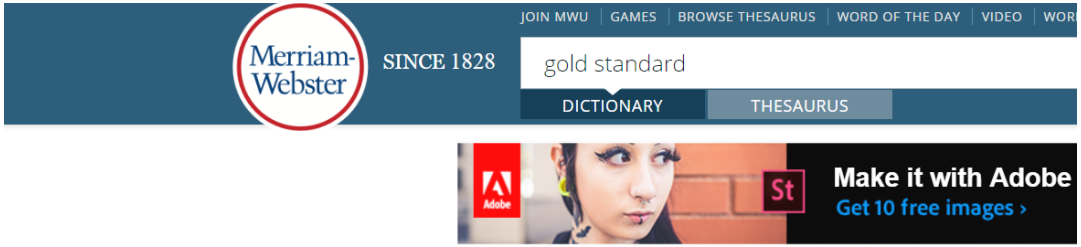
The Real Deal

Background on RWD and RWE

Ellen Schumacher,
Executive Director Commercial Regulatory Affairs,
Bristol-Myers Squibb

FDLI

Gold Standard of Evidence



gold standard noun

Definition of *gold standard*

1 : a monetary standard under which the basic unit of currency is defined by a stated quantity of gold and which is usually characterized by the coinage and circulation of gold, unrestricted convertibility of other money into gold, and the free export and import of gold for settling of international obligations

2 : BENCHMARK sense 1a

Examples of *gold standard* in a Sentence

// the *gold standard* for accurate experimental procedures is the double-blind medication trial

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

FDA

Disclaimer

- The views and ideas expressed during this presentation are my own and not endorsed by BMS, nor representative of BMS policies, procedures, rules or decisions.

Expenses of RCT

Generalizability of Data

- Patient Population
- Lack of true burden of disease
- Highly controlled setting

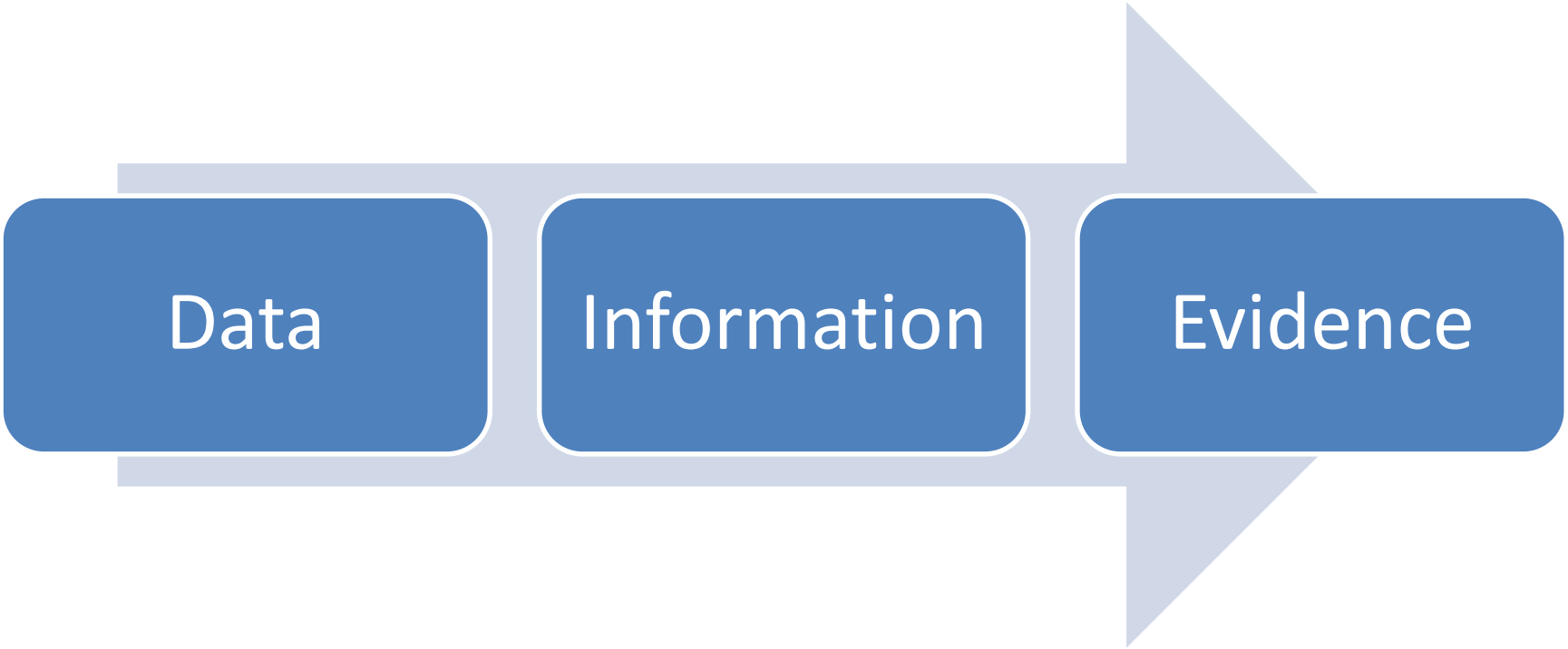
Real World Data

Real World Data

Historic Utility of RWD

- Observational setting
- Generalizability of interventional trials
- Safety Surveillance
- Therapeutic Use
- Quality of Healthcare Delivery

Evaluating the Process



RWD Standards – Considerations for Industry

- Minimize bias
- Usefulness in particular disease state
- Appropriate endpoint and database selection
- Standard definition
- Methodology
- Statistical considerations
- Limitations and Disclosures
- Dissemination
- Publication Standards

Future Regulatory Picture

Risk-benefit evaluation drugs?

