Chapter 5

Decision Making In Drug Crisis Situation

Drug shortage is a major problem that plagues the pharmaceutical industry. Drug shortage in the United States is defined as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level"[8].

The magnitude and impact of drug shortage has progressed to critical levels in the recent years. According to the Center for Drugs and Evaluation and Research (CDER) Drug Shortage Program of the FDA (U.S. Food and Administration), in 2010, there were 178 drug shortages reported to the U.S. Food and Drug Administration (FDA), 132 of which involved sterile injectable drugs. In 2011, there were 251 drug shortages reported, 183 of which involved sterile injectable drugs. In 2012, there were 117 new drug shortages, 84 of which involved sterile injectable drugs and in 2013, there were 44 new drug shortages, 35 of which involved sterile injectable drugs. Although in 2012 and 2013, there were fewer reported drug shortages, FDA continues to see shortages involving older sterile injectable drugs. These shortages have involved cancer drugs, anaesthetics used for patients undergoing surgery, as well as drugs needed for emergency medicine, and electrolytes needed for patients on IV feeding. When the drug in shortage turns out to be an orphan drug, the patient community using the drug is in a crisis as there are no alternate medicines that can be substituted in the place of these drugs.
5.1 THE CAUSES OF DRUG SHORTAGES

The factors that contribute to drug shortages are complex and multidimensional[20]. Many factors contribute to the shortage, namely, shortage of raw materials, shifts in clinical practices, wholesaler and pharmacy inventory practices, changes in hospital and pharmacy contractual relationships with suppliers and wholesalers, adherence to distribution protocols mandated by the FDA, individual company decisions to discontinue specific medicines, natural disasters, manufacturing challenges, issues related to manufacturers (pharmaceutical mergers and acquisitions, decisions based on projected profit), regulatory and legislative factor, labour disruption. It is worth noting that approximately 27% of the shortages are unexplained. The following pie chart given by the FDA[17] gives us a clear picture of the various reasons for drug shortages in the U.S.

![Figure 5.1.1 Reasons For Drug Shortages[17]](image)

5.2 THE EFFECTS OF DRUG SHORTAGES

The escalating increase in the shortage of drugs has compromised the quality of care received by patients and imposed a tremendous burden on our health care system. It has left
many patients in the lurch as they are unable to take proper medication in spite of having received the correct diagnosis and identifying the appropriate treatment. They adversely affect patient care by causing substitution of safe and effective therapies with alternative treatments, compromising or delaying medical procedures, or causing medication errors. Drug shortages also significantly burden health care providers and health care facility finances and personnel. Drug shortages have had a profound and widespread impact on the quality of health care in the U.S. and have created significant obstacles. In late 2010, the Institute for Safe Medication Practices (ISMP) conducted a national survey of 1,800 health care practitioners (consisting of approximately two thirds pharmacists) to assess the impact of drug shortages. The ISMP found that 84% of the respondents said they had never received advance warning of a shortage from manufacturers or the FDA, 80% said they faced difficulty obtaining comparable drugs, 78% said there were significant costs to obtaining comparable drugs., 70% said they had been unable to find comparable alternatives, 64% believed that shortages posed a risk of adverse patient outcomes. Respondents reported more than 1,000 adverse events and near-misses attributable to drug shortages. A management strategy that includes clear policies and procedures for information gathering, decision-making, collaboration, and timely communication should be established to effectively handle drug shortages. In response to the crisis, healthcare and government organizations have taken numerous initiatives, aiming to find rapid solutions. Nevertheless, the battle against drug shortage is likely to be long-term. Key elements to a successful program for managing drug shortages include a good understanding of the causes for the shortages, a clear channel for international communication and collaboration and identifying scientific solutions for often recurring problems that lead to drug shortages.
5.3 RECENT DRUG SHORTAGES IN THE PHARMACEUTICAL AND BIO
PHARMACEUTICAL INDUSTRY

A quick analysis of the recent drug shortages will give us an idea of the enormity of
the drug shortage problem, its evolution as a crisis and the need for immediate solutions to
prevent or reduce recurrence of such situations and also throw light upon the need to identify
a scientific solution for reducing the short supply by using scientific methods. The following
chart indicates the drug shortages reported to the F.D.A in U.S between 2011 and 2014.[17]

Figure 5.3.2 Drug Shortages Reported To FDA Between 2011 And 2014[17]

