscript{27} Informed consent is a subject's voluntary confirmation of willingness to participate in a particular trial. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconvenience, alternative treatment that may be available and the subjects rights and responsibilities. \textit{Ibid.}
The regulating authority will review a treatment protocol for a drug indicated for a serious disease either during phase 3 investigations or after all clinical trials have been completed. They may deny the request if there is insufficient evidence of safety and effectiveness to support treatment use. A drug indicated for an "immediately life threatening" disease on the other hand may be made available for treatment use during phase 2. The regulating authority may deny the latter request if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the (1) drug is either effective for the intended use of the intended patient population or (2) could not expose the patients to an unreasonable and significant additional risk of illness or injury. Thus the standard of review for treatment use for an "immediately life-threatening disease" is significantly lower than that for a serious disease. This is considered to be reasonable policy distinction in as much as that risk/benefit analysis in life-threatening situation is skewed so heavily in favour of use of any therapy which can be of some benefit.

An "immediately life-threatening disease" is defined as one in which there is reasonable likelihood that death will occur within a matter of months or in which pre-mature death is likely without early treatment28. The term "serious disease" is not defined. However, "advanced cases of AIDS" and "most advanced metastatic refractory cancers" can be included as immediately life-threatening cases - and "Alzheimer's disease" and certain forms of epilepsy can be included as serious diseases.

28 21 C.F.R 312. 34 (b) (3) (ii).
Treating physicians are considered to be investigators and patients are considered to be investigational subjects. Rules of Treatment use of an investigational drug requires informed consent from the subject or from his lawful guardian. It also requires supervision of the treatment by an institutional review board and collection of certain information by the sponsor and submission of reports to the regulatory authority.

A sponsor may charge for a 'drug under treatment use', but the charges cannot be more than what is necessary to meet the costs of manufacture, research, development and handling of investigational drug. To ensure that treatment use does not overshadow concurrent controlled investigations, no charge will be allowed unless there is adequate enrolment in an ongoing clinical investigation in pursuit of marketing. Promotion of the drug and other indices of commercialisation are prohibited. However the regulatory authority publishes announcements of treatment use approvals in medical journals to allow interested physicians to enroll. Many companies may feel that the good publicity gained by making the drug freely available outweighs the amount to be gained by charging and avoids unsavoury task of justifying the amount being charged and the negative publicity resulting from charging.

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29 Trial subject: The trial subject may be (a) a healthy person volunteering in a trial, (b) a person with a condition unrelated to the use of investigational product, or (c) a person (usually a patient) whose condition is relevant to the use of the investigational product and who participates in a clinical trial, as a recipient of the pharmaceutical product under investigation.
Procedure for implementation of “Parallel track’ proposal

Another proposal by name “Parallel track” proposal is devised by some research groups to expand access to promising new drugs that have adequate safety data demonstrated in Phase I studies itself. It has potentiality to make qualified investigational drugs available even earlier than might be possible under treatment IND. The major aspects of the programme are that certain drugs, with priority being granted to those showing encouraging signs of efficacy, are to be made available at the time they are entering efficacy trials, if adequate safety is demonstrated in Phase I studies. The intent of the programme is to provide research data, although safety data, probably in the form of adverse drug reaction reports as required for investigational drug, is expected. The programme is primarily targeted towards patients who cannot or will not participate in a clinical trial. It further appears that the programme may be limited to people with a condition for which there is no standard therapy and people who live far from or are too sick to participate in appropriate controlled trials.

This proposal, appears to be mainly, intended to allow the drug to be made available to AIDS patients whose disease has substantially progressed despite Zidomidine (AZT) therapy and who have no other treatment options. It is considered to be an interim measure to make a promising investigational

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therapy available for people with AIDS who do not have satisfactory treatment options\textsuperscript{31}.

