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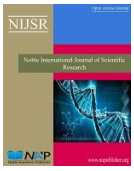

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Drug Tragedies: The Dark Epoch of Clinical Prosecutions That Made Manhood Mysterious Fatalities

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Abstract: Today, the highest importance is given to the patient's safety and ethics during the clinical trials. The regulatory authorities take each and every aspect into consideration to protect the safety, rights and consent of the subjects during the phases of clinical trials. Besides the applications like IND, NDA further strengthen these above parameters. However, all these safety measures are a result of our previous experiences in history such as Thalidomide tragedy, Sulphanilamide disaster, Nazi's experiments, Tuskegee syphilis studies. All these disasters are due to unethical behavior, lack of knowledge on safety, no keen idea on pharmacovigilance, no proper data storage, inexperience etc., which led to many disasters resulting in the deaths of many innocent lives and some permanent damage to the persons consuming these drugs either by force or voluntarily. This article mainly focuses on the drug tragedies and drugs introvert from the market, due to the lack of knowledge on clinical trials.

Keywords: Clinical Trials, Drug Tragedies, Regulatory Authorities, Safety, Efficacy.

1. Introduction

Now- a- days, all the novel drugs undergo the pre-clinical and clinical trials before entering into the market to ensure the safety [1] , efficacy [2] and quality [3] of the drug product. There are different types of regulatory authorities in different countries for reviewing this data. These reviews are done by Food Drug & Administration in India. The applications submitted are Investigational New Drug Application (IND) [4] and New Drug Application (NDA) [5]. IND is an application submitted to the FDA after the clinical trials and to get the permission for Clinical trials. NDA is the application for permitting the sales and marketing of new drugs. Another type of application is Abbreviated New Drug Application (ANDA) for the marketing of generic drugs [6].

All these applications are reviewed thoroughly by the regulatory authorities and permissions are given. Even after releasing into market, the patients taking these drugs are observed closely i.e., post marketing surveillance. All these pre-clinical, clinical trials, applications, regulatory authorities etc. are to confirm that the drugs are safe and effective enough. If this is not ensured, there may be some severe adverse drug effects or permanent damage, some events even leading to deaths of many people. There have been many tragedies in our history which led to some unwanted, serious effects which have costed

the lives of many and many have suffered irreversible damage. Some of the drugs having severe adverse effects which are now withdrawn from the market were depicted table 1 [7-10].

Table 1. Drug tragedies reported globally that troubled the mankind so far

Drug	**Category**	**Indication**	**Complications**	**Place**	**Year**	**Manufacturer**
Accutane	Vitamin-A formulation	Serious acne	Ulcerative colitis,liver damage	Switzerland	1982-2009	Roche pharmaceuticals
Alatrofloxacin	Fluoroquinolones antibiotic	Bacterial infection	Hepatic damage	US	2001-2006	Pfizer
Alcofenac	NSAID	Rheumatoid arthritis and spondylitis	Vasculitis	UK	1970-1979	-
Alosetron	5-HT_3 inhibitor	Inflammatory bowel disease	Ischemic colitis	Canada	2000 (Feb-Nov)	Prome theus laboratories
Alpidem	Anxiolytic	Anxiety	Hepato-toxicity	France	1991-1994	Sanofi-aventis
Althesin	Anesthetic	Outpatient surgery	Anaphylaxis	France, Germany, UK	1980-1984	Australian company
Amineptine	Anti-depressant	Depression	Skin allergies	France, US	1978-1999	Servier pharmaceuticals
Aminopyrine	Analgesic and Anti-inflammatory	Pain relieve	Agranulocytosis	France, US	1897-1999	Hoechst AG
Aprotinin	Beta blocker	After major cardiac surgeries	Dose dependant Myocardial infarction	US	1997-2003	Baeyer pharmaceuticals
Baycol	Anti-hyperlipidemic	Obesity	Rhabdomyolosis, Renal failure	Germany	1997-2000	Bayer pharmaceuticals
Bendazac	NSAIDs	Joints & Muscular pain	Hepatoxicity	Spain	1964-1993	Angelini group manufacturers
Bithionol	Anti-bacterial, Anti-helminthic and algecide	Algal infections	Skin allergies	US	1960-1967	Eli-Lilly
Bromofenac	Analgesic	Occular inflammation	Severe hepatitis	US	1997-1998	Sun pharmaceuticals
Chlormadinone	Progestin	Birth control	Animal carcinogenicity	UK, US	1963-1970	Merck & Co.
Chlormezanone	Anxiolytic and muscle relaxant	Anxiety and muscle spasms	Steven Johnson syndrome	US, South Africa	1958-1996	Runcorn
Cibutramine	Appetite suppressant	Obesity management	Stroke, heart attack, hypertension	Nottingham	1997-2010	Abbott laboratories
Cisapride	Gastro pro-kinetic agent	Gastric reflux	Cardiac arrhythmias	US	1980-2000	Janssen pharmaceuticals
Clioquinol	Anti-diarrheal	Diarrhea and other GI problems	Sub-acute neuropathy	Japan	1957-1970	Ciba-Geigy
Clobutinol	Anti-tussive	Acute dry cough infection	Ventricular arrhythmia	Germany	1961-2007	Brehringer-Ingelheim company
Cyclofenil	Gonadotropin stimulant	Menopausal therapy	Hepatotoxicity	France	1970-1987	_
Diethylsilbesterol	Steroid hormone	Prevent miscarriages in pregnant women	Tumors appeared in the daughters of treated women	UK	1938-1975	Many British companies

