Influence of Pharmaceutical industry on development of drugs

Harith Dhinakaran and Krish Punyarthi

HSS Day, July 14, 2023

Introduction: Development of a drug by the Industry

- Drugs are developed by the members of the Pharmaceutical Industry (chemists, pharmacologists, toxicologists, pharmacokinetic division, ADME, and clinical research).
- After the chemical is created, and patents have been issued, the drug goes into various animal testings such as acute and chronic toxicity, and studies in ADME.
- Of the thousands of chemicals that are screened, only a few may make it to be labeled for human use.
- The chemical selected for use in humans is then subject to a protocol that needs to be sent to the FDA for approval.
- File the Investigational New Drug Application (IND) with the FDA
- Test the drug in humans and get an approval from the Institutional Review Board (IRB).

Introduction, contd.

- Clinical Research Studies (Phases I, II, and III) are initiated, leading to the submission of a New Drug Application (NDA) to the FDA for marketing approval.
- Published segments of drug development appear in peer-reviewed scientific journals
- Most drug developments proceed smoothly
- However, there have been instances where the drug development process faced challenges and issues.
- Some pharmaceutical industry members acted dishonestly during development
- Shady post-marketing practices were also examined in our research.

Role of industry in managing the data

- Pharmaceutical industry's responsibility to ensure data fidelity in clinical trials
- Compliance with Good Clinical Practices (GCP) Guidelines for accurate data recording and adverse event monitoring
- Adherence to regulatory guidelines set by bodies like the FDA
- Conducting internal audits and quality checks to maintain data accuracy and completeness
- Transparency in reporting: Disclosing all trial data, including negative findings
- Risks of data mismanagement: Major oversights and potential life-threatening issues
- We researched a few cases where members of the pharmaceutical industry were less honest such as in the RECORD 4 trials of rivaroxaban.

Who dropped the ball?

- FDA identified data integrity concerns in the RECORD4 trial of rivaroxaban (Xarelto).
- New investigation initiated after concerns were revived.
- BMJ reported the investigation.
- Phase III trial compared rivaroxaban with enoxaparin for thromboprophylaxis after total knee arthroplasty.
- Rivaroxaban showed superiority in primary efficacy outcome
- FDA reviewed results of the four RECORD trials for rivaroxaban approval and revealed data integrity problems in RECORD4.
- The FDA ultimately approved rivaroxaban in July 2011

Who dropped the ball? contd....

- JAMA viewpoint (2020) highlights irregularities in clinical trials, including the problems in the RECORD4 trial.
- FDA excluded RECORD4 trial from evidence due to numerous and severe violations.
- The Lancet published the study in 2009 without mentioning data integrity problems.
- Authors of the study claim they were not fully aware of the issues.
- The Lancet issued a formal correction and apology in December 2022, acknowledging inaccuracies in the original paper.

Who dropped the ball? contd...

- The BMJ requested Turpie and The Lancet to consider retracting the paper, but they initially deemed the correction and correspondence sufficient.
- The Lancet changed its stance after being presented with details of the FDA review.
- McMaster University will conduct a new investigation into the matter.
- The Lancet follows best practice guidelines and takes scientific misconduct seriously.
- The issues are not expected to impact the clinical use of rivaroxaban.
- Janssen, the drug's marketer, acknowledged the FDA's concerns but stated that the study's safety and efficacy conclusions remain unchanged.

The Development of Rivaroxaban

- Rivaroxaban by Bayer/Janssen was FDA-approved in 2011 as an alternative to heparin for preventing venous thromboembolism (VTE) in knee and hip replacement surgery patients.
- The study included 8,101 patients aged 40 and above, comparing subcutaneous enoxaparin and oral placebo with subcutaneous placebo and oral rivaroxaban.
- Rivaroxaban was found to be noninferior to enoxaparin in preventing VTE for standard-duration thromboprophylaxis in acutely ill medical patients.

The Development of Rivaroxaban contd...

- Both treatments showed similar effectiveness in preventing VTE up to day 10.
- Rivaroxaban carried an increased risk of bleeding despite its effectiveness in preventing VTE.
- Extended-duration rivaroxaban reduced VTE risk compared to enoxaparin followed by placebo at day 35 but increased bleeding risk was observed.

The BMJ Report

- Brook Jackson filed a complaint with the FDA regarding issues in Pfizer's COVID-19 mRNA vaccine clinical trials.
- Jackson reported manipulated data, lack of blinding, and inadequate follow-up on adverse events at three trial sites.
- Only a small fraction of Pfizer, Moderna, and remdesivir trial sites underwent FDA inspections prior to vaccine approvals.

The BMJ Report contd...

- The FDA's oversight of clinical trials was criticized as "grossly inadequate,"
- Site inspections were suspended during the pandemic, despite the need for increased oversight during the rapid development of COVID-19 products.
- The FDA has a history of inadequate oversight, as highlighted by a 2007 report criticizing its auditing of clinical trial sites.
- The FDA responded to the report by creating a task force and implementing new regulations and guidance to enhance trial conduct and participant protection.

