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Table 2. Details of Clinical Trial tragedies and their root cause.

S. No	Name of Tragedy	Date of Approval	Date of withdrawal	Drug in the market	Drug	Medical Authority Holder	FDA approval	Indicated for use in	Trial outcome / adverse effects	Causes	References
1	Tuskegee syphilis Experiment /bad blood/ Doing bad in the name of Good. "Last Chance for Special Free Treatment"	1932	1972	40 years	Penicillin	-	-	Syphilis	Mortality-28 100 subjects died of related complications.	Unethical experiments	[10-12]
2	Sulfanilamide Disaster/Taste of Death/Taste of Raspberry/The 1937 Elixir Sulfanilamide Disaster	September -October 1937	1938	-	Sulfanilamide	S.E. Messing company of Bristol, Tennessee.	-	Streptococcal sore throat infection	Kidney failure, urine stoppage, severe abdominal pain, nausea, vomiting, stupor, Convulsions. Death cases more than 100 in 15 states.	Due to deadly poison diethyl glycol-an antifreeze agent. No regulations established and preclinical trial conducted for safety.	[15, 16]
3	Guatemala syphilis experiment	1946	1948	2 years	Penicillin	-	-	Syphilis	Mortality 83. Morbidity 1500.	Unethical experiments.	[23-25]
4	Thalidomide Tragedy / The Canadian Tragedy	1957	March 2 1962	5 years	Thalidomide	Chemie Grünenthal (German pharmaceutical company)	No	Respiratory infections, insomnia.	Phocomelia/ absent limbs or short limbs /flipper like limbs. Peripheral neuritis. Mortality - 2000 serious birth defects occurred more than 10000.	Lack of scientific data. Human safety data unavailable. Marketing of drug not Approved by regulatory authorities.	[27-31]
5	Clioquinol tragedy (1962-1970)	1960	1970	10 years	Clioquinol	CIBA-GEIGY Japan	-	Diarrhea and gastric disorders.	Cases of SMON (sub acute myeloptic neuropathy) in Japanese people only.	Spinal long tracts lesions and optic tracts e.g. distal dominant axonopathy.	[36-39, 41]
6	Tragedy of Accutane (Isotretinoin)	1982	2009	27 years	Accutane	Hoffmann-LaRoche Inc	Yes	To treat severe acne	Crohan's disease, congenital anomalies, 160 babies affected, depression, etc.	Due to close resemblance to retinoic acid birth defects found.	[42-45]
7	Tragedy of Pergolide (Pergolide)	1988	29-Mar 2007	19 years	Pergolide	Eli Lilly	Yes	To treat Parkinson's disease.	Heart valve damage.	Incompetency of heart valves	[47-49, 51, 52, 76]
8	Baycol disaster (Cerivastatin)	1997	August 2001	4 years	Baycol (Cerivastatin)	Bayer Pharmaceuticals	Yes	Cholesterol Lowering property.	Severe Rhabdomyolysis 31 people died.	Kidney failure resulting in death. Detection of increased levels of myoglobin in blood.	[53-55, 59]
9	Tragedy of Rezulin (Troglitazone)	January 1997	March 2000	3years	Rezulin	Parke-Devis	Yes	Type 2 diabetes.	Liver failure. Morbidity-90. Mortality -63.	Laboratory findings of elevated liver enzymes. Approval of drug even after poor clinical safety data	[60-64]
10	Raplon (Rapacuronium)	1999	March 2001	2 years	Raplon	Organon Inc	-	Muscle relaxant given with anesthetic drug.	Fatal bronchospasm. Morbidity 90.	Premarketing safety results were not significant	[65, 66]
11	Vigor (Vioxx GI Outcomes Research) study	May 1999	September 2004	5. 3 years	(Vioxx) Rofecoxib	Merck	Yes	Anti-inflammatory	Myocardial infarction and stroke. Morbidity-(88,000-140,000) Mortality-27000.	Increased risk of blood clotting.	[68-71]
12	Tragedy of Efalizumab (Raptiva)	2003	September 2009	6 years	Raptiva	Serono Europe Limited	Yes	Moderate to severe chronic plaque psoriasis.	Fatal brain infections e.g. progressive multifocal leukoencephalopathy (PML).	Immune suppression.	[72-74, 76]
13	Tragedy of Lotronex (Alosetron hydrochloride)	9 February 2000	November 2000	0.8 years	Lotronex	Glaxo Smith Kline	Yes	Diarrhea with Irritable bowel syndrome (IBS) in women.	Ischemic colitis. Morbidity-70 Mortality- 3	Inadequate blood flow to the colon.	[76, 77][79, 80]
