Is the Real-World Evidence for Effectiveness and Safety of Biosimilars Vis-À-Vis Originators FDA Compliant?

RWD71

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Introduction

- Food and Drug Administration (FDA)'s Biosimilars Action Plan recommends increased use of real-world evidence (RWE) instead of costly clinical outcome studies for biosimilars.
- According to the "Framework for FDA's Real-World Evidence Program, 2018", to consider the RWE robust enough for supporting regulatory decisions, the Real-World Data (RWD) should be fit for use, study design should provide adequate scientific evidence, and study conduct should meet FDA regulatory requirements.

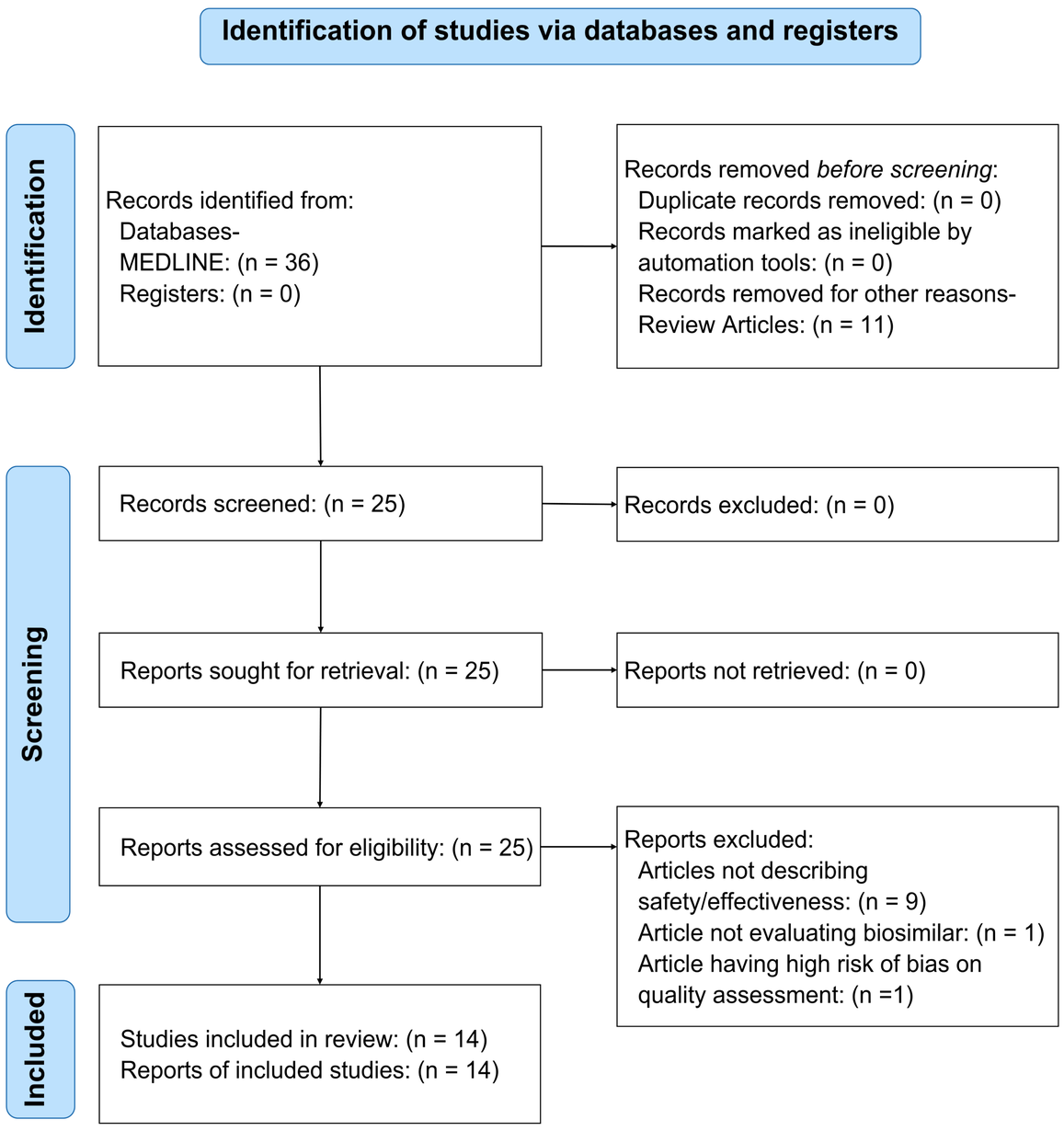
Objective

- The purpose of this study was to evaluate whether the published evidence from real-world studies meet these requirements.