Peter Loftus of The Wall Street Journal has reported the shortage of various drugs in
the U.S. on May 31st, 2015. There was a worldwide shortage of BCG used for the treatment
of high grade non invasive bladder cancer. In 2011, a malfunctioning sprinkler system
flooded the Toronto plant where Sanofi produces all of its BCG. The company discarded
tainted batches, cleaned the facility and resumed production. But more problems followed. In
April 2012, Sanofi halted distribution of BCG after encountering mold contamination problems on the floor of BCG production areas and on workers’ gloves. In June 2012, after consulting with regulators, Sanofi suspended production of BCG so it could renovate the plant. Initially, Sanofi planned to resume shipping BCG in late 2013. But in July 2013, a heavy rainstorm flooded the plant again, delaying repairs. After Sanofi’s production halt in 2012, the FDA asked Merck to boost BCG production to make up for the shortage but soon Merck halted production for six weeks because its routine monitoring of air quality in the plant detected mold. The manufacturing problems have led to the drug being in short supply even in the month of August 2015. Given below is a graph showing the number of drugs in short supply in the U.S. between 2010 and 2015.[17]

![Figure 5.3.3 Number Of Drugs In Short Supply In The U.S. Between 2010 And 2015](image)

Another drug shortage is that of the generic painkiller widely used in hospitals being in short supply after Hospira Inc. recalled more than 60 lots of vials due to contamination by crystal particles that could cause problems if injected into patients.
The Lake Forest, Ill, company, which has struggled to comply with manufacturing-quality requirements in recent years, notified customers in January 2015 that it was voluntarily recalling vials of ketorolac tromethamine that were distributed in the U.S. from February 2013 to December 2014, and in Singapore from January to July 2014, according to a Hospira press release posted in February 2015. Ketorolac has been in shortage from January this year, 2015 and the shortage continues in August 2015. The Forbes reports in April 2015, disturbing increases in the occurrences of the shortages of many important antibiotics.

The latest shortages catalogue of the European contains information on medicine shortages that affect or are likely to affect more than one European Union (EU) Member State, where the European Medicines Agency has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU. It does not give a complete overview of all medicine shortages occurring in the EU. It reports the shortages of drugs like Cerezyme (imiglucerase), Fabrazyme (agalsidase beta) in November 2013 Insuman Rapid, Basal and Comb (insulin human) supply shortages ongoing in 31/03/2015, Maci (matrix applied characterised autologous cultured chondrocytes) implant supply Shortage ongoing during 04/07/2014, Tygacil (tigecycline) supply shortage as ongoing in 22/05/2015. It also gives the information about three drug shortages that have been resolved in 2014 and one in 2015. In October 2013, Janssen Pharmaceutical Companies (Janssen), a division of healthcare giant Johnson & Johnson warned of impending shortages of its ovarian cancer drug Doxil (doxorubicin). Doxil is used to treat ovarian cancer, multiple myeloma and AIDS-related Kaposi’s sarcoma (a kind of skin cancer). Doxil had been in short supply since the production facility of Johnson & Johnson’s contract manufacturer Ben Venue Laboratories in Ohio was closed in November 2011 due to ‘significant manufacturing and quality concerns.
5.4 CHALLENGES IN MANUFACTURING ORPHAN DRUGS

The manufacturing process for orphan drugs is generally complex and time consuming. Many orphan drugs are biopharmaceuticals or biologics, that is, they can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living cells or tissues. They are isolated from natural sources—human, animal, or microorganism. Biopharmaceuticals pose several unique manufacturing and regulatory challenges due to their intrinsic complex profile. They have a high level of structural complexity and heterogeneity, are produced in living systems or supplemented with reagents derived from living systems, and consequently have a complex purity/impurity profile that poses unique analytical challenges. Additionally, production involves 10 or more manufacturing stages encompassing 18-30 unit operations with several hundred process parameters. A single change could have a cascade effect; the impact on the quality, safety, and efficacy of the biological is not predictable. Ensuring virological safety of biologicals is even more challenging. Iatrogenic accidents in the past have occurred due to contamination of the production system (e.g., avian retrovirus type C in yellow fever vaccine, SV40 in inactivated poliovirus vaccine), manufacturing process-related concerns (e.g., incomplete inactivation of live virus vaccines such as polio and rabies vaccines) and the use of contaminated excipients (hepatitis B virus (HBV) was transmitted via the human serum used in the yellow fever vaccine).

