BENEFIT RISK FRAMEWORKS

Introduction to safety sciences

ABSTRACT

A COMPARATIVE ANALYSIS OF BENEFIT-RISK

FRAMEWORKS FOR DRUGS, BIOLOGICS, AND

MEDICAL DEVICES.

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NAVIGATING THE RISK LANDSCAPE: A COMPARATIVE ANALYSIS OF BENEFIT-RISK FRAMEWORKS FOR DRUGS, BIOLOGICS, AND MEDICAL DEVICES.

Introduction:

Safety science is the concept of continuously collecting and analyzing data across the lifecycle of a drug/device/biologic's development and marketed use to understand how the drug/device/biologic impacts the human body and therefore, patient safety. (Russak, 2023, week-1 p. 22).

safety and efficacy of new medical products are the most important factors in the healthcare industry. A comprehensive framework is necessary to evaluate the potential benefits and risks that are associated with these products to achieve this goal of safety and efficacy. In the US, the FDA uses a robust Benefit: Risk (BRF) framework to guide its decision making throughout the product lifecycle. The concepts of safety science and pharmacovigilance, which are essential for locating, evaluating, and reducing possible risks, are largely relied upon in this framework.

Pharmacovigilance is the practice of active and systemic safety monitoring in clinical trials and in the post-marketing setting: applied in both pre-and post-approval settings. (Russak, 2023, week-1 p. 34). Pharmacovigilance involves activities such as collecting and analyzing data on adverse events, identifying new safety signals, and communicating safety information to healthcare professionals and patients.

SECTION-1

BENEFIT-RISK FRAMEWORK FOR NDAS/BLAS

Benefit-risk assessment in FDA's drug regulatory context is making an informed judgment as to whether the benefit of the drug outweighs the risk under the conditions of use described in the approved product labeling. (USFDA 2023, p. 4).

Risk With Regard To New Drug

Risk is the combination of the probability of occurrence of adverse event and severity of that adverse event is called risk. The risk can be occurred in multiple ways, which include Adverse events, serious adverse events, off-label use, Abuse, and misuse. The risk can be measured by identifying and characterizing the nature, frequency and severity of the risks associated with the use of the product. (Russak, 2023, week-4 p. 22).

Pre and Post -Market Risk Related Activities:

The benefit risk assessment is impacted by the decisions taken by the sponsor during the process of drug development. The decisions and activities by the sponsor are crucial for the sponsor's own drug development program and there is a necessity for building in long-term safety studies as appropriate with an open label or with some sort of control. FDA's framework involves the analysis of the condition, where the disease or condition are specified for the treatment and the intended effect of the treatment is described. The framework also includes current treatment options that are available (FDA approved), and its benefits along with emphasis on the risk and risk management. The understanding of current treatment landscape is crucial for evaluating the potential value of a new therapy. This analysis should identify the

limitations of existing options and highlight the unmet medical needs of the target population. The benefits are described in a structured manner which indicates a clear and concise picture of the potential value of the new therapy can be presented. This information is crucial for regulators and healthcare professionals when evaluating the overall benefit-risk profile of the drug and making informed decisions about its use.

There is also an element of uncertainty which potentially has an influence on benefit-risk assessment of novel drug, the FDA's approach to uncertainty varies based on the therapeutic context where greater uncertainty may be accepted for drugs treating serious diseases with unmet needs, especially through accelerated approval pathways and less uncertainty is accepted for drugs treating non-serious diseases with existing treatment options. The FDA strives to make informed decisions about benefit-risk assessment, considering both the potential benefits and risks for patients.

Pre- And Post-Market Regulatory Guidance And Reporting Tools For Gathering And Analysis Of Risk-Related Information About Novel Drugs/Biologics:

Obtaining enough information while developing to understand dose-exposure-response relationships for safety & tolerability as well as efficacy and combining this information to determine doses that can increase the advantages in relation to risk and guide dosing recommendations.

1. A performance-based assessment, a report from a patient, a non-clinician observer, or a clinician can all be used to evaluate a clinical outcome. Patient-reported outcome (PRO),

clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO), and performance outcome (PerfO) are the four categories of COAs. (USFDA 2023, p. 18).