21st Century Cures Act

The New York Times | http://nyti.ms/2h2lhrY

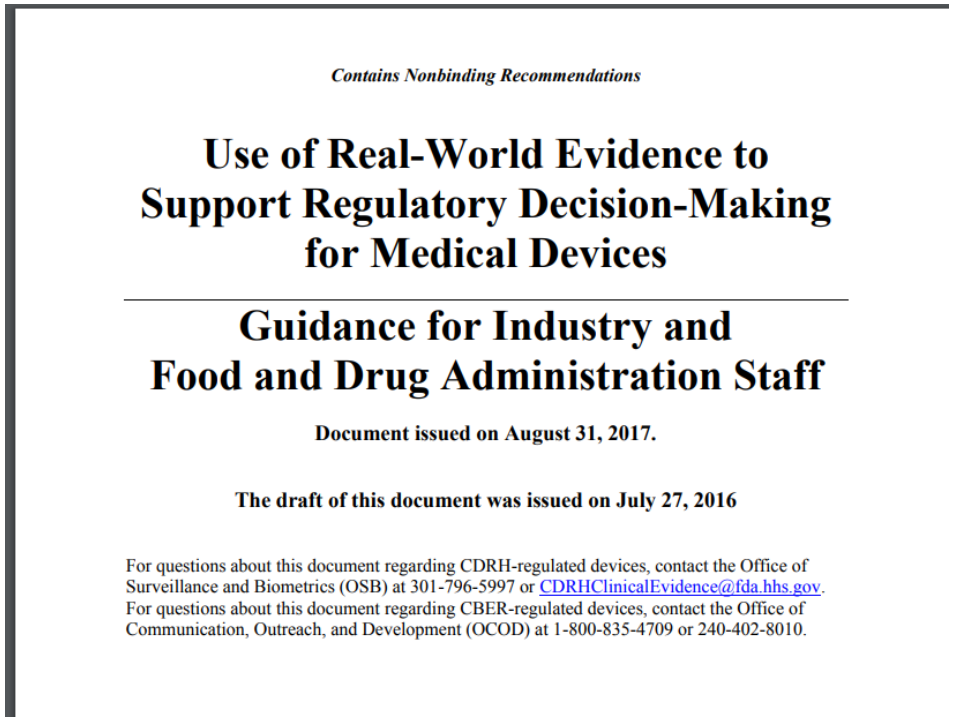
POLITICS | CONGRESSIONAL MEMO

Cures Act Gains Bipartisan Support That Eluded Obama Health Law

By ROBERT PEAR DEC. 8, 2016

FDA's position: Devices

FDA's position: Devices



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

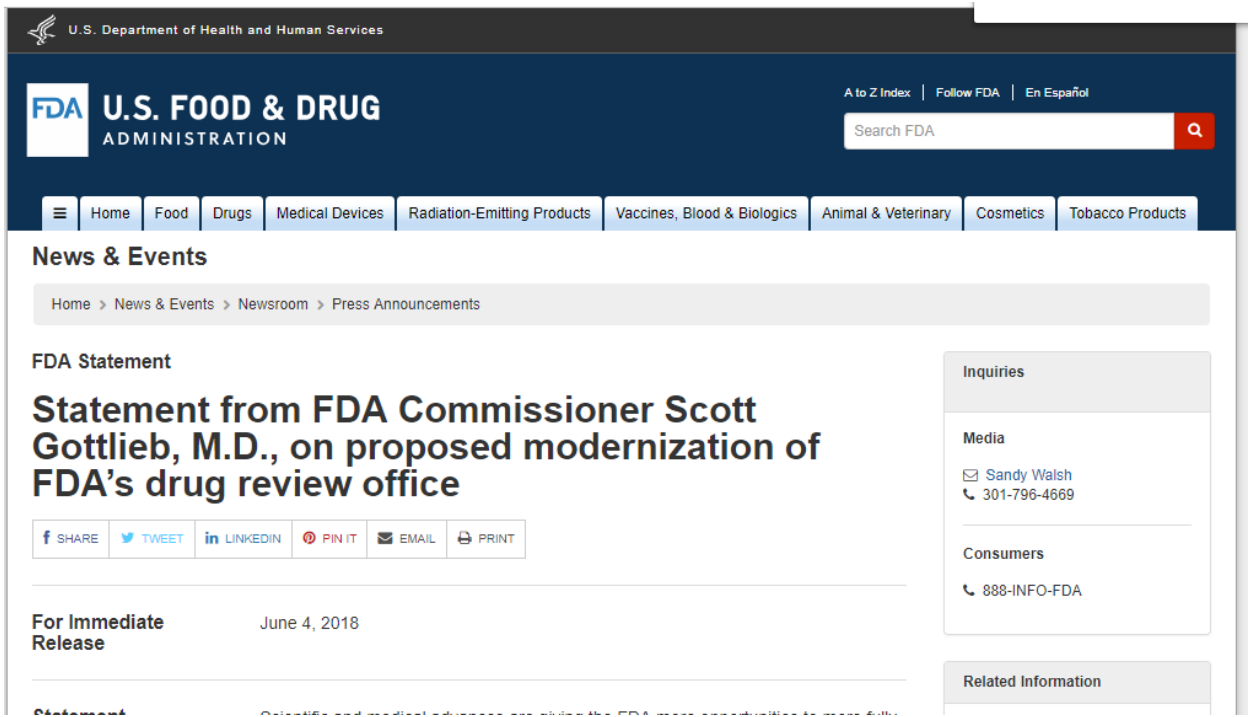
The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

