The role of RWE in FDA approvals

Prepared for EMA's Learnings Initiative workshop for Optimal Use of Big Data for Regulatory Purpose

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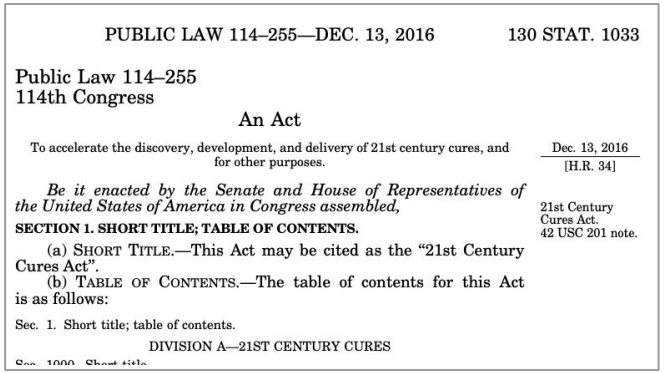
FDA has used RWE extensively for safety surveillance; “21st Century Cures” has expanded scope



PUBLIC LAW 114–255—DEC. 13, 2016 130 STAT. 1033

Public Law 114–255
114th Congress

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Dec. 13, 2016
[H.R. 34]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

21st Century Cures Act.
42 USC 201 note.

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the “21st Century Cures Act”.

(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

Sec. 1. Short title; table of contents.

DIVISION A—21ST CENTURY CURES

Sec. 1000. Short title.

Much of FDA regulatory use of RWE to date has been in the context of postmarket surveillance.

21st Century Cures Act (2016) required FDA to develop a program for RWE to support new indications for already-approved products and fulfill post-market requirements.

1 FDA sentinel system five-year strategy 2019-2023; 2019 . Accessed August 1, 2021.;
2 Text - H.R.34 - 114th Congress (2015-2016): 21st Century Cures Act." Congress.gov, Library of Congress, 13 December 2016

More recently, RWE has also informed effectiveness decisions

FDA

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FDA approves new use of transplant drug based on real-world evidence

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Today, the U.S. Food and Drug Administration approved a new use for Prograf (tacrolimus) based on a non-interventional (observational) study providing real-world evidence (RWE) of effectiveness. FDA approved Prograf for use in combination with other immunosuppressant drugs to prevent organ rejection in adult and pediatric patients receiving lung transplantation.

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Pfizer Uses EHR Data to Support Expanded Indication for Breast Cancer Drug

Posted 05 April 2019 | By Zachary Brennan

In a move that may become more common as the US Food and Drug Administration's (FDA) comfort with real-world data (RWD) increases, FDA on Thursday approved a new indication for Pfizer's Ibrance (palbociclib) in combination with an aromatase inhibitor or fulvestrant to include men with certain types of metastatic breast cancer.

The approval is based on RWD from electronic health records and postmarketing reports of Ibrance in male patients sourced from three databases: IQVIA Insurance database, Flatiron Health Breast Cancer database and the Pfizer global safety database, according to Pfizer.

The new label reads: "Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE."

Vinay Prasad, Associate Professor of Medicine at Oregon Health and Science University, told *Focus*: "I am glad the FDA has concluded that