2. ICH Guideline E6: Good Clinical Practice (GCP) This guideline provides internationally recognized standards for conduct, design, auditing, performance, monitoring, recording, analyses, and reporting in clinical experiments.
3. EMA Guideline on Good Manufacturing Practice (GMP) This guideline outlines the quality standards that must be met by manufacturers of medicines for human use.
4. FDA Adverse Event Reporting System (FAERS) This database collects reports of adverse events that occur in patients who are taking drugs or biologics.
5. Using a predictive biomarker for the recognition of patients who are susceptible to encounter benefit or less likely to experience serious adverse event.
6. MedWatch This program allows healthcare professionals and consumers to report adverse events to the FDA.
7. EMA EudraVigilance database This database collects reports of adverse events that happen in patients who are taking drugs or biologics in the European Union.
8. PPI (Patient Preference Information) is helpful at different phases of drug development process, such as when determining endpoints, defining the therapeutic context, and assisting with benefit-risk analysis. PPI studies can reveal which characteristics matter to patients, how significant they are, and what compromises they are willing to make.
9. Post-market evidence to support benefit-risk assessments can be obtained from a variety of sources, such as the medical literature, post-marketing studies, adverse event reports, medication error reports, product quality reports, REMS assessment reports, patient experience data, and, in some cases, new data from medications in the same class.

SECTION -2

BENEFIT: RISK FRAMEWORK FOR NEW MEDICAL DEVICES

Risk In Context Of Medical Devices:

A potential harm of a medical device's use to patients, end. Users and environment, which includes the harm of the device if it were to fail in normal and fault conditions, i.e., not operate as intended. (Tartel, 2023, p. 8).

Risks can be measured by various factors such as severity of harm, which has three levels, that are: Medical device-related deaths and serious injuries, medical device related non serious injuries, medical device related events without reported harm.

- Risk can also be measured by the probability of the medical device having problem and the probability of a patient having an experience of harm, and the total number of patients exposed.
- Risk can also be measured by the number of non-conforming devices has been distributed and are on the market.
- Risk can also be measured by the amount of time between a patient's first exposure to a device that has a known risk of harm and the point at which that risk is successfully managed is also known - the duration of exposure to population.
- Risk can also be measured by the occurrence of false-positives and false-negatives during the diagnosis.

Risk is an essential part in the classification and selection of appropriate approval pathway. There are basically 3 classes that the medical devices are classified into, they are:

a) Class I b) Class II c) Class III

a) **Class I Devices**: According to FDA and the EU, Class I medical devices are the lowest category of medical devices, these are typically considered safe and effective with minimum potential for harm. Class I devices don't require clinical trials and are exempt from premarket approval but require registration and compliance with general controls. Examples of Class I devices: Surgical drapes, Hand-held mirrors, non-electric wheelchairs.
b) **Class II Devices:** The class II devices are moderately risky, typically non-invasive. These devices are subject to more stringent regulatory requirements compared to class I devices. They require premarket notification of 510K application demonstrating substantial equivalence to an already marketed device. If there is a submission of513(g) application to reclassify the device as de novo device, the next step would be to file for PMN 510(K). This takes about 4.5 years' time in FDA and 11 months in EMA. If it is not approved by de novo, it follows the pathway of submitting PMA and IDE applications in anticipation of conducting clinical trials. Examples of Class II devices: Catheters, syringes, lenses.
c) **Class III Devices**: The class III devices are the devices with maximum risk, they represent the most complex and potentially dangerous devices used in health care. Class III devices are divided into:

1. Classification Based On Clinical Risk: This involves the submission PMA and IDE applications in anticipation of conducting clinical trials. Consult early with FDA regarding need for and type of clinical studies.
2. Classification Based On Default Classification Of A New Device: If the device has a predicate, then PMN can be submitted, if it does not have the predicate follows the path of 510(K) submission via 513(g) application (21 CFR 807). This process takes about 4.5 years. Examples of class III devices: deep-brain stimulators, pacemakers.