FDA's Position: Drugs… More to Come

- Public Workshops
- Pilot Studies
- Methodology Projects

FDA’s Position : Drugs



Expanding the Landscape of Real World Evidence: Case Studies in Innovative RW Study Designs

Eric Gemmen
Senior Director, Epidemiology & Outcomes Research
IQVIA

FDLI

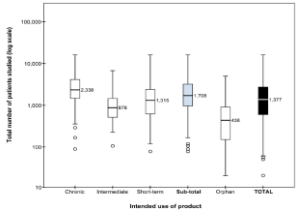
Value of Real-World Evidence in the Eye of the Regulators

FDA 21st Century Cures Act driving need for RWE

*"The more widespread use of RWE can make our **medical product development process more efficient….** This will ultimately help us achieve **better outcomes, and safer and more efficient use of expensive technology**."*[1] **Scott Gottlieb, MD, FDA Commissioner**

EMA 2010 EU PV Legislation driving need for RWE

'Need to Fill Knowledge Gaps in Safety Profile of New Drugs to Market' [2]
June M Raine, MD, Chair Pharmacovigilance Risk Assessment Committee



Patients studied prior to approval of new medicine [3]

*For **200** new "standard" medicines between 2000 - 2010 median total no patients= **1708**. For orphan drugs = **438** patients.*

Reinforced EU/US collaboration on medicines; Brusssels18-19 June 2018 bilateral meeting with EMA and FDA, discussed strategic priorities for the coming years, whereby EMA & FDA will regularly exchange information and work together on methodologies to optimise the use of RWE to support regulatory decision making throughout the product lifecycle

[1]https://www.fda.gov/NewsEvents/Speeches/ucm576519.htm; [2]EMA Pharmacovigilance Risk Assessment Committee Five years of operation. Eleventh Stakeholder Forum on the Pharmacovigilance Legislation 21 September 2017; [3]Duijnhoven et al PLoS March 2013; [4]European Commission Health and Food Safety Directorate General Reinforced EU/US collaboration on medicines and tobacco e-News 22/06/2018

A key moment to demonstrate the value of innovative RWE study approaches

The 21st Century Cures Act

Section 3022 calls for the use of Real-World-Evidence for

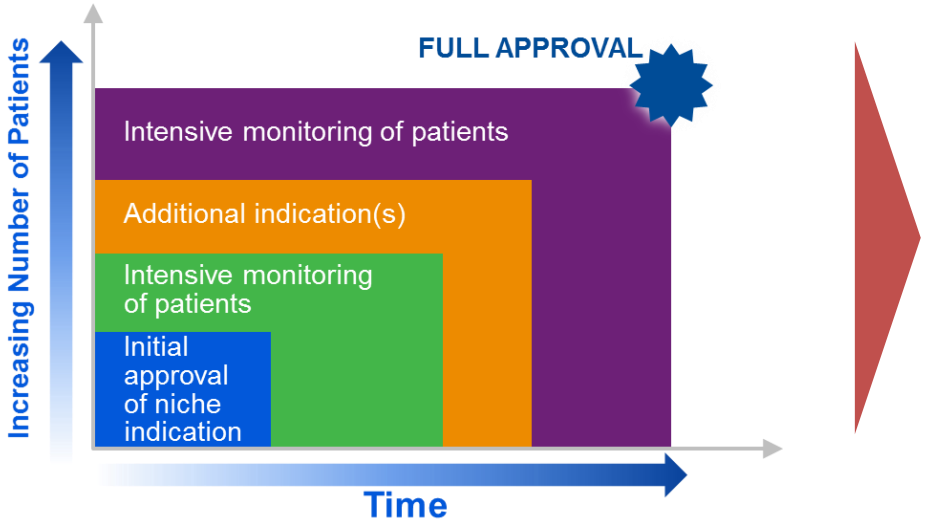
- Indication expansions
- Post approval safety studies

Scott Gottlieb, FDA commissioner

Cures Act requires FDA to draft a framework for the use of RWE within 2 years that addresses acceptable sources of RWE for various purposes.