Key questions in reviewing FDA's use of RWE from January 2019 to June 2021

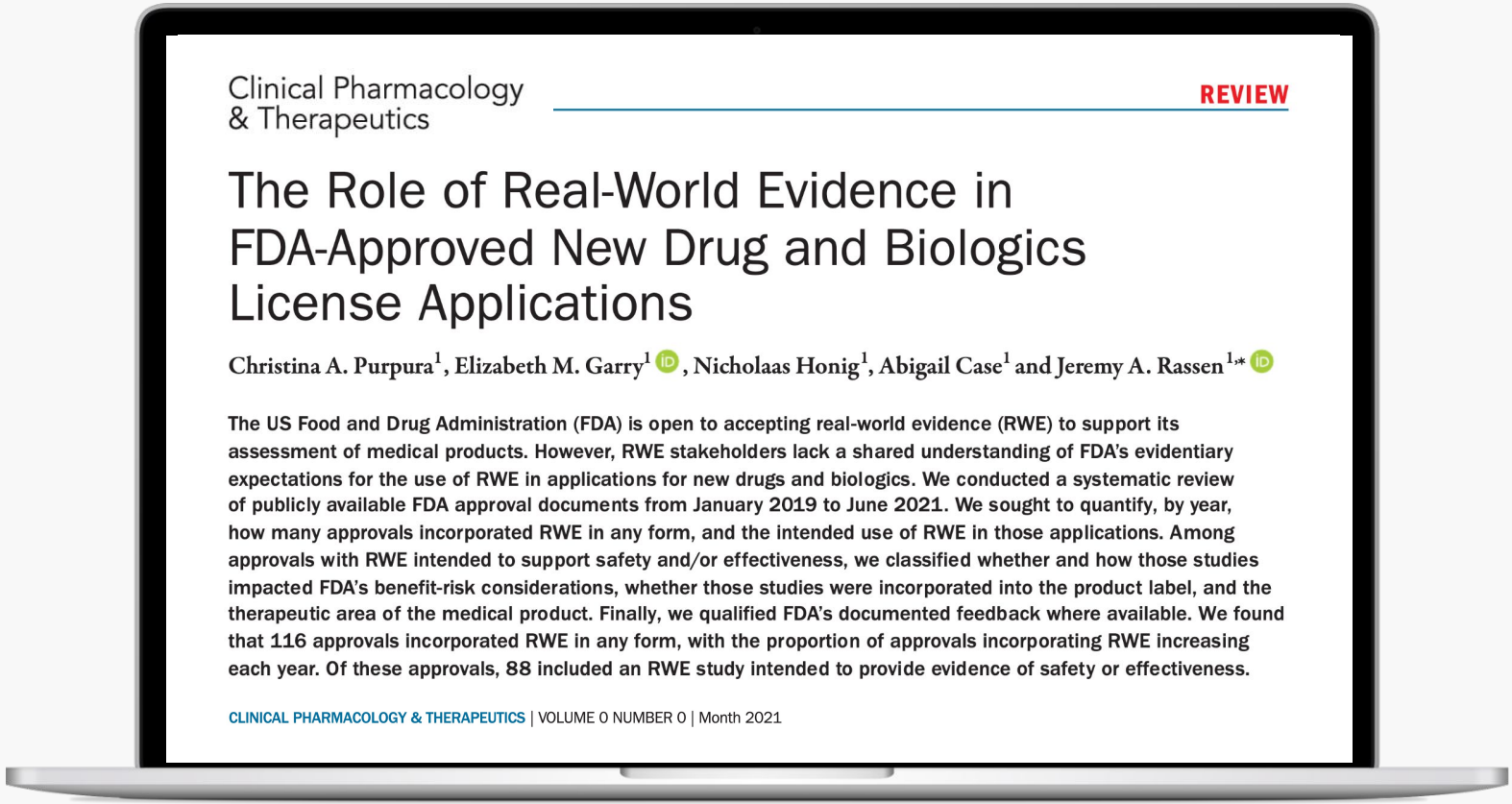
How often is RWE used in FDA approvals?

When used, what is RWE used for in FDA approvals?

How impactful are RWE studies in establishing evidence of safety and/or effectiveness?

Do RWE studies appear in product labels?

What feedback has FDA given on RWE study quality?



