Analysis of Real-World Evidence Role in US FDA Approvals of Novel Drugs and Post Marketing Requirements of RWE Study (Novel Drug Approvals US FDA 2023)

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INTRODUCTION

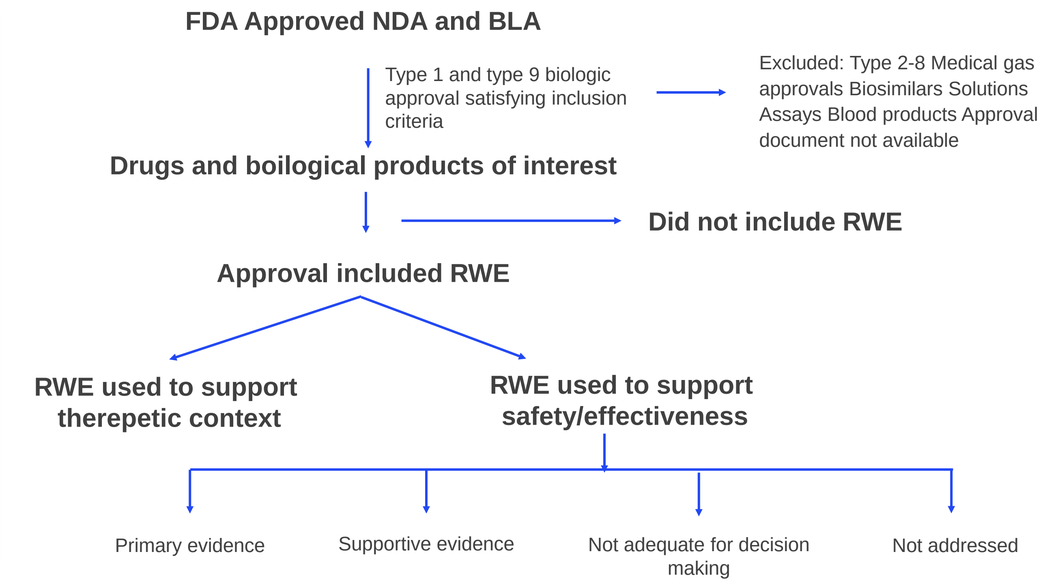
- The US Food and Drug Administration (FDA) is open to accepting real-world evidence (RWE) to support its assessment of medical product . This is reflected in 12 RWE guidance issued by FDA (2018 – Sep 2024) [1]
- The relevance and significance of RWE contribution in facilitating regulatory approvals depends on multiple factors including lack of understanding of FDA's evidentiary expectations for the use of RWE in applications for new drugs and biologics.[2]
- Due to the focus on development of complex drugs for targeting highly selected patient groups, traditional trials may lack the feasibility to generate pivotal evidence or limited evidence ability for all relevant questions (e.g .heterogeneity of treatment effects, or long-term effects in gene therapies) [2]

OBJECTIVE

- Analyse RWE Role in US FDA Approvals of Novel Drugs and Post Marketing Requirements of RWE Study(Novel Drug Approvals US FDA 2023)
- Analyse trends and patterns of use of RWE in drug approvals, and derive insights for designing patient-centric trials

METHOD

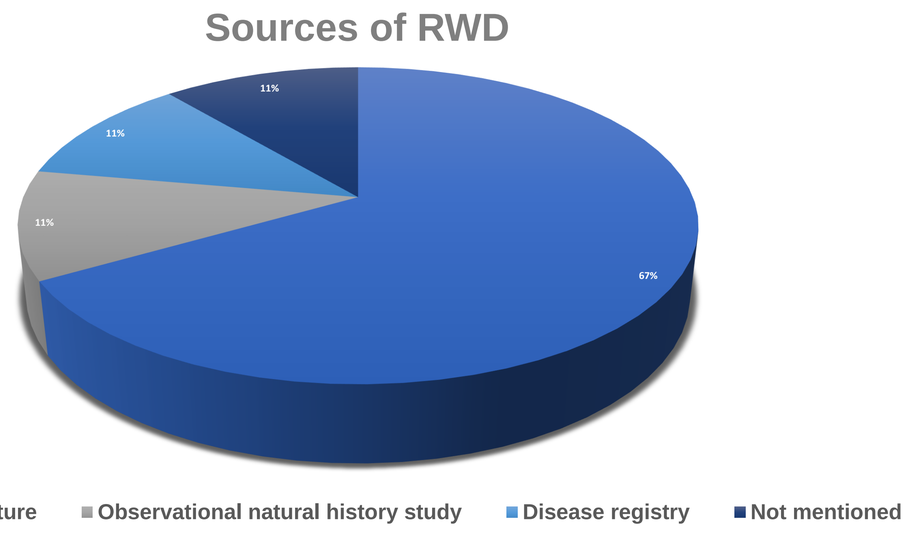
- All novel drug approvals including NDA (New Drug Application) and BLA (Biological License Application) submitted in 2023 by respective sponsors, were identified from Center for Drug Evaluation and Research(CDER) and Drugs@FDA were extracted and analyzed.
- The submission package data supported with RWE were segregated based on therapeutic areas.
- Sub categorization of two mutually non-exclusive groups:
  - *RWE used to support approvals from therapeutic context (e.g., epidemiology, natural history, incidence, or prevalence of the disease*
  - *RWE used to support safety and/or effectiveness which were further stratified into primary, supportive, not adequate for decision. The approvals were further analysed for to identify post marketing study (PMS) requirements with recommendation of adopting RWE Study design for PMS.*
- To measure whether the study was supportive of the benefit-risk assessment, preliminary review of FDA documentation and classified studies as informing FDA's benefit-risk assessment if they provided substantial evidence (by CDER), primary evidence (by CBER), or supportive evidence.
- Studies that were classified as not informing benefit-risk assessment were those that, from the FDA reviews, appeared inadequate to support FDA's decision making, or were simply not addressed in the reviews.