14	Tragedy of Rimonabant (Acomplia/ Zimulti)	June 2006	October 2008	2 years	Rimonabant	Sanofi-Aventis	No	Treatment of obese patients. Decreasing appetite.	Risk of Psychiatric side effects, severe depression, suicidal ideas, nausea, Vomiting. Mortality-2 people died.	-	[76, 83, 84]

15	Tragedy of Baxtra (Valdecoxib)	November 2001	2005	3. 3 years	Valdecoxib	Pfizer	Yes	Anti-inflam-matory	Cardiac complica-tions e.g. heart attack and stroke.	-	[88, 89]
16	Tragedy of Lumiracoxib	2005	December 2007	2 years	Lumira-coxib	Stellige Frexocel		Symptomatic treatment of osteoarthritis of hip and knee.	Serious liver prob-lems.	Elevated serum transaminase. Detection of auto antibodies	[76, 90, 91]
17	SCOUT Study (Sibutramine cardiovascular Outcome Trial) (Reductil)	1997	9 October 2010	11 years	Sibutramine (Meridia, Reductil)	Abott labora-tories	Yes	Weight loss in obese patients and in over-weight patients.	Serious complica-tions like stroke , Heart attack.	Increased blood pres-sure and tachycardia.	[92, 94]
18	Tragedy of Zelmid	1981	March 83	2 years	Zimelidine	Astra AB	Yes	Antidepressant.	Zimelidine syn-drome, Guillain-Barré syndrome. Suicidal thoughts.	-	[95-98]
19	Tragedy of Tic-rynafin	2 May 1979	1982	3 years	Ticrynafin	Smith Cline	Yes	Hypertension	Hepatitis and Jaundice.	Drug induced liver cell antigens and auto-antigens alteration followed by sensitiza-tion.	[99, 100]
20	Tragedy of Om-niflox (Temafoxacin)	30 January 1992	3 June 1999	5 months	Temafoxa-cin	Abott labora-tories	Yes	To treat lower respiratory infections, genital , Urinary infec-tions.	Temafoxacin syn-drome (Allergic reactions hemolytic anemia, liver and kidney de-fects). Mortality=3	Immune complex formation leading to destruction of red blood cells.	[101-104]
21	Tragedy of Trasylol (Aprotinin)	1993	2007	14 years	Trasylol	Bayer Pharma-ceuticals	Yes	To control bleeding during Heart surgery.	Myocardial infar-cation. Kidney failure. Cardiac failure. Mortality more than 22000.	Approval of drug with unsafe preclinical studies.	[105-107, 109, 110]
22	Clinical trial in Bhopal gas Tragedy. (Unethical clinical trials)	2005	2008	3 years	Tigecycline (Antibiotic)	Wyeth	-	For the treat-ment of skin and soft tissue infections, intra-abdominal infections, hospital pneu-monia, heart attacks and unstable angina.	Severe adverse events. Morbidity -279. Mortality- 12	Post operative hemor-rhage, Ventricular fibrillation, pulmonary embolism.	[111-115]
23	Cytokine storm /North wick Clinical Trial march 2006'The Elephant Man Clinical Trial' / First in Man Trial of TGN 1412	March 2006	-	-	TGN1412 (MONO-CLONAL ANTI-BODY)/ (CD-28 Super MAB)	Boehring-er Ingelhe-im	B cell chronic lymphocytic Leukemia (B-CLL). Rheumatic Arthritis.	Immuno-Modulators.	Erythemia vasodila-tion, hypotension, loss of consci-ousness, renal failure, lymphocytopenia signs of pulmonary deterioration, lung injury disseminated intra-vascular coagulation, monocytopenia, Morbidity- 6 Multi organ failure.	As a result of sud-den and rapid release of proinflammatory cytokines human subjects' mem-ory T-cells lost their sense of direction and started migrating into unwanted areas of the body and induced damage. Dissimilarity of preclinical and clinical results	[116-119]
24	Clinical Trial at AIIMS New Delhi, India.	January 2006	2008	2.5 year	1. Zinc tablets 2. olmesar-tan 3. Valsartan 4. Rituxi-mab. 5. Gene activated human glycocerebr-oxidase	-	Zinc defi-ciency. Blood pres-sure related problem Blood pres-sure Chronic fetal en-cephalitis. For the treatment of Gaucher's disease af-fecting liver.	49 babies died. Mortality rate was 1.18 percent.	Unknown	-	[120, 121]
25	Bill gates polio vaccine program me		2011	-	Oral polio vaccine	-	Polio erad-ication.	-	Non polio acute flaccid paralysis (NPAFP) more severe than polio infection. Morbidity -47500. Mortality-540.	Production of virulent strains by polio vaccine.	[122]

References

- [1]. http://en.wikipedia.org/wiki/Clinical_trial.