Pre-Market And Post-Market Risk Related Activities:

a) Pre-market approval/PMA process: The manufacturer is required to provide proof that the new device is safe and effective, usually in the form of clinical data.
b) Pre-market notification or 510(K) process: The manufacturer must prove to the FDA that the new device is essentially the same as one that is already lawfully available on the market and does not need a PMA.
c) A significant part of the FDA's post market duties is supervising recalls. FDA advice the recalling firm of the assigned recall classification and posts information about the recall in its weekly enforcement report.

Pre- And Post-Market Regulatory Guidance And Reporting Tools For Gathering And Analysis Of Risk-Related Information About Novel Medical Devices:

- MedWatch form (form FDA 3500A) is used for all device reporting, both for pre and post market, this includes 5,10,30-day reporting for devices.

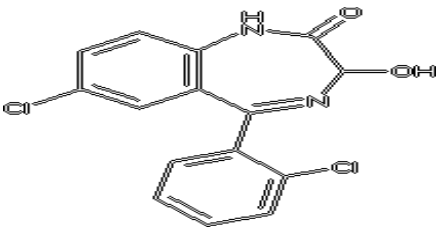
- 21 CFR 803, specifies how adverse events connected to medical devices must be reported to the Food and Drug Administration (FDA). Within 30 days reporting for adverse events, within 5 days reporting for deaths and 15 days reporting for serious injuries.
- MAUDE is a database maintained by the U.S. Food and Drug Administration (FDA) that tracks adverse events associated with medical devices and in vitro diagnostics.
- A risk management plan (RMP) outlines the processes and procedures for identifying, assessing, controlling, and monitoring risks associated with a product throughout its lifecycle.
- MDR reporting is for manufacturers, importers, and device user facilities to report certain device-related adverse events and product problems to the U.S. Food and Drug Administration (FDA).

SECTION-3

LORAZEPAM

Background: Lorazepam is also known by the brand name Atvin. This a medication belonging to the class of benzodiazepines. This drug is short-acting and used as a sedative and prescribed to treat anxiety disorders, insomnia.

STRUCTURE:



Class: Benzodiazepines.

Chemical Name: 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one

RISK (SAFETY INFORMATION):

a) **Preclinical Data From Animal Studies:**

- This study investigated the anti-anxiety effects of memantine in mice using two common anxiety models: the open field test and the passive avoidance response test. Memantine alone did not show significant anti-anxiety effects initially, but after 7 days of daily treatment, it significantly reduced anxiety-like behaviors in both tests. These effects included increased exploration in the open field, decreased freezing time, and improved performance in the passive avoidance task. Interestingly, combining memantine with lorazepam, a standard anti-anxiety medication, produced a synergistic effect, further enhancing the anti-anxiety response. Overall, this study suggests that memantine has potential as a novel treatment for anxiety disorders.

b) **Clinical Trial Data From Human Studies:**

- Study Summary: 2006-001085-17

  Purpose: This study investigates whether the anti-anxiety medication lorazepam, in two different doses, can effectively alleviate anxiety induced by inhaling 7.5% carbon dioxide in healthy volunteers. This model aims to simulate generalized anxiety disorder (GAD).

Participants: 18 healthy male adults (average age 20.6 years) participated in a double-blind, crossover study. They received each of the three treatments (lorazepam 2mg, lorazepam 0.5mg, and placebo) on separate days with one-week washout periods in between.

Treatments: Lorazepam 2mg: One-off dose, Lorazepam 0.5mg: One-off dose

Placebo: Matched capsule

Outcome Measures: The study primarily assessed anxiety levels using various scales (PSI, GAD-C, VAS Fearful, VAS Stressed) before, during, and after the carbon dioxide challenge on each test day.

Results: Both lorazepam doses significantly reduced anxiety compared to placebo on some measures, but not all and lorazepam 2mg showed a statistically significant effect on VAS Fearful and VAS Stressed scores at specific time points. No serious adverse events were reported. Non-serious side effects were mild and primarily related to drowsiness and dizziness.

Conclusion: This study provides evidence that lorazepam, particularly at the higher dose of 2mg, can effectively reduce some aspects of anxiety induced by the carbon dioxide challenge in healthy volunteers.