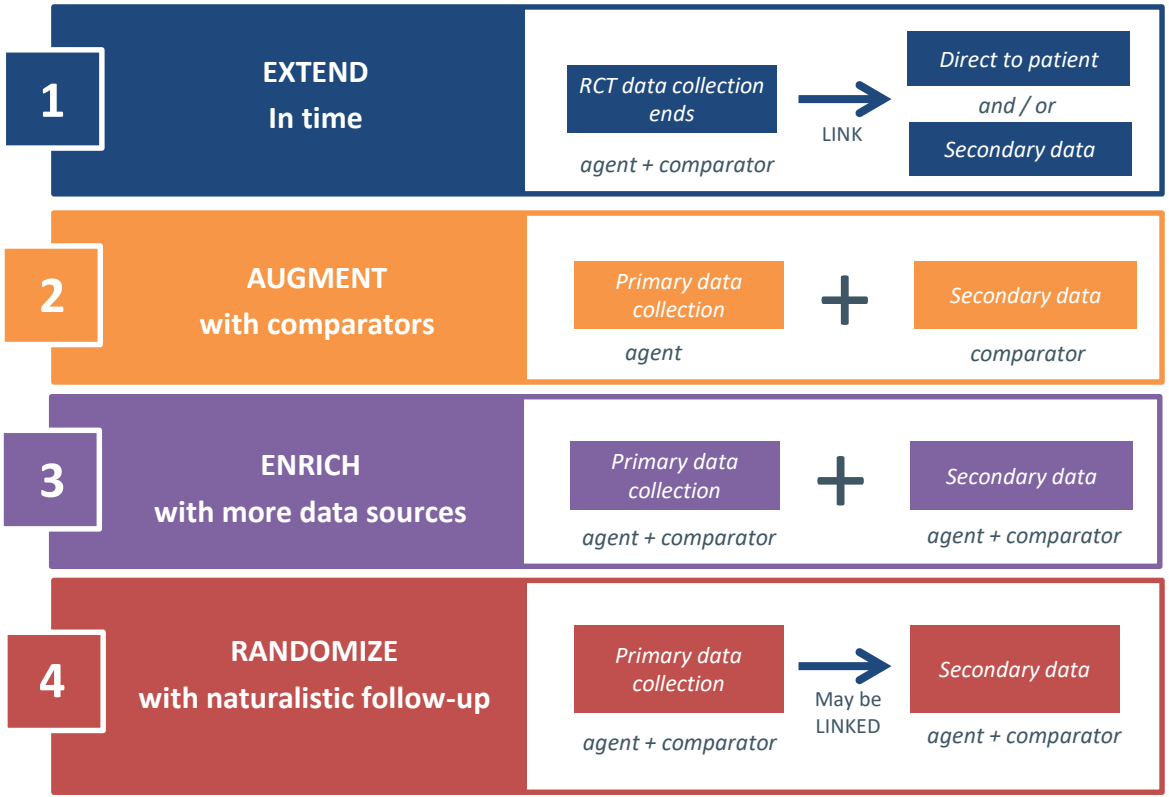
EMA and HTA bodies are looking for Real World Evidence (RWE)

EMA needs RWE to support adaptive approval pathways



*Monitoring patients in **observational studies** is the basis for EMA's adaptive pathways approach*

Innovative Design Options



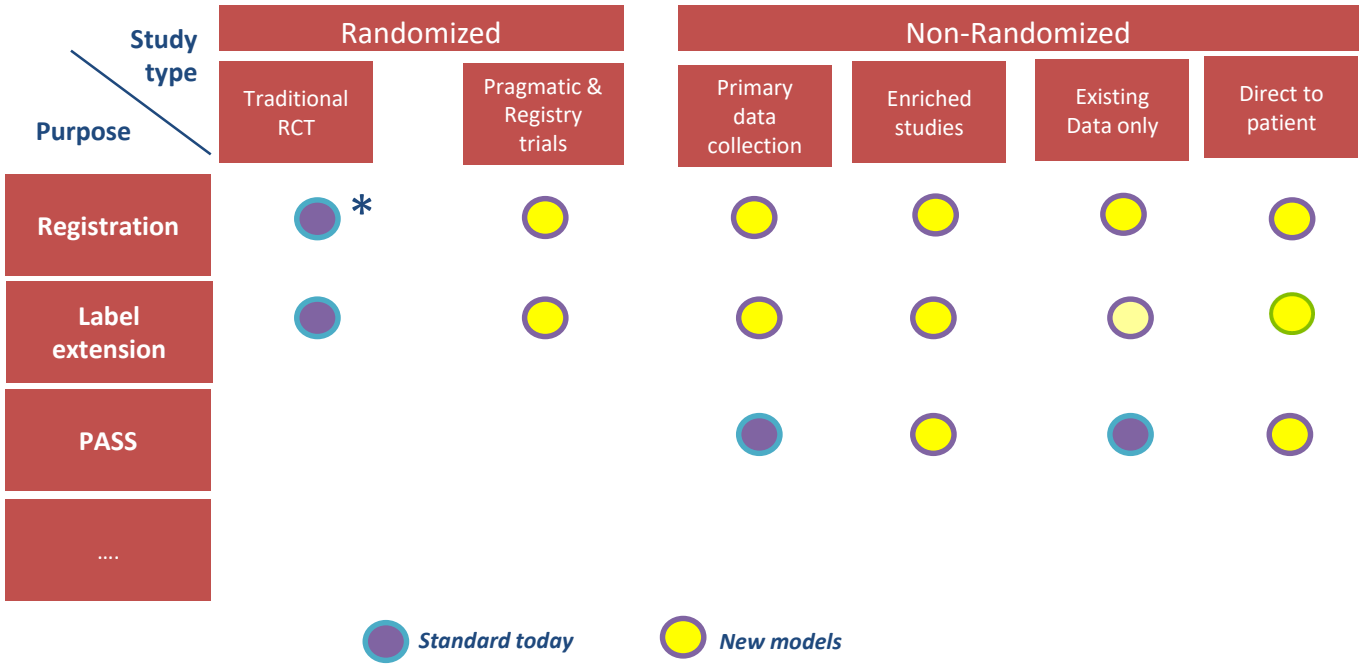
- *Low-cost follow-up for long-term safety & effectiveness*
- *Drive ROI from research spend*