Methods

- MEDLINE database was searched systematically for free full articles describing original research and published in English in any region since 2018. Last search was run on 7th May 2022.
- Eligible for inclusion were the real-world evidence studies in humans, which evaluated effectiveness and/or safety of biosimilars in a single arm or vis-à-vis the respective originators in any study population. Systematic reviews, randomized controlled trials, case studies, case series, and article types not describing original research were excluded.
- Two reviewers independently screened the articles in an unblinded standardized manner. "Assessment of Real-World Observational Studies" (ArRoWS) critical appraisal tool was used to assess the risk of bias. One reviewer extracted data from the included studies and the other reviewer validated the same. All the discrepancies were resolved by consensus among the co-authors.

Figure 1. PRISMA Flow-chart: Flow of the studies through the review process



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Results

- Out of 36 records retrieved, 21 articles (11 review articles, 9 articles not describing safety/effectiveness, one article not evaluating biosimilar) were excluded and one article did not pass the quality assessment. Eventually, 14 articles were included in the review. (**Figure 1**)
- The most researched diseases among the included articles were Rheumatoid arthritis (n=4), cancers (n = 4) and ankylosing spondylosis (n=3). Biosimilars of Infliximab (n=4), filgrastim (n=4), and rituximab (n=2) were most investigated. (**Table 1**)

Figure 2. Source of the real-world data for the included studies

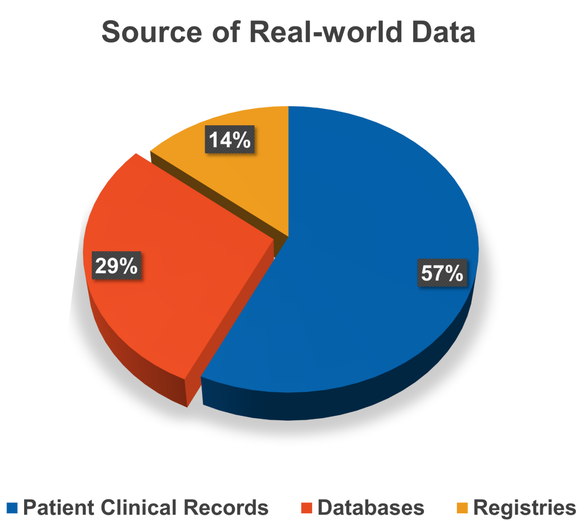


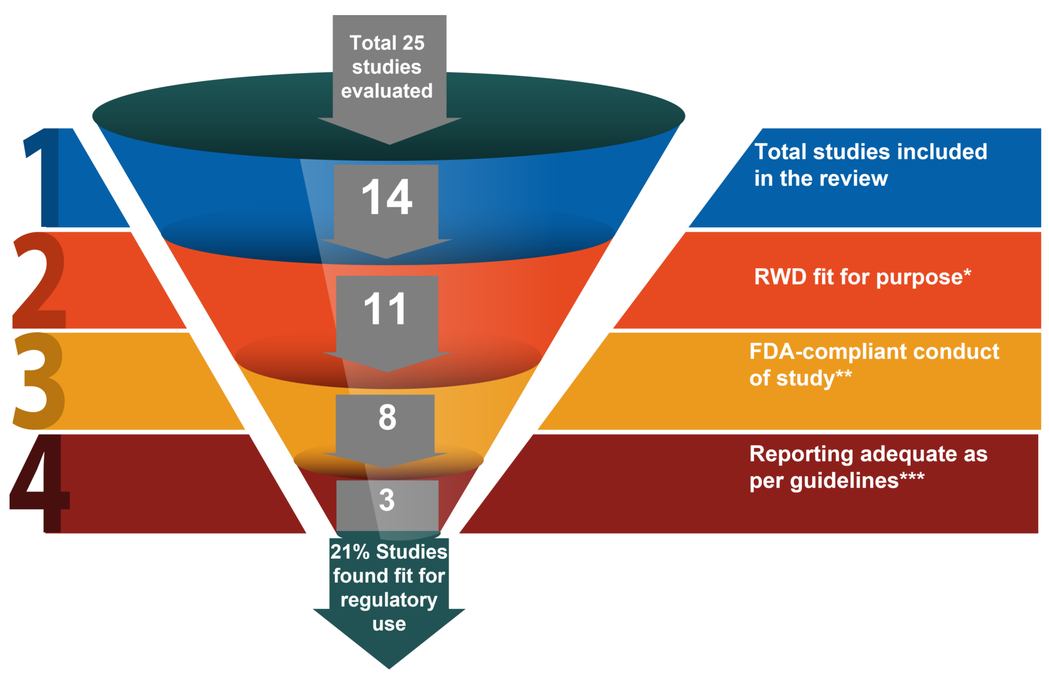
Table 1. Characteristics of the included studies