Clinical Pharmacology & Therapeutics

REVIEW

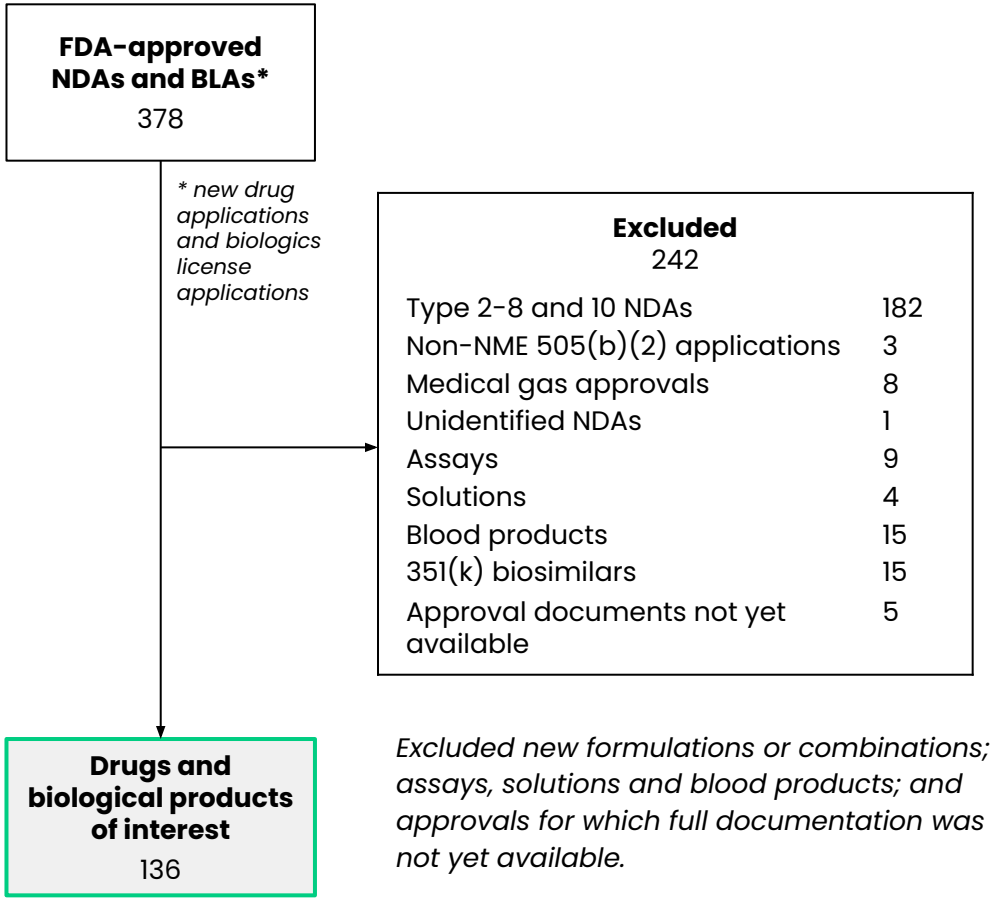
The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications

Christina A. Purpura[1], Elizabeth M. Garry[1], Nicholaas Honig[1], Abigail Case[1] and Jeremy A. Rassen[1,*]

The US Food and Drug Administration (FDA) is open to accepting real-world evidence (RWE) to support its assessment of medical products. However, RWE stakeholders lack a shared understanding of FDA's evidentiary expectations for the use of RWE in applications for new drugs and biologics. We conducted a systematic review of publicly available FDA approval documents from January 2019 to June 2021. We sought to quantify, by year, how many approvals incorporated RWE in any form, and the intended use of RWE in those applications. Among approvals with RWE intended to support safety and/or effectiveness, we classified whether and how those studies impacted FDA's benefit-risk considerations, whether those studies were incorporated into the product label, and the therapeutic area of the medical product. Finally, we qualified FDA's documented feedback where available. We found that 116 approvals incorporated RWE in any form, with the proportion of approvals incorporating RWE increasing each year. Of these approvals, 88 included an RWE study intended to provide evidence of safety or effectiveness.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 0 NUMBER 0 | Month 2021

Approvals considered Jan 2019 – June 2021



Excluded new formulations or combinations; assays, solutions and blood products; and approvals for which full documentation was not yet available.