- [2]. <http://www.nlm.nih.gov/medlineplus/clinicaltrials.html>.
- [3]. <https://clinicaltrials.gov/ct2/info/understand>.
- [4]. Singh H, Srivastava A (2013) Recent Trends in Scope and Opportunity of Clinical Research in India. *Indian Journal of Research in Pharmacy and Biotechnology* 1(3): 299-304.
- [5]. Lasker SP (2013) History of Clinical Research and Ethics. *Bangladesh Journal of Bioethics* 4(1): 20-29.
- [6]. <http://www.drugstudy.md/resource6.html>.
- [7]. http://www.psoriasisCouncil.org/docs/chapter_01.pdf.
- [8]. <http://www.iupui.edu/~histwhs/G504.dir/irbhist.html>.
- [9]. Katz RV, Russell SL, Kressin NR, Green BL, Wang MQ, et al. (2006) The Tuskegee Legacy Project: Willingness of Minorities to Participate in Biomedical Research. *J Health Care Poor Underserved* 17(4): 698-715.
- [10]. http://en.wikipedia.org/wiki/Tuskegee_syphilis_experiment.
- [11]. <http://www.sciencemuseum.org.uk/broughttolife/techniques/tuskegee.aspx>.
- [12]. Crenner C (2011) The Tuskegee Syphilis Study and the Scientific Concept of Racial Nervous Resistance. *J Hist Med Allied Sci* 67(2): 244-280.
- [13]. <http://www.cgu.edu/pages/1722.asp>.
- [14]. http://en.wikipedia.org/wiki/Belmont_Report.
- [15]. <http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm>.
- [16]. http://en.wikipedia.org/wiki/Clinical_trial.<http://www.thescientist.com/?articles.view/articleNo/35714/title/The-Elixir-Tragedy--1937/>.
- [17]. http://www.independent.org/pdf/policy_reports/2010-02-10-fda.pdf.
- [18]. Wax PM (1995) Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann Intern Med* 122(6): 456-461.
- [19]. http://en.wikipedia.org/wiki/Nazi_human_experimentation.
- [20]. <http://www.jewishvirtuallibrary.org/jsource/Judaism/naziexp.html>.
- [21]. Berger RL (1990) Nazi Science — The Dachau Hypothermia Experiments. *N Engl J Med* 322(20): 1435-1440.
- [22]. http://en.wikipedia.org/wiki/Nuremberg_Code.
- [23]. <http://en.wikipedia.org/wiki/Guatemala>.
- [24]. Cuerda E, Lopez-Munoz F (2013) Ethical Considerations of the Human Research: Syphilis Experiments and Denial of Drug Therapy. *Clin Exp Pharmacol* 3(4): e124.
- [25]. Reverby SM (2012) Ethical Failures and History Lessons: The U.S. Public Health Service Research Studies in Tuskegee and Guatemala. *Public Health Reviews* 34(1): 1-18.
- [26]. http://en.wikipedia.org/wiki/Guatemala_syphilis_experiment.
- [27]. <http://www.thalidomide.ca/the-canadian-tragedy/>.
- [28]. Moghe VV, Kulkarni U, Parmar UI (2008) Thalidomide. *Bombay Hospital Journal* 50(3): 472-476.
- [29]. <https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation>.
- [30]. Thalidomide: <http://en.wikipedia.org/wiki/Thalidomide>.
- [31]. <http://www.theguardian.com/society/2012/sep/01/thalidomide-scandal-timeline/>.
- [32]. Akhurst RJ (2010) Taking thalidomide out of rehab. *Nature medicine* 16(4): 370-372.
- [33]. http://en.wikipedia.org/wiki/Kefauver_Harris_Amendment.
- [34]. Kim JH, Scialli AR (2011) Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. *Toxicol Sci* 122(1): 1-6.
- [35]. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandProviders/UCM222649.pdf>.
- [36]. http://www.locostindia.com/chapter_4/Drug%20Marketing_10.htm.
- [37]. Paul H, Steinbrecher R, Keyek D, Michaels L (2003) Hungary corporations (1st edtn), Zed Books Ltd., UK.
- [38]. Meade TW (1975) Subacute myelo-optic neuropathy and Clloquinol. An epidemiological case-history for diagnosis. *Br J Prev Soc Med* 29(3): 157-169.