Characteristics of the enrolled studies (n = 14)					
Report characteristics		**Study characteristics**			
Range of years of publications	**n**	**Population under study**	**n**	Epoetin alfa (human erythropoietin)	1
2018	2	Adult patients with ankylosing spondylitis	2	Etanercept	1
2019	2	Adult patients with rheumatoid arthritis patients	2	**Comparator**	**n**
2020	3	Adult patients with rheumatoid arthritis or axial spondylarthritis	1	Originator	11
2021	5	Adult patients with inflammatory bowel disease	1	No comparator drug	3
2022	2	Adult patients with chronic kidney disease	1	**Outcome**	**n**
Language	**n**	Adult patients receiving infliximab for various indications*	1	Both effectiveness and safety	9
English	14	Adult patients with malignant solid tumors and on chemotherapy	1	Safety	3
Region	**n**	Adult patients with malignant solid tumors or hematological malignancies and on chemotherapy	1	Effectiveness	2
European countries	8	Elderly male patients with hematological malignancies undergoing autologous stem cell transplant	1	**Study design**	**n**
Korea	2	Adult patients with Gaucher's disease	1	*Direction*	
Canada	2	Adult patients with non-metastatic breast cancer and Non-Hodgkin's Lymphoma	1	Prospective	8
Mexico	1	Women of reproductive age group undergoing infertility treatment with assisted reproductive technology	1	Retrospective	6
Japan	1	**Intervention (Biosimilar)**	**n**	*Design*	
Species	**n**	Infliximab	4	Cohort study	6
Human	14	Filgrastim	4	Longitudinal follow-up study	4
Article type	**n**	Rituximab	2	Cross-sectional study	2
Original research article	13	Follitropin alfa	1	Safety evaluation study	1
Letter to the editor	1	Abcertin and Asbroder	1	Post-marketing surveillance study	1

*Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

- Majority of the studies were designed as a cohort study (n = 6) or longitudinal follow-up study (n = 4), with eight studies being prospective and six studies being retrospective in nature. (**Table 1**)
- Source of RWD for the studies were patient clinical records (n=8), databases (n=4), and registries (n=2). (**Figure 2**)
- Majority of articles reported that biosimilars were as effective (n=13) and safe (n=12) as the originators.
- The generated evidence could not conform to the FDA requirements for RWD fitness of use (n=3) and conduct of the study (n=3), in 43% papers, while 36% studies (n=5) did not use a reporting guideline like STROBE. Only 3 (21%) of the included studies conformed to FDA guidance and their findings were fit for regulatory use. (**Figure 3**)

Figure 3. Fitness of evidence for regulatory use as per FDA guidance



RWD, real-world data; RWE, real-world evidence; FDA, food and drug administration.

* One study used questionnaire, one used administrative database and one identified misreporting of records in the database. Hence all three studies were deemed unfit for regulatory use as per FDA framework.

**One study had no predefined visits, tests, or procedures decided at the onset of data collection. One study had no central monitoring of data. The choice of study design for another study suggested slight increase of risk and less precise estimation of the Hazard Ratios. Hence all three studies were deemed unfit for regulatory use as per FDA framework.

***Five studies did not use any guideline such as STROBE, for reporting the data.

Conclusions

- Majority of the published real-world evidence is not fit for regulatory use in current condition.
- Real-world researchers should conform to FDA framework, guidelines like STROBE, and planning templates like STaRT-RWE to make the evidence fit for regulatory use.

References

1. The U.S. Food and Drug Administration (FDA) (2018a) BIOSIMILARS ACTION PLAN: Balancing Innovation and Competition. Online Report. Available at: https://www.fda.gov/media/114574/download
2. The U.S. Food and Drug Administration (FDA) (2018b) FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM. Online Report. Available at: : https://www.fda.gov/media/120060/download1.

Disclosures

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