A review of FDA's use of RWE from 2019–2021

Of the January 2019 - June 2021 FDA approvals, how many of the applications included RWE?

- What was the apparent intent of including RWE in the application?
  - If intended to support safety/effectiveness, in what light did FDA consider the RWE in the final approval decision?*
- Did the RWE submitted appear on the product label?*
- On how many applications did FDA give explicit feedback on the RWE?
  - What was the substance of that feedback?

* overall and by therapeutic area

Frequency of inclusion of RWE

Observed use of RWE in included NDAs/BLAs, January 2019 to June 2021.

Included NDAs and BLAs	2019 n=51 approvals	2020 n=59 approvals	2021 (Jan 1–June 30) n=26 approvals	Total n=136 approvals
Incorporated RWE for any purpose	38 (75%)	53 (90%)	25 (96%)	**116 (85%)**

Measuring intended purpose of a study

Of the January 2

What was the apparent intent of including RWE in the application?

If intended to support safety/effectiveness, in what light did FDA consider the RWE in the final approval decision?*

Categories*	Examples
RWE supports therapeutic context	Natural history / burden of disease
RWE supports the demonstration of product safety	Rates of adverse events in non-US markets
RWE supports the demonstration of product effectiveness	Real-world external (synthetic) control arm

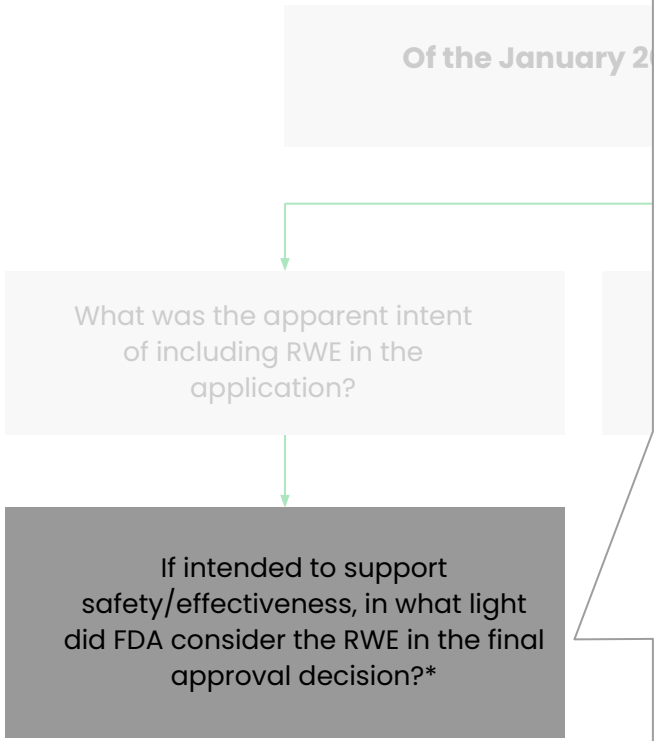
* not mutually exclusive

Observed intent of RWE

Observed apparent intended use of RWE in included NDAs/BLAs, January 2019 to June 2021. **Categories are not mutually exclusive.**

Included NDAs and BLAs	2019 n=51 approvals	2020 n=59 approvals	2021 (Jan 1–June 30) n=26 approvals	Total n=136 approvals
Incorporated RWE for any purpose	38 (75%)	53 (90%)	25 (96%)	**116 (85%)**
Used RWE to provide therapeutic context	25 (49%)	36 (61%)	22 (85%)	**83 (61%)**
Used RWE to support safety and/or effectiveness	27 (53%)	46 (78%)	15 (58%)	**88 (65%)**
… Safety only	17 (33%)	21 (36%)	5 (19%)	**43 (32%)**
… Effectiveness only	7 (14%)	6 (10%)	2 (8%)	**15 (11%)**
… Safety and effectiveness	3 (6%)	19 (32%)	8 (31%)	**30 (22%)**