Despite the initial use of the "Parallel track" concept, the overall reactions to the concept of expanded access to investigational drugs after only phase I data seems somewhat cautious. Many AIDS activists may applaud the proposal\textsuperscript{32}, but there are others who raise significant questions regarding procedures to identify eligibility criteria, informed consent and liability issues\textsuperscript{33}. The source of this concern may stem from the apprehension that it may cripple the clinical trial system because many patients may not be willing to participate in clinical trials because of the wide availability of experimental treatments. Drug manufacturing associations are also concerned about the potential product liability issues relating to adverse events and decrease in the regulatory authorities motivation to expedite the approval if the drug is already widely available and also the possibility of black market copies of drugs in the parallel track system\textsuperscript{34}. Others question is whether the safety can be determined on the basis of phase I studies. Phase I studies typically involve so few patients, some times from twenty to eighty, that it is difficult to draw conclusions from the data\textsuperscript{35}.

\begin{itemize}
\item[\textsuperscript{33}] F.D.C. Reports ("The Pink Sheet"), July 24, 1989, at p. 18 quoted in ibid.
\item[\textsuperscript{34}] Ibid.
\item[\textsuperscript{35}] Ibid.
\end{itemize}
"Sub part E" procedure

To reduce regulatory burdens, the FDA announced its new ‘sub part E’ procedures for therapies intended to treat "life threatening" and "seriously debilitating" illness. The procedures are in the form of amendments to the IND regulation. They apply to new drugs, antibiotics and biological products, and are of potential importance to many new products under development. The new “subpart E” of IND regulations signals the FDA’s willingness to approve, not just make available, products for marketing after phase 2 clinical trails instead of the traditional phase 3. These regulations do not represent a change in the procedures as such but only formalize the set of procedures already permitted under existing laws on therapies for life threatening and severely debilitating diseases.

Nevertheless, while ‘sub part E’ is neither procedurally nor conceptually new, it does constitute formal recognition by the agency of something previously done on an ad hoc basis and significantly, it demonstrates further willingness on the part of the FDA to adjust the approval process to expedite the marketing of important new drug.

‘Sub part E’ defines37, “Life-threatening diseases or conditions” as those “where the likelihood of death is high unless the course of the disease is interrupted” or those “with potentially fatal outcomes,” Examples of life-threatening diseases include progression from asymptomatic to symptomatic

36 Id. at pp. 89-91.
37 Ibid.
HIV infection or further progression to a later stage of AIDS, metastatic senses, or amyotrophic lateral sclerosis. Also included are conditions in which treatment may have a beneficial effect of survival, such as after a stroke of heart attack.

Sub part E defines \(^{38}\) "severely debilitating" diseases or conditions as those "that cause major irreversible morbidity." Examples of severe debilitating diseases include severe functional deficits* in multiple sclerosis, Alzheimer's disease or progressive ankylosing spondylitis, and the prevention of blindness due to cytomegalovirus infection in AIDS patients.

Under traditional IND procedures, especially in the cases of new molecular entities or major new uses of marketed drugs, the FDA encourages the sponsor to request an end-of-phase 2 meeting. The purpose of such meeting is to establish agreements between FDA and the sponsor on the overall plan for phase 3, and objectives and designs of particular studies. Phase 3 studies are usually large. These are clinical efficacy trials which are the central piece in the sponsor's marketing application. The new 'sub part E' offers the opportunity to have such meeting at the end of phase I, rather than waiting until the end of phase 2 to enable them to use the drug for treatment for life threatening and severely debilitating illnesses.

It appears from this that 'subpart E' is truly eliminating phase 3 testing. From the point of view of the sponsors who desire to market the drug at the earliest it appears as though it is only a means of merging phase 3 in phase 2

\(^{38}\) Ibid.
so that there is a net saving of time and resources. But it would severely compromise the quality of data submitted to the agency for review in marketing application. 'Sub-part E' proposal contains the use of phase 4 (post marketing) studies. Although these are a requirement of approval under this system, it is expected that, to the extent this system is used to conduct post marketing studies will be a routine element of approval because of agreement with the sponsor.

It is clear that the agency, FDA, is under political pressure in AIDS related diseases to be receptive to an end-of-phase I meeting. How far the agency will be pushed to use these procedures for diseases that do not come so clearly under the definitions of "life threatening" or "severely debilitating"?