ANALYSIS OUTCOMES

- Total Number of Novel Drug Approvals in 2023 = 55
- Total no. of Novel Drug Approval submission package analyzed = 55
- Total number of NDA which included RWE component=22
- Total no. of BLA which included RWE = 7
- Total no. of NDA which included RWE = 15
- Total number of non-mutually exclusive categories of RWE which were included for NDA application=9
- RWD as a Historical Control Arm/External Control Arm/Synthetic Control Arm = 2
- RWE used to support the application's therapeutic context (e.g., prevalence and incidence of a disease) = 4
- RWE studies to support the demonstration of product safety and/or effectiveness = 5
- RWD evidence rejected by FDA = 1
- Number of post marketing requirements in the form of RWE study design = 12

REAL WORLD DATA SOURCES FOR RWE SYNTHESIS OF FDA APPROVALS



CHALLENGES IN USE OF RWE OF REGULATORY APPROVALS

- **Data Quality**: The variation , accuracy, completeness , reliability and quality of real-world data (RWD)
- **Data Standardization**: lack of standardization in the collection and analysis of RWD, inducing complexities in data comparison across different sources.
- **Data Privacy**: Patient privacy , Data De Identification and Anonymization challenges
- **Methodological Issues**: Developing appropriate methods for analysing and interpreting RWE, including issues related to confounding, bias, and generalizability.
- **Regulatory Acceptance**: There is a need for greater clarity and consistency in the regulatory framework for the use of RWE in regulatory decision-making
- Despite these challenges, the FDA has recognized the potentials and issued 12 guidance documents on the use of RWE in regulatory decision-making.

FUTURE OUTLOOK

- Strategic use of RWE will continue to evolve and become more integral in regulatory frameworks. By adhering to the recommendations outlined, stakeholders can leverage RWE more effectively, ensuring that it contributes to safer, effective, and efficient drug approval processes.
- Industry needs to adopt innovative technology solutions like Generative Artificial Intelligence for scanning the approvals with RWE components and leverage it as critical reference for evidence generation planning, including Randomized Controlled Trials Planning
- This proactive approach will not only benefit regulatory bodies and pharmaceutical companies but ultimately enhance patient outcomes and public health.

CONCLUSIONS

Overall Integration of RWE:

- Approximated 40 % of the NDA approvals included RWE as part of the regulatory dossier.
- This signifies a notable adoption of RWE in the drug approval processes for 2023
- The use of RWE varies widely across different therapeutic areas and drug types, indicating a selective yet strategic utilization aimed at enhancing the robustness of the regulatory submissions

Therapeutic Areas and RWE Utilization:

- RWE was predominantly used in therapeutic areas where traditional clinical trials face challenges due to ethical concerns, rare diseases (2 approvals includes RWE), or where patient recruitment is difficult.
- This utilization highlights RWE's capability to provide critical insights that might not be feasibly captured through conventional clinical trials alone.

Impact of RWE on Regulatory Decisions:

- The drugs that included RWE , leveraged this evidence to support various aspects of their applications, such as extending understanding of drug efficacy and safety profiles in real-world settings beyond the controlled clinical trial environments.
- This suggests that RWE is not merely supplementary but is increasingly considered integral in certain contexts, potentially influencing FDA's decision-making process towards a more favorable outcome.

Comparison with Historical Data:

- When compared to data from previous years, the 40% integration rate of RWE in 2023 represents an increase, indicating a gradual but steady acceptance and recognition of the value of real-world data in regulatory submissions.
- This trend is aligned with the global shift towards evidence-based medicine where regulatory bodies are increasingly acknowledging the relevance of RWE in understanding drugs' performance in typical clinical settings.

References

1."Real-World Evidence." *U.S. Food and Drug Administration*, 2019, www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

2. Eichler, H.G. *et al*. Randomized controlled trials versus real world evidence: neither magic nor myth. *Clin. Pharmacol. Ther.* 109, 1212–1218 (2021).