- [39]. Tateishi J (2000) Subacute myelo-optico-neuropathy: Clloquinol intoxication in humans and animals. *Neuropathology* 20: S20-24.
- [40]. <http://newint.org/features/1981/01/01/devils/>.
- [41]. Mao X, Schimmera AD (2008) The toxicology of Clloquinol. *Toxicol Lett* 182(1-3): 1-6.
- [42]. <http://www.drugs.com/accutane.html>.
- [43]. <http://www.acne.org/accutane.html>.
- [44]. <http://www.drugwatch.com/accutane/side-effects.php>.
- [45]. <http://www.drugwatch.com/accutane/>.
- [46]. Choi JS, Koren G, Nulman I (2013) Pregnancy and isotretinoin therapy. *CMAJ* 185(5): 411-413.
- [47]. <http://www.drugbank.ca/drugs/db01186>.
- [48]. <http://www.parkinsoninfo.org/?gclid=CK2Ux4yYucICFQ4pjgod648AHg>.
- [49]. <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm078944.htm>.
- [50]. <http://www.healio.com/endocrinology/neuroendocrinology/news/print/endocrine-today/%7Bd41efd98-9475-4378-b54f-baf86b74281e%7D/ pergolide-voluntarily-withdrawn-from-market>.
- [51]. <http://consumer.healthday.com/general-health-information-16/misc-drugs-news-218/parkinson-s-drug-pergolide-withdrawn-over-heart-concerns-603251.html>.
- [52]. <http://en.wikipedia.org/wiki/Pergolide>.
- [53]. <http://www.spacedoc.com/baycol.htm>.
- [54]. <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/302/baycol-cerivastatin-sodium>.
- [55]. Psaty BM, Furberg CD, Ray WA, Weiss NS (2004) Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of Cerivastatin and risk of rhabdomyolysis. *JAMA* 292(21): 2622-2631.
- [56]. <http://en.wikipedia.org/wiki/Cerivastatin>.
- [57]. <http://www.webmd.com/cholesterol-management/news/20050322/baycol-removed-from-market>.
- [58]. <http://www.seegerweiss.com/drug-injury/baycol/>.
- [59]. <http://www.consultox.com/toxicology-baycol.shtml>.
- [60]. <http://www.medicinenet.com/script/main/art.asp?articlekey=12814>.
- [61]. <http://en.wikipedia.org/wiki/Troglitazone>.
- [62]. <http://diabeteshealth.com/read/2000/05/01/4832/rezulin-pulled-after-death-toll-mounts/>.
- [63]. <https://nfb.org/images/nfb/publications/vod/vsum0003.htm>.
- [64]. <http://www.pulitzer.org/archives/6485>.
- [65]. <http://en.wikipedia.org/wiki/Rapacuronium>.
- [66]. <http://www.nytimes.com/2001/03/31/us/anesthesia-drug-is-removed-from-market-after-the-deaths-of-5-patients.html>.
- [67]. <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173891.pdf>.
- [68]. <http://en.wikipedia.org/wiki/Rofecoxib>.
- [69]. <http://money.cnn.com/2004/09/30/news/fortune500/merck>.
- [70]. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108361.htm>.
- [71]. <http://www.pharmaceutical-journal.com/news-and-analysis/feature/still-feeling-the-vioxx-pain/20066485.article>.
- [72]. <http://www.streetdirectory.com/etoday/popular-psoriasis-drug-raptiva-linked-to-deadly-brain-infection-ucpawfu.html>.
- [73]. <http://en.wikipedia.org/wiki/Efalizumab>.
- [74]. <http://www.webmd.com/skin-problems-and-treatments/psoriasis/news/20081016/psoriasis-drug-raptiva-gets-black-box>.
- [75]. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandProviders/UCM143346.pdf>.
- [76]. Gupta SK (2011) Drug Discovery and Clinical Research. (1stedn), Jaypee Brothers Medical Publishers (P) Ltd., New Delhi.
- [77]. <http://en.wikipedia.org/wiki/Alosetron>.
- [78]. <http://www.ibstales.com/lotronex.htm>.
- [79]. <http://www.nytimes.com/2002/06/08/us/us-lets-drug-tied-to-deaths-back-on-market.html>.
- [80]. Moynihan R (2002) Alosetron: a case study in regulatory capture, or a victory for patients' rights? *BMJ* 325(7364): 592-595.
- [81]. <http://www.drugs.com/lotronex.html>.
- [82]. Lewis JH (2010) Alosetron for severe diarrhea-predominant irritable bowel syndrome: safety and efficacy in perspective. *Expert Rev Gastroenterol Hepatol* 4(1): 13-29.