Already comments were submitted to the agency that these procedures should be available to all treatments. In such context, it may be difficult for the agency to justify a restrictive use of this procedure.

It is likely that the following three criteria will be employed on a sliding scale in determining whether the phase 2 approval mechanism is appropriate. (1) Quality of Phase I data and the prospects for Phase 2 studies producing data adequate for approval.

This will probably be the single most important factor in determining whether the FDA will agree to pursue a 'sub part E' IND with the sponsor.

39 Id. at p. 90.
42 21 C.F.R. § 312. 82.
There is nothing mandatory about sub part E. The entire process is dependent on agreement between FDA and the sponsor of a new drug. The FDA must be persuaded that this is an appropriate development strategy and FDA is best persuaded by good data.

(2) Availability of alternative treatment:

Probably more significant than argument over "life threatening" or "severely debilitating," the agency could be strongly influenced in its decision in 'sub part E' if no suitable alternative treatment exists.

(3) Seriousness of the Disease

If the FDA is presented with strong phase I data with a sound plan for phase 2 that should produce adequate data for an NDA, and it is widely accepted that no suitable alternative treatment for the disease exists, the FDA will carefully consider the ramifications of refusing to use 'sub part E' procedures merely because the disease is not sufficiently "life threatening" or "severely debilitating." It is unlikely that the FDA will risk the potential political fallout of refusing to use 'sub part E' procedures over issues as sensitive as definition of "severely debilitating." Conversely, where there is no question that the disease in question is "life threatening" or "severely debilitating," but the phase 1 data are not especially impressive and/or there exists alternative therapy, the FDA probably will be reluctant to proceed under 'sub part E'.

Therefore, while much attention has been focused on the definition of 'life threatening' and 'severely debilitating,' in fact these terms may become
sufficiently broad as not to present serious hurdle for the FDA to widen the concept of ‘subpart E.’

Regulating authorities have no doubt been traditionally loathe to approve any drug without detailed evidence of safety and efficacy. But in the cases of AIDS where patient, will certainly die without some drug therapy, the authorities may be willing to be more lenient both with respect to treatment use of unapproved drugs and relax approval standards. In sum, the era of expedited drug approvals has not fully arrived except for AIDS drugs where the risk/benefit ratio of drug approval coupled with strong voiced activists politically have demanded action. The future of these expediated procedures for approvals is unclear partially due to concern raised by scientists about safety, the sanctity of the clinical trial, and traditional intransigence of the regulatory authorities to new ideas concerning drug approvals.

**Need to control clinical trial procedure in India**

There is urgent need for such legal controls in India for undertaking clinical trials. The aim of such legal controls should be protect the safety and rights of the subjects participating in the trials. It should allow only trials which may lead to conclusive data. The system must allow for on-site inspection of the quality of the data obtained. The drug regulatory authority should ensure that protocols of clinical trials be submitted in advance for its review. It may propose revisions or request additional data on a clinical trial or may direct termination of a trial. It should also be possible for the authorities to check the reliability and quality of the reported results.
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**Duties of the physicians in bio-medical research involving human subjects**

It is the mission of the physician to safeguard the health of the people. His or her knowledge should be dedicated to the fulfilment of this mission. The Helsinki Declaration,\(^{43}\) binds the physician with the words: “The health of my patient will be my first considerations”. The International Code of Medical Ethics declares that “A physician shall act only in the patient’s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”\(^{44}\)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World medical Association has prepared the guidelines to be followed by every physician in bio-medical research involving human beings. European Council has also adopted similar resolution for the protection of human rights and dignity of the human being with regard to the application of biology and medicine\(^{45}\). These are only a guide to physicians all over the world. It must be stressed that they are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

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\(^{43}\) See *supra* n.4.

\(^{44}\) *Ibid.*

\(^{45}\) See *supra* n.2.
(1) **Basic principles**

Bio-medical research involving human subject must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.\(^{46}\) The design and performance of each experimental procedure should be clearly formulated in the protocol which should be transmitted for consideration to a committee independent of the investigator and sponsor.\(^{47}\) This research should be conducted only by qualified persons under the supervision of a clinically competent medical person.\(^{48}\) The responsibility for human subject must always rest with a medically qualified person even through the subject has given his or her consent.