- *Comparative evidence for product registries or single-arm clinical trials*
- *Drive ROI from research spend*

- *Improved efficiency of data capture to address several research questions*
- *Accelerated evidence generation*

- *Significant cost reductions vs. a classical RCT*
- *Randomization guarantees early product use*

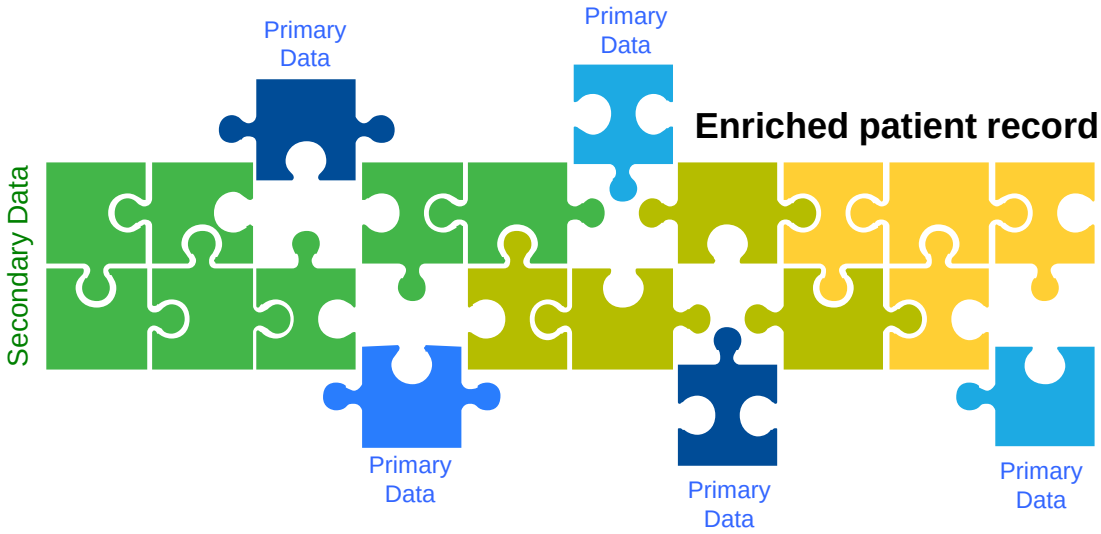
Purpose drives new RW study designs



* Some rare disease treatments are being approved using historical or real-world comparators

Enriched studies utilize complementary data collection methods

Enriched studies integrate **two methods of data collection** to build a **comprehensive patient record** and increase researchable data



- **Primary data:** Data collected from first-hand sources for the specific purpose of the study
  e.g. Electronic Case Report Forms (eCRF), Patient Reported Outcomes (PRO)
- **Secondary data:** Data from existing sources collected during routine practice
  e.g. Electronic Medical Records (EMR), Claims

Multiple Protocols Rolled Over Into Extension Study

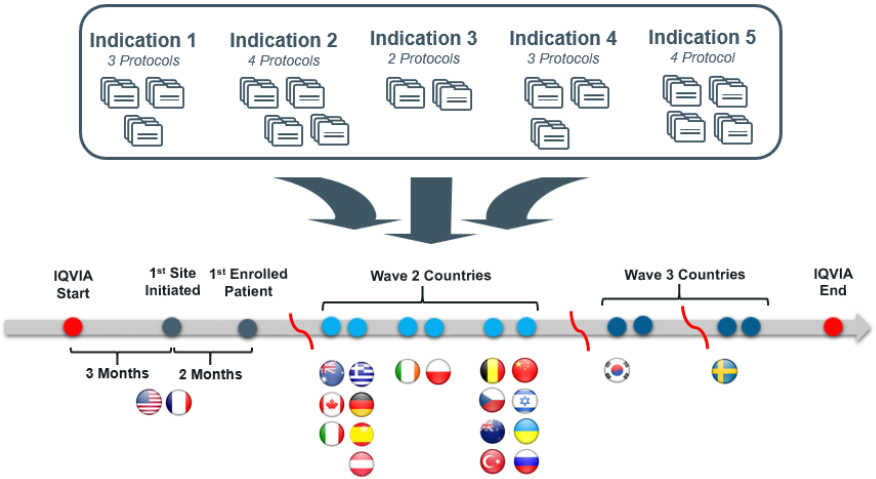
Extending the treatment access for patients with B-cell malignancies

Client Situation

- Rollover 400+ patients from up to **16 clinical trial protocols spanning multiple indications** into a single extension protocol.
- Deploy a **light touch approach** to collect safety data
- Effectively collaborate with site and vendors managing parent protocols to **transition patients under** extension study in a timely manner

IQVIA Solution

- Engage **extensive local regulatory expertise** to shape protocol design and drive efficient start up and subject rollover across all 21 target countries
- Design tailor-fit, country-specific processes to ensure **continued access to drug** up to commercial availability throughout protocol duration
- Implement **customized management and monitoring plans** to ensure quality data capture at the lowest cost possible



How much reliable evidence can patients provide?