There are several lessons to be learned from the abovementioned incidents. Adventitious agents can potentially contaminate the production system and go undetected; in many cases, particular raw materials have been implicated. Changes in critical process parameters can impact the safety profile. Also, virus detection systems are not always sensitive enough to detect low levels of pathogenic virus. Hence the problem of viral
contamination of bio pharma products cannot be totally eliminated. The viral contamination in biologics is a recurrent affair that has to be managed efficiently.

Virus contamination has several serious consequences, the most crucial being the potential to impact patient safety. In addition to a direct impact, lack of drug availability for patients with life-threatening illnesses has serious consequences, as many products are still under patent and may be single sourced. Other factors involve impact on public perception, regulatory implications, facility production shutdown, financial losses, competition and lost opportunities and legal problems.

The recent Ebola outbreak is an example of how important it is to develop drugs for rare diseases. Ebola is a rare disease that occurs more commonly in developing countries, but has recently affected the United States. With very few companies developing Ebola-related drugs, Ebola patients did not have access to life-saving Ebola drugs. Mapp Biopharmaceuticals, one of the few companies developing an Ebola treatment, had limited supplies of its drug, ZMapp. Mapp exhausted its supplies after providing experimental doses to a handful of medical workers who contracted Ebola, including the first two Ebola patients flown from West Africa back to the United States for treatment. There were just not enough drug makers in the Ebola rare disease space to develop these orphan drugs, so when the sudden need arose for these treatments, the medical community was caught off guard. But even if orphan drugs are available to treat rare diseases, they are still prone to shortages due to manufacturing difficulties and the drug class in which most fall. A majority of orphan drugs are biologics — drugs that are produced from living cells. And like sterile injectables, almost all biologics are administered through the same route of administration. Due to this shared delivery mechanism, biologics are susceptible to the same manufacturing quality
issues facing sterile injectables. As a result, many orphan drugs fall within a drug class historically most prone to shortages.

### 5.5 SHORTAGES OF ORPHAN DRUGS – A DRUG CRISIS SITUATION

Drug shortages of any kind are detrimental to the patient society but the shortage of drugs for rare diseases becomes a crisis because there are no alternate treatments as one manufacturer produces the entire supply. The Orphan Drug Act has granted marketing exclusivity to orphan drugs, so there would be no competitive products available in the market also. The biggest incentive that orphan drug companies receive is a seven-year market exclusivity period for any orphan drug produced. However, with Congressional incentives come side effects. Market exclusivity effectively stops competitors from selling drugs in that specific rare disease space. For seven years, orphan drug makers do not have to worry about competitors vying for their market share. Without competitive products, patients of a specific rare disease have only one treatment option for their rare conditions. The drug development incentives that Congress offered to orphan drug companies may eventually backfire when the combination of market exclusivity and drug shortages occur. Therefore, if an orphan drug maker enjoys market exclusivity but experiences a drug shortage, patients are left without an available treatment. Recently, courts have held that drug manufacturers do not have a duty to keep manufacturing drugs and supply them to the market. Therefore, patients do not have tort remedies available when there is a disruption in drug supply. Patients suffering from orphan diseases and their families are left in the lurch till supply resumes. Unfortunately, there is not a silver bullet to solve orphan drug shortages, but there are various solutions to mitigate them[24].
Thus when drug shortages hit the Orphan Drug Industry the shortage assumes alarming proportions and balloons into a huge crisis, affecting both the patients as well as the pharma company. Take the case of Robert Logan, who was on primidone, and had his seizures under control for a long period of 20 years. When his drug was switched due to non availability Logan suffered two grand mal seizure and was admitted in hospital reports Epilepsy News Newsletter Fall 2011. Dr. William Schubert, a Genzyme patient, allegedly died because of the Fabrazyme shortage. After Genzyme rationed Dr. Schubert’s Fabrazyme doses, his health deteriorated quickly[24].

Total eradication of manufacturing problems is an impossible task, especially in the case of orphan drugs, particularly biologics or bio pharma. The solution then lies in tackling the shortage arising as an aftermath of the problem in such a way that the situation does not turn into a big crisis. In many situations, drug shortages can be minimized by taking alternate steps. It becomes imperative to choose one among numerous available alternative plans of action to redress the shortage problem as much as possible. Decision making in such crisis situations is usually done by conducting meetings, reviewing proposals and lengthy discussions. This is not only a time consuming process, but even after a decision is reached, a doubt about the effectiveness of the decision taken remains an unanswered question. There is no proof that the decision taken is ideal for the situation or is at least the one that would give maximum benefit. Scientific solutions can go a long way to fill this lacuna.