- [83]. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J (2006) Effect of Rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *The Journal of American Medical Association* 295(7): 761-775.
- [84]. <http://en.wikipedia.org/wiki/Rimonabant>.
- [85]. <http://www.bestdietpillreviewsforwomen.com/acompia-review-side-effects/>.
- [86]. http://www.drugs.com/nda/acompia_060217.html.
- [87]. <http://www.dietspotlight.com/acompia-review/>.
- [88]. <http://en.wikipedia.org/wiki/Valdecocix>.
- [89]. <http://www.medscape.com/viewarticle/502642>.
- [90]. <http://en.wikipedia.org/wiki/Lumiracoxib>.
- [91]. <https://espace.library.uq.edu.au/view/UQ:276187>.
- [92]. <http://en.wikipedia.org/wiki/Sibutramine>.
- [93]. <http://www.medscape.org/viewarticle/730515>.
- [94]. Scheen AJ (2011) Sibutramine on Cardiovascular Outcome. *Diabetes Care* 34(Suppl 2): S114-S119.
- [95]. Greenberg G (2013) Manufacturing Depression: The Secret History of a Modern Disease. Bloomsbury Publishing, New Delhi.
- [96]. <http://www.aboutbirthdefects.org/zelmld/>.
- [97]. <http://www.nyupress.org/webchapters/0814736696intro.pdf>.
- [98]. <http://www.vivisionresearch.ca/ch2.htm>.
- [99]. http://en.wikipedia.org/wiki/Tienilic_acid.

- [100]. Neuberger J, Williams R (1989) Immune mechanisms in tienilic acid associated hepatotoxicity. *Gut* 30(4): 515-519.
- [101]. Gentry LO (1991) Review of quinolones in the treatment of infections of the skin and skin structure. *J Antimicrob Chemother* 28: 97-110.
- [102]. Dudley MN (1991) A review of the pharmacokinetic profile of temafloxacin. *J Antimicrob Chemother* 28: 55-64.
- [103]. Finch RG (1993) The Withdrawal of Temafloxacin. Are there implications for other quinolones? *Drug Saf* 8(1): 9-11.
- [104]. http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL49.pdf.
- [105]. <http://en.wikipedia.org/wiki/Aprotinin>.
- [106]. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142720.htm>.
- [107]. <http://www.lawyersandsettlements.com/articles/drugs-medical/trasylol-fraud-00515.html#.VaYlWNKqkko>.
- [108]. Magana DT, Tudor IC, Dietzel C (2006) The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 354(4): 353-365.
- [109]. <http://www.rightinginjustice.com/news/2008/05/26/fda-announces-withdrawal-of-remaining-trasylol/>.
- [110]. <http://www.yourlawyer.com/topics/overview/trasylol>.
- [111]. <http://indiatoday.intoday.in/story/drug-trials-kill-10-bhopal-gas-victims/1/129397.html>.
- [112]. <http://www.independent.co.uk/news/world/asia/from-tragedy-to-travesty-drugs-tested-on-survivors-of-bhopal-6262412.html>.
- [113]. <http://www.ndtv.com/article/india/illegal-drug-trials-on-victims-of-bhopal-gas-tragedy-137952> Illegal drug trials on victims of Bhopal gas tragedy.
- [114]. <http://ibnlive.in.com/news/12-bhopal-gas-tragedy-victims-die-in-drug-trials/272086-3-236.html>.
- [115]. <http://www.thehindu.com/todays-paper/tp-national/tp-newdelhi/bhopal-gas-leakvictims-subjected-to-unethical-clinical-trials/article2345651.ece>.
- [116]. <http://en.wikipedia.org/wiki/TGN1412>.
- [117]. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, et al. (2006) Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412. *N Engl J Med* 355(10): 1018-1028.
- [118]. Sandilands GP, Wilson M, Huser C, Jolly L, Sands WA, et al. (2010) Were Monocytes Responsible for Initiating the Cytokine Storm in the TGN1412 Clinical Trial Tragedy? *Clin Exp Immunol* 162(3): 516-527.
- [119]. <http://www.outsourcing-pharma.com/Preclinical-Research/Northwick-trial-tragedy-scientists-reveal-how-cytokine-storm-started>.
- [120]. <http://timesofindia.indiatimes.com/india/49-babies-die-during-clinical-trials-at-AIIMS/articleshow/3374492.cms?referral=PM/>.
- [121]. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(12\)60855-1/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60855-1/fulltext).
- [122]. <http://nbc.com/2013/05/08/bill-gates-polio-vaccine-program-caused-47500-cases-of-paralysis-death/>.