Post-Market Surveillance Data:

The FDA Division of Pharmacovigilance (DPV) reviewed adverse event reports submitted to the FAERS database for Ativan Injection (lorazepam injection) in pediatric patients

(age 0-17 years) from 1980 to 2018.A total of 126 U.S. FAERS pediatric reports with a serious outcome were identified and after excluding duplicates and cases for various reasons (labeled events, alternative causes, insufficient information), only one non-fatal serious case remained for discussion. This case involved a 9-year-old girl who experienced hallucinations and oculogyric crisis after receiving lorazepam injection. The report lacked further details, making it difficult to assess the causality of the events. A search for additional cases of oculogyric crisis with lorazepam injection in both adults and children yielded no further results.

Conclusion: Based on the limited data available, the DPV did not identify any new safety concerns for lorazepam injection in pediatric patients.

REMS **Of Lorazepam**:

FDA doesn't have any specific REMS for Lorazepam but have several recommendations for the safe use of lorazepam, which are:

- Lorazepam is not recommended to the patients who are hypersensitive to benzodiazepines or to similar components of that formulation.
- Lorazepam is not recommended to the patients with acute narrow angle glaucoma.
- Death, coma, respiratory depression, sedation may be caused due to the use of combinations of opioids and benzodiazepines.
- If there is a necessity to prescribe lorazepam with opioids, it is recommended to prescribe the lowest effective dosages and the shortest possible times for concurrent use and keep a close eye out for any signs or symptoms of sedation or respiratory depression in the patients.

- Lorazepam use may cause pre-existing depression to surface or worsen.
- Lorazepam can be habit-forming, may lead to physical and psychological dependence and may also lead to drug abuse.

Labelling Information:

Name: Lorazepam **Brand**: ATIVAN

Indications And Uses: Anxiolytic - sedative.

Dosage And Administration: a) Oral Tablets: 0.5 mg, 1 mg, 2 mg. b) Sublingual Tablets: 0.5 mg, 1 mg, 2 mg.

Contraindications And Warnings: Patients with myasthenia gravis, acute narrow angle glaucoma, and those with a history of benzodiazepine hypersensitivity should not take Ativan (lorazepam).

Precautions And Side-Effects:

- There is a possibility of begetting Suicidal thoughts due to the use of lorazepam. So, it is not recommended to use this drug without adequate anti-depressant therapy.
- Patients who are elderly or disabled may be more vulnerable to lorazepam's sedative effects. So, the drug's dosage should be frequently monitored and adjusted according to the reaction of the patients.

- In children and elderly patients, there is a chance of occurrence of paradoxical reactions due to exposure to lorazepam. The use of drug should be stopped if this case is observed.
- Lorazepam should be used cautiously in patients with severe hepatic insufficiency and/or encephalopathy because it can worsen hepatic encephalopathy. So, the dosage should be carefully monitored and be adjusted to the response of the patients.

CONCLUSION

FINDINGS AND ANALYSIS

According to me I would say that there are still areas where improvement can be made to further enhance safety and public trust. The areas that need improvement are:

Pre-Market Approval:

- Strengthening pre-clinical and early-phase clinical trial design: Addressing concerns about limited data on long-term safety and efficacy, particularly for novel and complex drugs and devices.
- Enhancing diversity and inclusion in clinical trials: Ensuring trials better represent the population who will use the product, leading to more generalizable safety data.
- Improving risk assessment methodologies: Developing more robust and standardized methods for identifying and evaluating potential safety risks, especially for emerging technologies and personalized medicine.

- Streamlining the approval process for low-risk devices and drugs: Reducing unnecessary burdens for low-risk innovations while maintaining adequate safety standards.

Post-Market Surveillance:

- Improving adverse event reporting systems: Addressing underreporting and streamlining reporting processes for both healthcare professionals and consumers.

  Strengthening post-market surveillance activities: Implementing more robust and proactive monitoring systems to identify potential safety issues early on.

  Utilizing real-world data (RWD) and artificial intelligence (AI): Leveraging these technologies to analyze large datasets and identify safety signals that might be missed through traditional methods.

  Enhancing transparency and communication: Providing clear and timely information to the public about safety concerns and regulatory actions taken.

  Promoting patient education and engagement: Empowering patients to make informed decisions about their medical care and report potential safety issues.

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