How Real-World Evidence Is Playing Out In The Real World
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Agenda

• FDA’s RWE Framework & what it means for industry

• Review of FDA’s acceptance of RWE in approvals

• Panel discussion on the effects of RWE on regulatory, clinical and commercial strategy

• Q&A
Defining Real-World Evidence/Data

**Real-world data (RWD):** data relating to the patient health status and/or delivery of health care routinely collected from a variety of sources.

**Real-world evidence (RWE):** the *clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Examples: electronic health records, medical claims/billing data, product/disease registries, patient-generated data (including wearables, apps, diaries)
Types Of Real-World Trials

Definitions per FDA’s Framework for Real-World Evidence Program

**Observational study**: non-interventional clinical study designs that are not considered clinical trials

*Retrospective* observational studies identify the population and determines the exposure/treatment from historical data.

*Prospective* observational studies identify the population of interest at the start of the study, and exposure/treatment and outcome data are collected from that point forward.

**Pragmatic trials**: clinical study designs that include elements that closely resemble routine clinical practice

**Historical controls**: Using data generated prior to the initiation of the study as a comparator
FDA & RWE
Framework Issued Late 2018
FDA’s RWE Framework

Key factors to consider in evaluating RWE and RWD

• Whether the RWD are fit for use
• Whether the study design used to generate RWE can provide adequate scientific evidence to help answer the regulatory question
• Whether the study conduct meets FDA regulatory requirements (for example, for monitoring and data collection)
FDA’s RWE Framework

Key Considerations for Pragmatic Trials

- What types of interventions and therapeutic areas might be well suited to routine clinical care settings?
- What is the quality of data that can be captured in those settings?
- How many patients can be accessed, particularly when outcomes are rare?
- What are the variations inherent in clinical practice?
FDA’s RWE Framework

Key Considerations For Retrospective Observational Studies

• What are the characteristics of the data (e.g., relevant endpoints, consistency in documentation, lack of missing data) that improve the chance of a valid result?

• What are the characteristics of the study design and analysis that improve the chance of a valid result? Can an active comparator improve the chance of a valid result? Given potential unmeasured confounders in non-randomized RWD studies, is there a role for non-inferiority designs?

• What sensitivity analyses and statistical diagnostics should be pre-specified?
## RWE In FDA Efficacy Decisions

<table>
<thead>
<tr>
<th>Sponsor &amp; Product</th>
<th>Indication</th>
<th>Real-World Evidence Used In Efficacy Decision</th>
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</thead>
<tbody>
<tr>
<td>Amgen’s Blincyto (blinatumomab)</td>
<td>Relapsed or refractory B-precursor acute lymphoblastic leukemia</td>
<td>Matched historical control data and model-based projection study to justify response rate efficacy threshold for accelerated approval; pediatric label expansion relied on retrospective cohort and model-based analysis</td>
</tr>
<tr>
<td>EMD Serono/Pfizer’s Bavencio (avelumab)</td>
<td>Merkel cell carcinoma</td>
<td>Matched historical controls from retrospective electronic health record review, supported by literature review including a retrospective case series</td>
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<td>BioMarin’s Brineura (cerliponase alfa)</td>
<td>Late infantile neuronal ceroid lipofuscinosis type 2</td>
<td>Natural history cohort</td>
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<td>Genzyme’s Lumizyme and Myozyme (algucosidase alfa, produced at different scales)</td>
<td>Pompe disease</td>
<td>Lumizyme: Clinical outcomes data for infantile-onset patients from international Pompe Registry supplemented placebo-controlled trial in late-onset disease; Myozyme: historical control group</td>
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*Pink Sheet, Aug. 7, 2018*
## RWE In FDA Efficacy Decisions