The Lancet challenge

- The Lancet Challenge was introduced in 2003 by the editors of The Lancet, Dr. Richard Horton and Dr. Sabine Kleinert.
- The Lancet Challenge called for pharmaceutical companies to provide the raw data of their clinical trials for independent review.
- The goal of the challenge was to promote openness in reporting clinical trials and to ensure that published projects were accurate and unbiased.

The Lancet challenge contd...

- The challenge was introduced in response to concerns that pharmaceutical companies had too much control over the analysis of results, leading to under-reporting of negative results and over-exaggeration of positive ones.
- This could potentially harm patients as healthcare providers rely on published results to make treatment decisions.

The Lancet challenge contd...

- Several pharmaceutical companies responded to the challenge, including GlaxoSmithKline and Pfizer.
- These companies provided free access to the raw data of their clinical trials, which independent researchers reviewed.
- In other cases, the researchers found several cases where the published results didn't accurately represent the raw data, highlighting the need to be more open with the reporting of clinical trials.

The Lancet challenge contd...

- The Lancet Challenge was a huge step towards promoting honesty in the reporting of clinical trials.
- It opened the way for other efforts aimed to improve the reporting of clinical trial results, such as the International Committee of Medical Journal Editors (ICMJE) conditions for clinical trial registration and reporting, and the AllTrials campaign.

The Rezulin story

- Troglitazone was developed by Parke-Davis as the first anti-diabetic drug for patients with insulin resistance.
- It was widely believed that by Rezulin addressing the primary metabolic defect associated with Type 2 diabetes, they would benefit by avoiding the risk of hypoglycemia associated with insulin.
- It was further believed that reducing insulin resistance would potentially reduce the very high rate of cardiovascular disease that is associated with diabetes.
- The FDA’s medical officer assigned to evaluate troglitazone, Dr. John Gueriguian, cited Rezulin's potential to harm the liver and the heart, and recommended against the drug's approval.

The Rezulin story contd...

- Gueriguian and Parke-Davis had a single meeting where Gueriguian would use "intemperate" language.
- Parke-Davis said its objections were based on the remarks made by Dr. Gueriguian.
- Parke-Davis complained to the FDA, and Dr. John Gueriguian was removed from his post.
- Parke-Davis said at the advisory committee that the risk of liver toxicity was comparable to placebo and this was confirmed by other studies.
- The drug was approved on January 29, 1997, and it appeared in pharmacies in late March.
- Dr. Solomon Sobel, a director at the FDA overseeing diabetes drugs, said in a New York Times interview that adverse effects of troglitazone appeared to be rare and relatively mild.

The Rezulin story contd...

- On May 17, 1998, a 55-year-old patient named Audrey LaRue Jones died of acute liver failure after taking troglitazone.
- The patient had been monitored closely by physicians at the National Institutes of Health as a participant in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) diabetes prevention study.
- The NIH responded on June 4 by dropping troglitazone from the study.
- Dr. David J. Graham, an FDA epidemiologist charged with evaluating the drug, had warned on March 26, 1999 of the dangers of using it and concluded that patient monitoring was not effective in protecting against liver failure.

The Rezulin story contd...

- He estimated that the drug could be linked to over 430 liver failures and that patients incurred 1,200 times greater risk of liver failure when taking Rezulin.
- Dr. Janet B. McGill, an endocrinologist who had assisted in the Warner–Lambert's early clinical testing of Rezulin, wrote in a March 1, 2000 letter to Sen. Edward M. Kennedy (D-Mass.): "I believe that the company... deliberately omitted reports of liver toxicity and misrepresented serious adverse events experienced by patients in their clinical studies."
- On March 21, 2000, the FDA withdrew the drug from the market.

The story of Atul Laddu's personal experience.

- Data showed that the drug had a high incidence of fainting/dizziness in the elderly.
- When the data was presented to Atul's boss, the boss asked Atul to get the data reanalyzed since the incidence of dizziness was very high, and he could not show this data to his boss.
- Atul got the data reanalyzed, the incidence of dizziness did not change, and the boss continued to ask Atul to get the data reanalyzed since he could not show that data to his boss.
- Finally it dawned on Atul that the boss wanted Atul to change the data to a lower incidence of dizziness, a thing that Atul was not ready to do due to his high level of honesty and integrity.
- Atul resigned from his lucrative post on the spot, rather than resort to dishonesty.

Making claims for non approved indications

- These are some frequently asked questions about direct-to-consumer (DTC) advertising.
- FDA requirements, as well as activities of the Office of Prescription Drug Promotion (OPDP) do not require following any specific guidelines, and leaves the marketing efforts to the integrity of the company.
- In most cases, federal law does not allow the FDA to require that drug companies submit ads for approval before the ads are used.