Pilot Study with European Medicines Agency for Pharmacovigilance

Situation

Are data collected directly from women throughout pregnancy suitable for research purposes?

- How well can consumers report drug use and outcomes?
- How much medication usage is not recorded in electronic health records (EHR) or R_x data?
- Are there additional risk factors not typically recorded?

Solution

- Data collected in 4 countries, 4 languages
- Compared self-reported medication use with data from EHR and national R_x data in 2 countries.

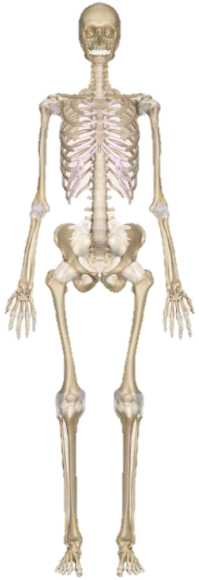
Results

- 83% used ≥ 1 non-pregnancy-related medication during pregnancy or preceding month, 24% reported using OTC medications, 7% reported not using prescribed medications
- 83% agreement with Danish National Rx register for medications for chronic use, but only 54% agreement with prescriptions written for medications indicated for short-term use.
- Clinical events of special interest often need validation

*Dreyer et al.. **JMIR Public Health & Surveillance** 2015; 1(2); e22. doi:10.2196.

Augmentation study for label expansion

Bioventus Observational Non-interventional EXOGEN Studies (BONES) Program



PROSPECTIVE REGISTRY

Direct-to-Patient Device Registry

- Potentially eligible patients identified and enrolled via physician prescription
- Direct-to-patient recruitment and surveys to capture baseline demographics and medical history as Non-union outcome well as co-medications during follow-up
- Non-union outcome assessed by presence of ICD coding diagnosis in claims

Patients Matched Via Propensity Score

MARKETSCAN® COMMERCIAL CLAIMS DATABASE

External Control Via Claims Data

- Comparator cohort identified in MarketScan claims data
- Patients matched with Registry patients using baseline demographic and clinical characteristics
- Non-union outcome assessed by presence of ICD coding diagnosis in claims

Study protocol approved by FDA in 2017 after several meetings

Example: AUGMENTATION – New Drug Approval

Accelerated approval of Avelumab for MCC based on a single-arm trial with historical database control group

- **BAVENCIO® (avelumab),** the first immunotherapy for metastatic Merkel Cell Carcinoma (MCC)
- Approved under **FDA accelerated approval** based on tumor response and duration of response
- JAVELIN Merkel 200 trial: **open-label, single-arm**, multi-center study (n=88)
- **External control group** based on the Study Obs001 database

AVELUMAB	N = 88
Overall response rate (ORR)	33%
Median duration of response (DOR) among 29 responding patients	• 86% > 6 months • 45% > 12 months
Complete response (%)	11%
Partial response (%)	22%