The research cannot legitimately be carried out unless the importance of the objectives is in proportion to the inherent risk or benefit to the subject. It should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subjects or to others.\(^{49}\) Concern for the interests of the subject must always prevail over the interests of science and society.\(^{50}\) The right of the subject to safeguard his or his integrity must always be respected. Every precaution should be taken to respect the privacy of the subject.\(^{51}\) The physicians must abstain from engaging in research projects

\(^{46}\) *Ibid.*

\(^{47}\) *Id.*, Article 4.

\(^{48}\) *Ibid.*

\(^{49}\) *Id.*, Article 16 (ii).

\(^{50}\) *Supra* n.4 at p. 187.

\(^{51}\) *Supra* n.2 Article 10.
involving human subjects unless they are satisfied that hazards involved are believed to be predictable. They should cease any investigation if the hazards are found to outweigh the potential benefits.\textsuperscript{52}

\textbf{Rights of the subject}

In any research on human beings, each potential subject must be adequately informed about the anticipated benefits and potential hazards of the clinical study and the discomfort it may entail.\textsuperscript{53} He should be informed that he is at liberty to obstain from participation in the study and that he is free to withdraw his consent to participation at any time. The physician should then obtain the subjects freely - given informed consent preferably in writing.\textsuperscript{54}

While obtaining the consent, the physician should be cautious if the subject is in a dependent relation to him. In such conditions, the consent, if obtained, would be deemed to be under undue influence. In such situation consent should be obtained by another physician who is completely independent of this relationship. In case of legal incompetence of the subject to give consent, it must be obtained from the legal guardian\textsuperscript{55}. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative should be obtained.

\textsuperscript{52} Ibid.

\textsuperscript{53} Ibid.

\textsuperscript{54} Id., Article 5.

\textsuperscript{55} Id., Article 6.
Whenever the minor child is in fact able to give a consent, the minor’s consent must be obtained in addition to the consent of the minor’s legal guardian.\textsuperscript{56}

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.\textsuperscript{57} The investigator or his team should discontinue the research if in his or their judgement it may if continued, be harmful to the individual.

The tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes and subject to appropriate genetic counselling.\textsuperscript{58} An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendent.\textsuperscript{59} The use of techniques of medically assisted procreation should not be allowed for the purpose of choosing a future child’s sex, except where hereditary sex-related disease is to be avoided.\textsuperscript{60}

Removal of organs or tissue from a living person for transplantation purposes may be carried out solely for the therapeutic benefit of the recipient.

\textsuperscript{56} Id., Article 7.
\textsuperscript{57} Id., Article 8.
\textsuperscript{58} Id., Article 12.
\textsuperscript{59} Id., Article 13.
\textsuperscript{60} Id., Article 14.
and where there is no suitable organ or tissue available from a deceased person and no other alternative therapeutic method of comparable effectiveness is available. The necessary consent for such removal must be given in written form before an official body. No organ or tissue removal may be carried out on a person who does not have the capacity to consent. But it may be authorised when there is no compatible donor available who has the capacity to consent and the recipient is a brother or sister of the donor and donation has the potential to be life saving to the recipient and potential donor concerned does not object. No financial gain should be allowed to be made out of any human body or its parts. When in the course of intervention any part of the human body is removed, it may be stored and used for a purpose other than that of which it was removed, only if this is done in conformity with appropriate information and consent procedures.

Where the law allows research on embryos in vitro, it must ensure adequate protection of the embryo. The creation of human embryos for research purposes is prohibited.

The idea behind all these guidelines appear to be that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject. All these guidelines

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61 Id., Article 19(1).
62 Id., Article 19(2).
63 Id., Article 20.
64 Id., Article 21 & 22.
65 Id., Article 18.
66 Id., Article 2.
should as far as possible be incorporated in the new drug regulation system so as to have a binding effect on all concerned in this research.