Making claims for non approved indications contd...

- We see many ads at about the same time the public sees them.
- Many drug companies release ads based on the vision of the vice president of marketing. However, if the ad violates the law, the FDA sends a letter to the drug company asking that the ads be stopped right away.

Making claims for non approved indications contd...

- Except in unusual instances, the FDA does not require drug companies to submit ads for approval before they are used.
- Drug companies must only submit their ads to the FDA when they first appear in public.
- This rule is the same whether the ads are aimed toward healthcare providers or consumers.
- Consumers should know that they may not necessarily be able to tell whether any specific DTC ad includes false or misleading information.

Making claims for non approved indications contd...

- So the FDA gives a lot of freedom for the drug company to handle its marketing after the drug has been approved.
- However, it depends on the honesty of the members of the company to follow the instinct of truth, that each one of us must follow.

JAMA article

- In a recent article, “Efficacy and Safety of Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Danuglipron for Glycemic Control Among Patients With Type 2 Diabetes: A Randomized Clinical Trial” by Saxena, Frias, Brown, et al that was published in JAMA.
- Different doses of danuglipron or placebo were administered to each group.
- Primary efficacy endpoint: Change in glycated hemoglobin (HbA1c) levels at week 16.
- Secondary endpoints: Changes in fasting plasma glucose (FPG) levels and body weight.

JAMA article contd...

- Danuglipron, at various doses, led to a significant reduction in glycated hemoglobin (HbA1c) levels compared to placebo.
- The proportion of participants achieving HbA1c levels below 7% was higher in the danuglipron groups.
- Fasting plasma glucose (FPG) levels significantly decreased in all danuglipron groups compared to the placebo.
- Body weight reductions were observed in the higher-dose danuglipron groups.
- The safety profile of danuglipron was generally favorable, with a similar incidence of adverse events across treatment groups.

JAMA article contd...

- "The study of patients with T2D, danuglipron demonstrated an efficacy and safety profile consistent with peptidic glucagon-like peptide 1 receptor agonists, without injection or fasting restrictions."
- It should be noted that 5 of the 7 authors were from the manufacturer, Pfizer.
- We hope that the data is a honest effort and has transparency and independent verification of findings that are crucial in such circumstances.

Conclusions

- There is an ongoing debate about whether the pharmaceutical industry should play a role in writing articles that report on the results of clinical trials.
- Some think that industry involvement can make sure that the articles are written in a more accurate and credible way because they are very close to the actual data.
- Others, however, argue that industry involvement can lead to biased reports and results, with a chance of reducing the impact of negative findings and emphasizing the positive ones a little more.
- They also think that the financial interests of the industry can lead to biased reports that are inaccurate and in favor of the companies that create them, which could lower the credibility of the research.
- Each drug company is expected to abide by the instructions given in the package insert (PI) and not go overboard to make outlandish, undocumented claims for the drug efficacy and safety.

Conclusions, contd...

- Overall, while industry involvement in writing articles that report clinical trial results can have its advantages, it's also important to make sure this involvement is kept open, and that any possible conflicts of interest, such as financial interests, are managed with caution and honesty.
- This can be done through ways such as being honest, asking authors to reveal their financial relations to the industry, and through the process of professional peer review.
- In our research, we have attempted to cite a few examples where someone from the industry dropped the ball and the real facts from the data were concealed.
- Our message to the workers in pharmaceutical companies is that honesty is the best policy, and before anyone even thinks of venturing into the area of changing the results, or making deceptive marketing claims, the thought that, "What if I am given this drug by my physician, will I take it?" should come to their mind.

Acknowledgements

We would like to thank Dr. Atul Laddu, the GTF board, and our family for their full support throughout this project.

References

- Rivaroxaban: Lancet opens investigation into anti clotting drug trial after BMJ report: https://www.bmj.com/content/379/bmj.o3071
- Effect of Rivaroxaban vs Enoxaparin on Major Cardiac Adverse Events and Bleeding Risk in the Acute Phase of Acute Coronary Syndrome: The H-REPLACE Randomized Equivalence and Noninferiority Trial: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2801235
- BMJ Investigation: FDA oversight of clinical trials is "grossly inadequate," say experts: https://www.bmj.com/content/379/bmj.o2628
- Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients: https://www.nejm.org/doi/full/10.1056/NEJMoa1111096
- RECORD4 Trial of Rivaroxaban, Published in 2009, Still Turning Heads: https://www.tctmd.com/news/record4-trial-rivaroxaban-published-2009-still-turning-heads

References continued...

- Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies: http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf
- Singh, Yashaswini, Matthew D. Eisenberg, Mathew, and Sood, Neeraj: Factors Associated With Public Trust in Pharmaceutical Manufacturers, JAMA, 6, 1-4, 2023: https://jamanetwork.com/searchresults?author=Matthew+D.+Eisenberg&q=Matthew+D.+Eisenberg
- https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2805054