Dihydrostreptomycin	Aminoglycoside antibiotic	Veterinary purpose	Neuropsychotropic reaction	US	1951-1970	American biochemists
Dinoprostone	Prostaglandin	To prepare cervix for child birth	Uterine hypnotus and fetal distress	UK	1977-1990	American chemist E.J. Corey
Ebrotidine	Antihistamine	Gastro protective activity	Hepatotoxicity	Spain	1995-1998	Faes company
Efalizumab	Immunomodulator	Psoriasis (adults)	Severe neurological infections like meningitis		2003-2009	Genetech Inc.
Exifone	Psychotropic drug	Neuro protection	Hepatotoxicity	France	1970-1989	-
Fenfluramine	Appetite suppressant	Obesity	Pulmonary hypertension and Cystic fibrosis	EU, India	1963-1997	Zogenix company
Flunitrazepam	Benzodiazepine	Insomnia	Skin rashes	France	1974-1991	Roche Pharmaceuticals
Levamisole	Anti-helminthic, NSAID and Anti-cancer	Worm infestation, Colon and breast cancer	Neutropenia and agranulocytosis	US	1989-2000	Janssen
Limuracoxib	NSAIDs	Menstrual pain relieve	Hepatotoxicity	World wide	2006-2007	Novartis
Mebifradil	Calcium channel blocker	Hypertension	Drug interactions	EU	1997-1998	Roche pharmaceuticals
Oxeladin	Anti-tussive	All types of cough	carcinogen	Canada, UK	1970-1976	-
Pemoline	CNS stimulant	Attention Deficit Disorder and Attention-Deficit Hyperactivity Disorder	Liver damage	Canada and UK	1975-2010	Abbott laboratories
Pergolide	Psychotropic	Parkinson	Valvular diseases	US	1996-2007	Brohringer Ingelheim
Phenformin	Anti-diabetic	Hyperglycemia	Lactic acidosis	France	1958-1977	Ciba- Geigy Company
Phenylpropalamine	Psychostimulant	Obesity	Cardiac events, stroke	Canada, US	1941-2000	No principal manufacturer
Propoxyphene	Opioid analgesic	Mild to moderate pain	Heart attack	World wide	1978-2010	Eli-Lilly
Rapacurarium	Adjunctive anesthesia	Minor surgeries	Bronchospasms	USA	1999-2001	Akzo nobel company-Netherlands
Rimonabant	Anti-cholesterol	Obesity, appetite suppressant	Depression, Suicidal thoughts	World wide	2006-2008	Santoni-Avenitis company
Roficoxib	NSAIDs	Relieve menstrual pain	Myocardial infarction, Arrhythmias	World wide	1999-2004	Merck & Co.
Sertindole	Anti-psychotic	Schizophrenia	Arrhythmias, Sudden cardiac arrests	EU	1996-1998	Abbott laboratories
Temafloxacin	Floro quinolones	RTIs, UTIs and Skin allergies	Temafloxacin syndrome, Chills, high fever	US	1992	Abbott laboratories

Terfenadine	Anti-histamine	Allergies (without drowsiness)	Cardiac arrhythmia	US	1985-1997	Hoechst Marion Roussel company
Tetrazepam	Benzodiazepine	Anti-convulsant and Hypnosis	Cutaneous reaction	EU	1967-2003	Sanchez-Morillas
Thalidomide	Anxiolytic	Morning sickness in women	Phocomelia	Australia	1960-1962	Chemie grunenthal
Theralizumab	Immuno-modulator	Leukemia, Auto-immune disorders	Allergies, chronic organ failure	London	1999-2006	Barhringer-Inelheim
Tienillic acid	Loop diuretic	Hypertension	Hepatitis, abdominal pain and Jaundice	France	1979-1982	Smith, Kline & French pharmaceuticals
Tolcapone	Psychotropic drug	Parkinson Disease	Hepatotoxicity	EU, Australia	1997-2004	Roche pharmaceuticals
Triglitazone	Anti-diabetic, Anti-inflammatory	Pain Relief, hyperglycemia	Hepatitis	UK	1999-2000	Warner-Lambert company
Valecoxib	NSAID	Rheumatoid arthritis and Osteomalacia	Heart attack, Stroe and GI complications	US	2000-2005	G.D. searle
Zimeludin	Anti-depressant	Depression	Guillain-Barre syndrome and Muscle paralysis	US	1982-1983	Arvid carlsson

Source: The source and references mentioned at the top i.e. [7-10].

