Trust in Pharmaceutical Companies

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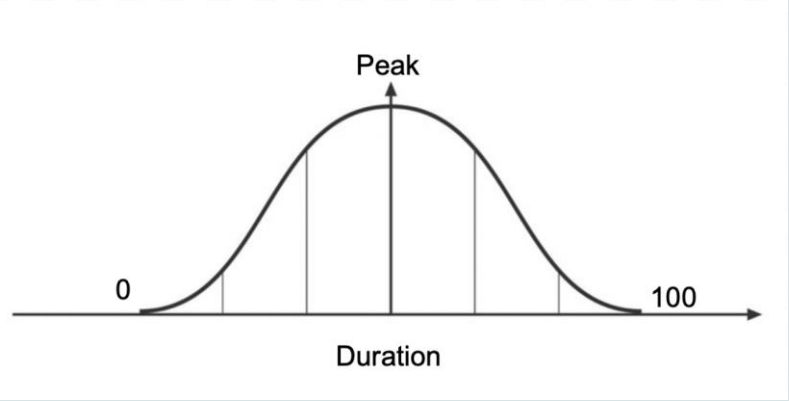
INTRODUCTION

Patients trust that what they receive from the pharmaceutical company contains the correct active ingredients in the correct amounts, that the inactive ingredients function as intended, that they don't contain other harmful substances, and have been tested in animals as well as in humans. Clinical studies are conducted and submitted to the FDA for approval. In a business that relates to fundamental aspects of health and well-being, a key ingredient of trust is transparency, especially around clinical trials and science. We need to make every effort to raise pharma’s credibility with the public. The industry must carry these functions forward by emphasizing compassion, embracing shared goals, and committing to flexibility and agility.

Clinical Development of a drug by the Industry: Phase 1

- Clinical trials typically are conducted with a small number of healthy volunteers, typically fewer than 100, to determine the safety, tolerability, and pharmacokinetics and pharmacodynamics of the potential drug
- Absorption, Distribution, Metabolism, and Excretion (ADME) in human subjects
- Area Under the Curve
- Onset of action: The time it takes for a drug to take action after it is administered
- Peak: The time that the drug takes to reach its peak action
- Duration of action: The time elapsed from when the drug has been administered to when it has completely left the body.
- Half life: The half life of a drug is the time it takes for the substance's presence in the body to be reduced by half.



Clinical Development of a drug by the Industry: Phase 2

- Phase II clinical trials begin if the drug successfully passes Phase I testing.
- This phase generally involves between 100 and 500 patients to assess the efficacy and dose response of the investigational drug in development, including identification of common, short-term potential side effects.
- Phase II studies typically last several months to two years.
- Absorption, Distribution, Metabolism, and Excretion in patients.

Clinical Development of a drug by the Industry: Phase 3

- Phase III studies are then initiated to test the medication on larger groups of patients
- Phase III clinical trials are initiated if the potential new medication is found to be both safe and efficacious through Phases I and II testing
- Phase III trials may enroll 1,000 to 5,000 patients or more across numerous clinical trials sites across states and around the world
- These randomized, controlled trials generate large amounts of data to support submission to the FDA for approval. Phase III studies typically last one to four years.
- Phase 4 is the post-marketing phase

Who Dropped the Ball?

Record 4 trial of Rivaroxaban, DOAC

1. BMJ (British Medical Journal) reported the investigation.

2. Phase III trial compared rivaroxaban with enoxaparin for thromboprophylaxis after total knee arthroplasty.

3. Rivaroxaban showed superiority in primary efficacy outcome

4. FDA reviewed results of the first three RECORD trials for rivaroxaban approval and revealed data integrity problems in RECORD4.

5. The FDA ultimately approved rivaroxaban in July 2011

6. JAMA (Journal of American Medical Association) viewpoint (2020) highlights irregularities in clinical trials, including the problems in the RECORD4 trial.

7. FDA excluded RECORD4 trial from evidence due to numerous and severe violations.

Who Dropped the Ball? (contd.)

8. The Lancet published the study in 2009 without mentioning data integrity problems.

9. Authors of the study claim they were not fully aware of the issues.

10. The Lancet issued a formal correction and apology in December 2022, acknowledging inaccuracies in the original paper.

11. The BMJ requested Turpie and The Lancet to consider retracting the paper, but they initially deemed the correction and correspondence sufficient.

12. The Lancet changed its stance after being presented with details of the FDA review.

13. The Lancet follows best practice guidelines and takes scientific misconduct seriously.

The issues are not expected to impact the clinical use of rivaroxaban.

Who Dropped the Ball? (contd)

15. Janssen, the drug's marketer, acknowledged the FDA's concerns but stated that the study's safety and efficacy conclusions remain unchanged.

16. 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.

17. The study included 8,101 patients aged 40 and above, comparing subcutaneous enoxaparin and oral placebo with subcutaneous placebo and oral rivaroxaban.

18. Rivaroxaban was found to be noninferior to enoxaparin in preventing VTE for standard-duration thromboprophylaxis in acutely ill medical patients.

19. Both treatments showed similar effectiveness in preventing VTE up to day 10.

20. Rivaroxaban carried an increased risk of bleeding despite its effectiveness in preventing VTE.

21. Extended-duration rivaroxaban reduced VTE risk compared to enoxaparin followed by placebo at day 35 but increased bleeding risk was observed.

Pfizer’s COVID-19 vaccine story

- 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 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 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 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.
- 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.

The Rezulin Story (contd.)

- 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.
- 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.

The Rezulin Story (contd.)

- 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.
- 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.

Atul Laddu’s Personal Experience

- Atul Laddu was working on a drug for treating prostate enlargement.
- Upon completion of the clinical studies, the incidence of dizziness was found to be an alarming one percent.
- While discussing the results with his supervisor, the supervisor made a comment that this incidence was too high and recommended that the data be reanalyzed.
- Upon reanalysis of the data, the incidence of dizziness did not change.

Atul Laddu’s Personal Experience (contd.)

- The supervisor insisted that he was not willing to submit this data to the FDA, because of the high incidence of dizziness.
- At this time, it dawned on Atul Laddu, the real motive of the supervisor, which was change the data to reduce the incidence, a clear indication of dishonesty.
- At this time, Atul Laddu resigned from his post due to his firm belief in professionalism and honesty.

Making claims for unapproved 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.
- 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 unapproved 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.
- 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.

The 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.
- 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 levels significantly decreased in all danuglipron groups compared to the placebo.

The Jama Article (contd.)

- 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.
- “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.

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