Measuring RWE's impact



Categories	Examples
Substantial evidence (CDER) or primary evidence (CBER)	FDA documents identify study as "substantial evidence"
Supportive evidence	FDA documents note that the study influenced its decision
Not adequate for decision making	FDA documents state that the RWE study was not sufficient
RWE studies that FDA did not address	FDA documents make no reference to the study

Decision-making impact of RWE

Observed FDA use of applicant-submitted RWE in considered approvals, January 2019 to June 2021

FDA's use of RWE	2019 n=27 approvals	2020 n=46 approvals	2021 (Jan 1-June 30) n=15 approvals	Total n=88 approvals
Substantial or primary evidence	3 (11%)	4 (9%)	1 (7%)	**8 (9%)**
Supportive evidence	16 (59%)	30 (65%)	11 (73%)	**57 (65%)**
Not adequate for decision making	6 (22%)	4 (9%)	3 (20%)	**13 (15%)**
RWE studies that FDA did not address	2 (7%)	8 (17%)	0 (0%)	**10 (11%)**

FDA's feedback

Of the January 2019 - June 2021 FDA approvals, how many of the applications included RWE?

What was the apparent intent of including RWE in the application?

If intended to support safety/effectiveness, in what light did FDA consider the RWE in the final approval decision?*

Did the RWE submitted appear on the product label?*

On how many applications did FDA give explicit feedback on the RWE?

What was the substance of that feedback?

* overall and by therapeutic area

FDA’s feedback

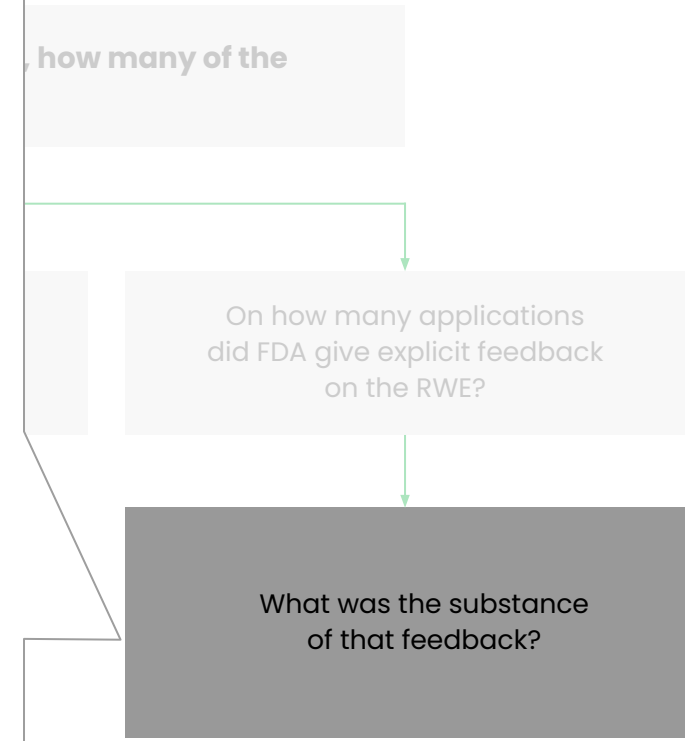
Observed FDA feedback, by benefit/risk evidence classification, January 2019 to June 2021.

	All of n=116 approvals
Received any FDA feedback	**37 (32%)**

Qualifying FDA's RWE study concerns

Categories*	Examples
Methodological issues	Immortal time bias, confounding, lack of comparability between trial data and RWD
Sample size concerns	Underpowered/unstable estimates
Omission of patient-level data	Lack of transparency and the ability for FDA to re-analyze the data
Other limitations	*(Those that did not fit into the above categories)*

* not mutually exclusive



FDA's feedback

Observed FDA feedback, by benefit/risk evidence classification, January 2019 to June 2021. **Categories are not mutually exclusive.**