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<td>Recordati/Orphan Europe’s Carbaglu (carglumic acid)</td>
<td>Hyperammonemia due to NAGS deficiency</td>
<td>Retrospective case series summary data on plasma ammonia reductions</td>
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<td>Asklepion’s Cholbam (cholic acid)</td>
<td>Bile acid synthesis disorders</td>
<td>Retrospective chart review of treatment IND and expanded access program patients; Historical control from retrospective literature review</td>
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<td>BTG’s Voraxaze (glucarpidase)</td>
<td>Methotrexate toxicity</td>
<td>Data from NIH treatment protocol; Historical control based on well-characterized methotrexate excretion curves from 40+ years of clinical trials</td>
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<td>Wellstat’s Vistogard (uridine triacetate)</td>
<td>5-FU overdose</td>
<td>External historical control based on cases in literature and review of safety reports submitted to FDA regarding fluorouracil overdoses</td>
</tr>
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<td>Fresenius Kabi’s Omegaven (fish oil triglycerides)</td>
<td>Pediatric patients with parenteral nutrition-associated cholestasis</td>
<td>Pair-matched historical controls</td>
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<td>Provepharm’s ProVay Blue (methylene blue)</td>
<td>Acquired methemoglobinemia</td>
<td>Retrospective case reports from multicenter chart review and literature search</td>
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<td>Aegerion’s Myalept (metreleptin)</td>
<td>Lipodystrophy</td>
<td>NIH protocol and treatment IND patient data</td>
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<td>Advanced Accelerator Application (Novartis)’s Lutathera (lutetium dotatate LU-177)</td>
<td>GEP-NET</td>
<td>Expanded access protocol data supported broader indication than was supported by clinical trial</td>
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<tr>
<td>Vertex’ Kalydeco (ivacaftor)</td>
<td>Expansion of cystic fibrosis indication to include an additional 23 mutations</td>
<td>Registry data and mechanistic information from lab studies</td>
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Incremental Regulatory Steps

FDA is increasingly open to incorporating RWE in clinical development programs outside of pivotal efficacy assessment

• Advanced safety assessment of potential drug class risk
  Shire’s Motegrity (prucalopride)
  • Retrospective cohort study of relative incidence of major CV events among prucalopride patients and matched comparators from five European data sources

• Support of new outcome measures in clinical trials
  Biohaven’s troriluzole
  • Justified modifying primary endpoint in pivotal trial program by applying modified scale to natural history reference cohort
  bluebird bio’s Lenti-D gene therapy
  • Efficacy in pivotal Starbeam trial will be compared against clinically meaningful benchmark based on retrospective natural history analysis
  • Safety analysis will compare Starbeam with prospective and retrospective observational study
FDA RWE Framework: Planned Guidance Topics

• Reliability and relevance of RWD from medical claims, electronic health records, registries and international electronic health care data
• Potential gaps in RWD sources
• Clinical trial design considerations, including
  • Pragmatic design elements
  • External control arms
  • Observational study designs
• Use of electronic source data and electronic records in clinical studies
Clinical Trial Applications
Bavencio

External control study to support innovative clinical development

Avelumab developed in Merkel cell carcinoma (MCC), a rare (≈1500 new cases per year in the US) and aggressive skin cancer, with no evidence-based standard of care

Question
What is the progression-free survival in metastatic MCC 2L+ patients to properly contextualize outcomes of the single-arm clinical trial?

Data
oncology-specific electronic health record (EHR) system maintained by McKesson Specialty Health – Collaboration with McKesson


Patients were randomized 1:1 to receive FF/VI 100/25 mcg or 200/25 mcg once daily or to continue on usual asthma maintenance therapy.

4,233 patients
- Patients in primary care
- Aged ≥18 years
- GP diagnosis of asthma
- Taking ICS or ICS/LABA
- Symptomatic
- Consented

64% prescribed ICS/LABA pre-randomization
36% prescribed ICS pre-randomization

During the 1-year treatment period, patients could have their maintenance treatment adjusted (stepped-up, stepped-down or switched) at the GP’s/Investigator’s discretion as would have been in normal clinical practice.

Constant real-time data collection of all interventions/safety monitoring

FF/VI open label*

Randomization visit
- Routine respiratory review
- Device instruction
- Questionnaires

End of study visit
- Routine respiratory review
- Severe exacerbations
- Questionnaires

Usual Care (ICS or ICS/LABA)

3 monthly phone calls (if no regular visits)

12 months of usual care

Week 24
Primary endpoint
ACT score


*Randomization at Visit 2 was stratified by ACT score (≥20, 16–19, or ≤15) and prescription written prior to randomization (ICS or ICS/LABA). ACT = Asthma Control Test; FF = fluticasone furoate; GP = general practitioner; ICS = inhaled corticosteroid; LABA = long-acting β₂ agonist; VI = vilanterol.
RWE In The Real World

Effects on regulatory, clinical and commercial strategy
External Control Arms: Better Than Single-Arm Studies But No Replacement For Randomization

02 Jan 2019 | ANALYSIS

by Sue Sutter
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Executive Summary

Synthetic control group derived from historical clinical trial data could augment smaller randomized trials and yield better information than single-arm studies, but this approach should not be viewed as a substitute for randomized trials where feasible, US FDA officials said at a Friends of Cancer Research meeting.
UK MHRA Spells Out Do's And Don'ts Of Real-World Evidence For Showing Efficacy