2. Some of the Other Drug Tragedies

2.1. Tuskegee Syphilis Study

This study was conducted in the year 1932-1972 at the place called Alabama (a south eastern US state) [11, 12]. The human subjects were forced to undergo these experiments. The main objective of these experiments was to study about the progression of syphilis in untreated people. The drug that was available for treatment was "penicillin". These experiments were stopped in 1972 when the media somehow discovered about these unethical and unholy studies.

2.2. Sulfonamide Disaster

This incident is also called as the "Taste of Raspberries" or "Taste of death" or "the 1937 Elixir Sulfonilamide incident". It took place at East Virginia and West California in 1937. As we all know Sulfonamide belongs to antimicrobial class, used for the handling of Streptococcus infection [13]. It was available as a tablet and capsule at that time. But S.E. Massengil Company prepared an oral liquid formulation (Elixir) in which diethylene glycol was used as a solvent. More than 100 people died in 15 states of USA after consuming this formulation. This is because Diethylene glycol is an anti-freezing agent and is toxic to the body. After this incident, FDA in 1938 established a rule for premarketing safety data for each and every drug.

2.3. Nazi's Experiments

During early 1940's in Germany some unethical and brutal experiments were conducted on the prisoners and disabled persons without their consent which led to death of many lives. Some were even murdered for performing autopsy [14, 15]. Some of the examples of these experiments are:

2.3.1. Twins Experiments

These were conducted for procuring information about the reproductive system and ethnic duplication of twin babies which involved brutal tests on many sets of twins.

2.3.2. Bone, Nerve and Muscle Experiments

These studies are conducted to understand the process of transplantation of organs from one person to another. They involved much brutal torturing and involuntary amputation of limbs and muscles.

2.3.3. Malarial Experiments

These studies primarily emphasis on knowing the subjects' immunity against parasitic infections. The human subjects were induced with malaria parasite (*Plasmodium sps*) and treated with Pharmaceutical products to find out their immunity against the parasite.

2.3.4. Sea water experiments

These studies are to check whether the sea water is suitable for drinking. During these studies the human subjects were provided with only sea water instead of potable water. As a result, a large number of subjects suffered from chronic dehydration which ultimately led to their deaths.

2.3.5. Poisonous Experiments

These studies were to assess the mortality rates of human subjects with the poisons. Innumerable kinds of toxic substances were injected or mixed in the food of these subjects without their awareness and autopsies were performed on their corpses.

2.3.6. Sterilization Experiment

These experiments were to test the sterility of certain chemicals. Those chemicals were injected into the genital organs of the human subjects irrespective of their gender and are directly exposed to radiation. This resulted in many complications like painful uterus, impotency, cancers and internal bleeding.

2.3.7. Guatemala Syphilis

This incident took place during 1946-1948 at Guatemala of Central America. These studies were performed for determining the therapeutic efficacy of penicillin in the treatment of syphilis and other Sexually Transmitted Diseases (STD's). Healthy human subjects were infected with *Treponoma pallidum* and other STD causing organisms. Only 1/3rd of these subjects were treated with penicillin while the other were left untreated. As a result, 83 people died during these experiments.

2.4. Able laboratories Generic Prescription Drugs

All the products of these Able Laboratories have been recalled from the market on May 23rd 2005 by FDA due to some defects in the manufacturing process of the drugs [16], which resulted in either over potent or null potent drugs. Also it was claimed that four of the company managers distributed misbranded and adulterated drugs which resulted in the recall of drugs from the market.

3. Conclusion

Over the years, there has been a significant improvement and advances in the clinical research of the drugs. This is to ensure the drug safety, efficacy and potency. These drugs undergo both pre-clinical and clinical trials from which the results are obtained and this data is submitted to the authorities for review. The authorities after evaluating all these clinical data decide whether the drug has to release in to the market or not. Even, after the release of drug into the market, these authorities keep a close observation on the consumers of these drugs to know whether any long term side effects are present. These clinical trials are not only beneficial for safety, efficacy but also for the economic purposes. These trials are the foundation for the production of new drugs to treat many kinds of diseases. The lack of knowledge of these trials has led to many disasters, for which our history is evidence. These disasters although were very severe, have also led to the development of new rules and regulations for the proper usage of safe and effective drugs.

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