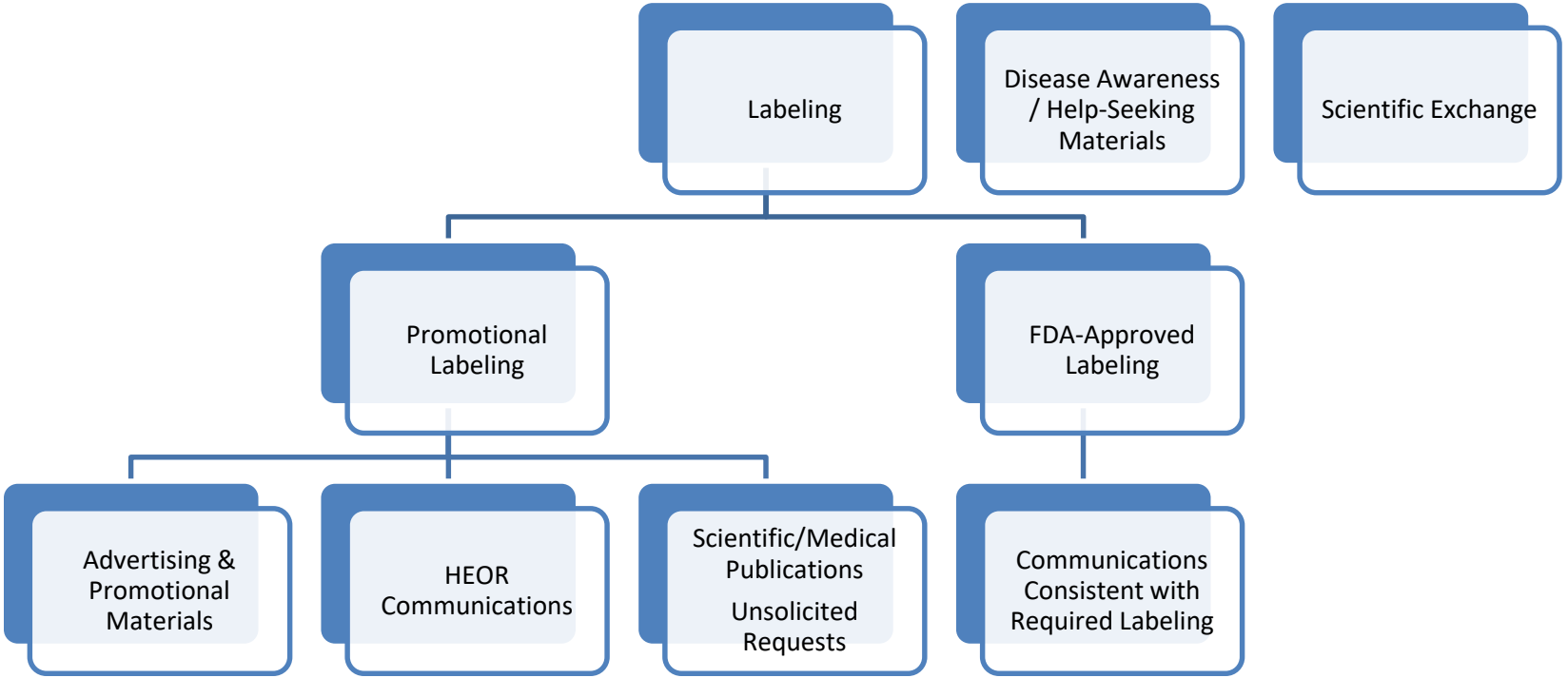
Compared to control group from database

Natural history control group with chemotherapy	N = 14
Overall response rate (ORR)	29%
Median duration of response (DOR) among 4 responding patients	1.7 months

Source: www.accessdata.fda.gov

Categories of Communications

FDA Perspective



Categories of Communications

FDA Guidance Documents

- **Guidance regarding various promotional practices**
- **Communications consistent with FDA-required labeling (2017)**
- Payor/formulary communications (2017)
- Dissemination of reprints, clinical practice guidelines and reference texts
- Unsolicited requests/questions
- 3 social media guidances (of which, 2 are relevant to devices)
- Presentation of risk information and direct-to-consumer communications

Technical

For Labeling

- CDISC
  - SDTM
  - ADaM

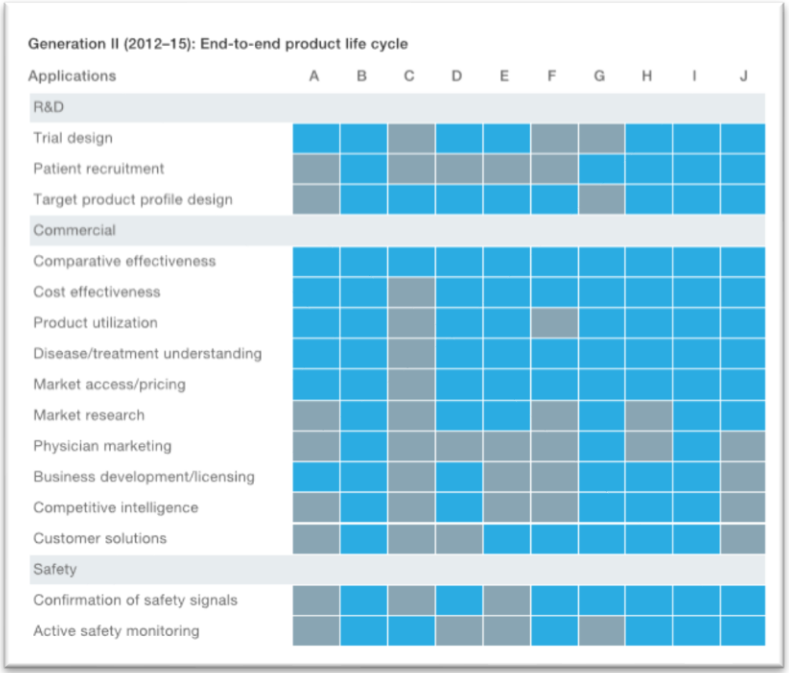
REAL-WORLD EVIDENCE: PRACTICES FOR PROMOTIONAL USE

Colleen M. Heisey, Partner
Jones Day – Washington, DC
cmheisey@jonesday.com
202-879-3449

DISCLAIMER

- Any presentation by a Jones Day lawyer or employee should not be considered or construed as legal advice on any individual matter or circumstance. The contents of this document are intended for general information purposes only and may not be quoted or referred to in any other presentation, publication or proceeding without the prior written consent of Jones Day, which may be given or withheld at Jones Day's discretion. The distribution of this presentation or its content is not intended to create and receipt of it does not constitute, an attorney-client relationship. The views set forth herein are the personal views of the authors and do not necessarily reflect the views of Jones Day.