14 Aug 2018 | NEWS

by Vibha Sharma
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Executive Summary
A senior UK regulator explains why the MHRA agreed to a complex real-world evidence study instead of an RCT to demonstrate a drug's efficacy, despite the challenges posed by potential for bias.
Real-World Evidence: US FDA Framework Emphasizes Data Fitness And Study Quality

09 Dec 2018 | NEWS

by Sue Sutter

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Executive Summary

Agency’s approach to assessing real-world evidence for effectiveness will be guided by three key principles: fitness for use of the underlying data, adequacy of the study design, and satisfactory monitoring and data collection.
US FDA Is Hesitant About Using Observational Studies In Real-World Evidence Framework

06 Dec 2018 | ANALYSIS

by Sue Sutter
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Executive Summary

Agency plans guidance on whether observational studies can provide real-world evidence to support regulatory decisions about drug effectiveness; however, RWE framework includes critical questions about retrospective studies, and reflects agency concerns about transparency.
Executive Summary

Agency releases open source code and technical documents for new mobile app designed to gather real-time information about medication use and patient-reported outcomes; app will be incorporated into several PCORI-funded studies that FDA is leveraging as it explores the regulatory utility of real-world data.
Real-World Evidence Could Speed Development Of Drugs Offering Incremental Improvements

By Derrick Gingery

US FDA Commissioner Gottlieb says common diseases need new treatments and argues streamlining trials may pique industry interest.

Real-World Evidence: US FDA’s Prucalopride Review Shows Datasets' Utility And Limitations

By Sue Sutter

A European pharmacoepidemiology study helped reassure advisory committee members about the constipation drug’s cardiovascular safety, but confounding factors limited interpretability...
Executive Summary

CAR T-cell therapies have resulted in the industry and regulators exploring unconventional approaches to collecting real-world safety and efficacy data from existing registries. Can this approach also work for other types of cell and gene therapy products in the future? Delegates at a conference in London explored the topic.
Real-World Evidence At US FDA: Bavencio, Blincyto Approvals Point Way Toward Broader Use

07 Aug 2018 | ANALYSIS

by Bridget Silverman
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Executive Summary

Breakthrough-designated oncologics used historical comparator data to determine efficacy threshold for pivotal Phase II studies supporting accelerated approval; Blincyto’s subsequent full approval offers validation with conventional controlled study.
Next-Generation Roche: How Data Analytics Will Keep It In The Lead In Oncology

08 Jun 2018  |  ANALYSIS

by Mary Jo Laffler

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Executive Summary

Roche used its ASCO investor briefing to highlight its digital and personalized healthcare strategy, including examples of how it’s facilitating R&D and reimbursement – and how that should position it to be an oncology leader in the future.
Real World Data Helping To Drive Rise Of Novartis' Entresto

29 May 2018 | NEWS

by Kevin Grogan
kevin.grogan@informa.com

Executive Summary

Patients with heart failure on Entresto say they have fewer symptoms and greater quality of life, according to a registry study and Novartis is hoping that this and other real world data will propel the drug towards its peak sales target of $5bn.
Interview: Real World Evidence’s Commercial Facet

07 Aug 2017 | ANALYSIS

by Anju Ghangurde

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Executive Summary

Senior QuintilesIMS officials tell Scrip that harnessing real world evidence (RWE) insights on the commercial side is not quite the “norm” yet across pharmaceutical companies, although it can provide up to $1bn in value across lifecycle. They also explain the growing significance of RWE in the Middle East.
Real World Evidence Is Critical To Pharma’s Future: Can We Agree On What It Is?

15 May 2017 | OPINION

by Melanie Senior
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Executive Summary

Urgent calls for industry to generate and apply real world evidence were matched at a recent conference only by complaints about challenges faced by this growing, ill-defined evidence category.
Takeda Enlists Real World Evidence To Boost Marketed Entyvio

09 May 2017 | NEWS

by John Davis
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Executive Summary

Japan’s Takeda says it has confirmed the benefits of its best-selling inflammatory bowel disease therapy Entyvio in US medical practice through the collection of real world evidence.
Executive Summary

President of R&D Andrew Plump notes that much of the work to rationalize Takeda's pipeline after its Shire acquisition took place years ago when the Japanese pharma streamlined its R&D organization, but investments in data science to improve clinical trial outcomes and R&D efficiency are ongoing.
Thank you for listening

Questions: pharma@informa.com