	All of n=116 approvals
Received any FDA feedback	**37 (32%)**
… Methodological issues	**23**
… Sample size concern	**8**
… Omission of patient-level data	**3**
… Other limitations	**13**

FDA feedback examples

Methodological issues	"Due to **major methodological issues** (including immortal time bias, selection bias, misclassification, confounding, and missing data), FDA did not consider RWD adequate to support regulatory decision making."
Omission of patient-level data	"While FDA considers [real world] data from [the submitted studies] to be supportive, **[the sponsor] did not submit this data,** and thus FDA cannot independently verify these results."
Methodological issues, Other limitations	"Several important methodological issues impact interpretability of these findings, including… **differential selection of comparison groups**, specifically, that trial patients were enrolled from academic medical centers primarily from Europe, while [RWD] controls were enrolled from community oncology centers in the US."

FDA multi-disciplinary reviews and evaluations

Impact on product labeling

Of the January 2019 - June 2021 FDA approvals, how many of the applications included RWE?

What was the apparent intent of including RWE in the application?

If intended to support safety/effectiveness, in what light did FDA consider the RWE in the final approval decision?*

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What was the substance of that feedback?

* overall and by therapeutic area

Impact on product labeling

Observed inclusion of RWE in product labels, January 2019 to June 2021.

	Approvals including RWE in product label of n=116 approvals
All	**38 (33%)**

Impact on product labeling

Observed inclusion of RWE in product labels, by benefit/risk evidence classification, January 2019 to June 2021.

	Approvals including RWE in product label of n=116 approvals
All	**38 (33%)**
… Substantial/ primary evidence	**7 (18%)**
… Supportive evidence	**30 (79%)**
… Not adequate for decision making	**0 (0%)**
… Unaddressed by FDA	**1 (3%)**

RWE in FDA approvals by therapeutic area (1 of 2)

Therapeutic area	Total approvals per therapeutic area of n=136 approvals	RWE included in submission of n=116 approvals	RWE intended to support safety and/or effectiveness in n=88 approvals
Oncology	43	**41 (95%)**	30 (70%)
Neuroscience	25	**20 (80%)**	13 (52%)
Infectious disease	17	**17 (100%)**	16 (94%)
Endocrinology & metabolism	14	**11 (79%)**	8 (57%)
Radiology	6	**6 (100%)**	6 (100%)
Hematology	4	**4 (100%)**	2 (50%)
Dermatology	4	**3 (75%)**	2 (50%)
Cardiovascular	2	**2 (100%)**	2 (100%)
Gastroenterology	3	**2 (67%)**	2 (67%)

RWE in FDA approvals by therapeutic area (2 of 2)

Therapeutic area	Total approvals per therapeutic area of n=136 approvals	RWE included in submission of n=116 approvals	RWE intended to support safety and/or effectiveness in n=88 approvals
Ophthalmology	4	**2 (50%)**	0 (0%)
Allergy	2	**1 (50%)**	1 (50%)
Anesthesiology	2	**1 (50%)**	1 (50%)
Autoimmune	1	**1 (100%)**	1 (100%)
Cosmetic	1	**1 (100%)**	1 (100%)
Gynecology	2	**1 (50%)**	1 (50%)
Hematologic	1	**1 (100%)**	0 (0%)
Respiratory	1	**1 (100%)**	1 (100%)
Urology	2	**1 (50%)**	1 (50%)
Inflammation & Immunology	2	**0 (0%)**	0 (0%)

Conclusions

Use of RWE is frequent and is included in the vast majority of US approvals from 2019-2021, with particularly frequent use in oncology, neuroscience and infectious disease

Successful use of RWE in regulatory approvals required:

- fit-for-purpose data
- good study design, appropriate data collection, and thoughtful data analysis
- proactive communication with FDA

FDA has issued three draft guidances since September 2021 (assessment of EHR and claims real-world data, assessment of registry data, data standards), with more to come.

Thank you

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