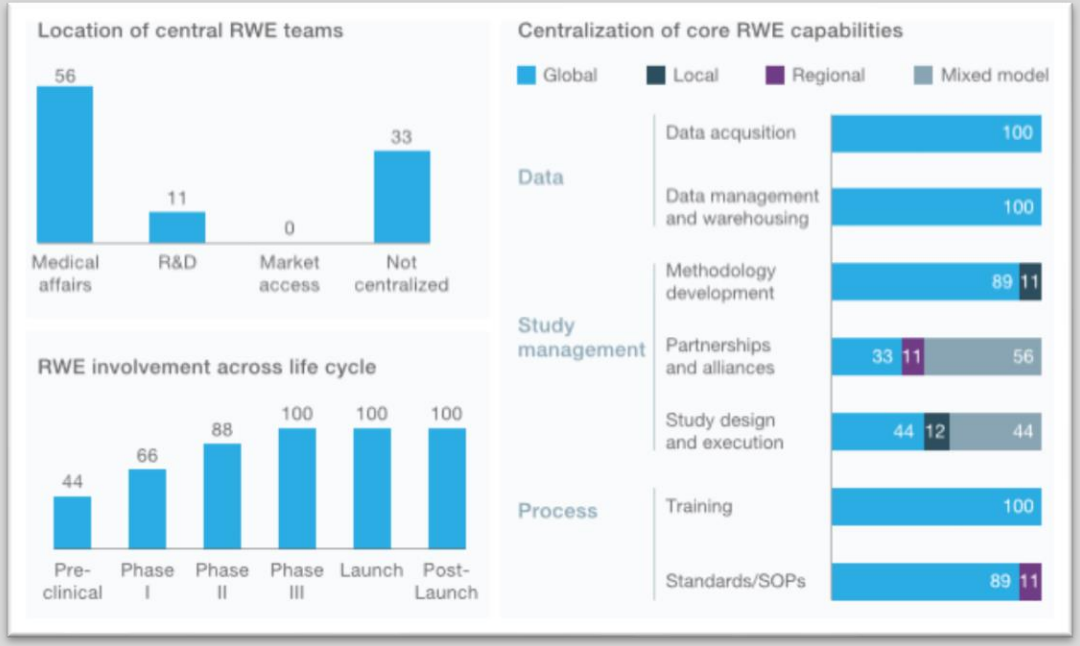
PHARMACEUTICAL COMPANY USE OF REAL-WORLD EVIDENCE: 2011 VS 2012-2015



McKinsey & Company, “Real-world evidence: From activity to impact,” Exhibit 3. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/real-world-evidence-from-activity-to-impact-in-healthcare-decision-making

JONES DAY

PHARMACEUTICAL COMPANY RWE TEAMS



McKinsey & Company, “Real-world evidence: From activity to impact,” Exhibit 5. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/real-world-evidence-from-activity-to-impact-in-healthcare-decision-making

JONES DAY

TRADITIONAL CORE PROMOTIONAL PRINCIPLES

- Consistent with approved labeling
- Truthful and not misleading
- Balanced
- Reveal material facts
- Supported by substantial evidence

SUBSTANTIAL EVIDENCE: FDCA § 505(d)

- The term "substantial evidence" means:
  - Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof

SUBSTANTIAL EVIDENCE: 21 CFR § 202.1(e)(6)(i)

- An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it:
- (i) Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients . . ., safer, has fewer, or less incidence of, or less serious side effects or contraindications *than has been demonstrated by substantial evidence or substantial clinical experience* . . . whether or not such representations are made by comparison with other drugs or treatments, and whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references.

JONES DAY

CFL GUIDANCE & SUBSTANTIAL EVIDENCE

- What evidentiary support should a firm have for its CFL promotional communications?
  - Truthful and non-misleading
    - Grounded in fact and science, presented with appropriate context
    - *Scientifically appropriate and statistically sound* data, studies, or analyses to support the representations
  - FDA would not consider representations in a CFL promotional communication to be false or misleading based ***only*** on the lack of evidence to satisfy the applicable approval/clearance standard

CFL GUIDANCE & SUBSTANTIAL EVIDENCE

- Evidence other than that which meets the new drug approval standard of “substantial evidence” of effectiveness could be used to support certain representations about a prescription drug in a CFL promotional communication
  - In such circumstances, FDA does not intend to interpret its regulations (e.g., 21 CFR § 202.1(e)(6)(i)) “to the contrary”
- The amount and type of evidence needed to support a particular CFL promotional communication depends in part on the topic addressed

“SCIENTIFICALLY APPROPRIATE AND STATISTICALLY SOUND”

The Guidance explains that the standard is a flexible one, and “**a variety of types and studies and analyses can provide useful additional information**” so long as the communications “**do not overstate the findings of or the conclusions** that can be drawn”

Acknowledges conflict with 21 C.F.R. § 202.1(e)(6).

“Evidence other than that which meets the new drug approval standard of ‘substantial evidence’ of effectiveness could be used to support certain representations or suggestions about a prescription drug”

ENFORCEMENT

- Product communications that are consistent with a product's FDA-required labeling but are false or misleading may subject a firm to enforcement action under the Federal Food, Drug, and Cosmetic Act

SECTION 3037: HEALTH CARE ECONOMIC INFORMATION

- 21st Century Cures Act, enacted in December 2016, facilitates communication between pharmaceutical companies and payers about a drug's health economic impact
- "Competent and reliable scientific evidence" as long as such claims are made to the sophisticated "payor" audience and relate to an approved indication
  - Material differences disclosed, where applicable
- Communication of health care economic information to payors, formulary committees, and other similar entities → promotional
  - Firm communications with payors regarding unapproved products and unapproved uses of approved products

JONES DAY

RWE & CFL COMMUNICATIONS

- Companies internalizing RWE and its multiple uses
  - Potential use in product promotion
  - Limitations
- Appropriate promotional use of RWE

AND ONE MORE CONSIDERATION…

- What about the 1st Amendment in all of this?

JONES DAY

QUESTIONS?