CONSIDERATIONS FOR PHARMACEUTICAL COMPANIES REGARDING THE USE OF HEALTHCARE ECONOMIC RESEARCH STUDIES, REAL WORLD EVIDENCE, AND COMPARATIVE EFFECTIVENESS RESEARCH

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Disclaimer

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Agenda

1. HEOR, comparative effectiveness research (CER), and Real World Data (RWD)
   - What are they
   - Why are they gaining interest

2. Considerations for the use of RWD by pharma companies:
   - To support appropriate product use
   - To support access and reimbursement
   - To support Clinical Decision Making

3. 21st Century Cures Act
   - Amendments to FDAMA 114
   - Use of RWD

4. New FDA Draft Guidance on Communications to Payors
5. Considerations and Mitigations
The biopharma industry is facing a "perfect storm"
Health Economics and Outcomes Research (HEOR)

- HEOR is a growing field that provides important information for healthcare decision making such as access and reimbursement.
- With increasing utilization and cost of healthcare prioritization is important.
- HEOR complements traditional data sources such as RCTs to make access decisions because it can provide data to help payers determine if treatments work in the populations they serve, and how much of the cost should be reimbursed by the healthcare system.
- Many global reimbursement agencies ask for HEOR data as part of their standard assessment process, including the NICE in the UK as well as health technology assessment (HTA) agencies.
Health Economics and Outcomes Research (HEOR)

Common Research Questions:
- Comparative effectiveness
- Adherence studies
- Treatment patterns (such as switching, discontinuation)
- Cost-effectiveness analysis and budget impact analysis
- Benefit-risk analysis
- Direct and indirect disease burden
- Healthcare resource utilization

Methodology:
- Retrospective claims/medical records analyses
- Non-interventional studies
What Is Comparative Effectiveness Research (CER)?

- "Effectiveness" = “efficacy in real-world care”
- (CER) compares outcomes between patients on different therapies in routine care settings
- CER is now becoming a major healthcare research focus in the USA, Europe, Australia, Canada

CER

- Challenge is addressing potential biases from physicians’ choice of patients for therapies
- Requires special study design and analytic techniques
Real World Data and Evidence can Address a Range of HEOR-related Research Questions

<table>
<thead>
<tr>
<th>Real World Data (RWD)</th>
<th>Healthcare data used for decision making that is not collected in conventional randomized controlled trials (RCTs)</th>
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<tbody>
<tr>
<td>Real World Evidence (RWE)</td>
<td>Evidence generated from analysis of RWD</td>
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<tr>
<td>Sources of RWD</td>
<td>Public/licensed databases, Pragmatic trial data, EHR, claims, registries, specialty pharma</td>
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Randomized Clinical Trials (RCTs) versus Real World Data (RWD)

**RCTs** are randomized, blinded clinical trials conducted to test the safety and efficacy of healthcare products or services under carefully controlled conditions.

**RWD** is observational in nature and generally uses data from actual practice settings to perform analyses on comparative effectiveness, comparative costs, quality of life, and signal detection among others.

<table>
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<th>RWD Compared to RCT</th>
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<td>• Include a broader patient population</td>
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<td>• Generate data within the routine healthcare system</td>
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<tr>
<td>• Can address research questions which require large patient numbers and long follow-up periods</td>
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<td>• Can address research questions which can’t be studied by experiments for ethical reasons</td>
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RWE can be a powerful approach to address multiple stakeholder needs in a proactive way.
Current Trends that Raise Interest in RWD

Key Trends Over the Next 5 Years

- **Increased number of assets, and regimen/combination complexity**
- **Increasing demands for robust (i.e., competent and reliable) RWE by multiple stakeholders to aid in their treatment decision-making**
- **Increasing scrutiny on rising cost of therapies; leading to access challenges and therapy management**
- **Use of Value Frameworks, Value of Medicine, and Pathways to aid in treatment decision-making**
- **Rapid growth of HIT and digitization allows stakeholders to access their own data**
- **Analyzing RWD requires robust analytics capabilities to ensure competent and accurate results**

**Multiple Stakeholders are using RWD to aid in their treatment decision-making; Multiple channels exist for communicating RWE; publication represents the cornerstone of the communication journey**
RWD Challenges and Limitations

- Data Completeness, Consistency
- Access to Data, Privacy / Security
- Requires lots of pre-processing, scrabbling, standardization
- Structured vs. Unstructured Data
- Not Meant for Research
- Data Richness
- Interoperability / Data Linking (OMICS, Sensors, patient reported, etc.)

![Chart showing challenges: Hard to Use Data, Missing Information, Inaccurate Information, Incorrect Conclusions]
Examples how real world evidence can be used by pharmaceutical companies

<table>
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<tr>
<th>Medical/Scientific Communications</th>
<th>To Support Access / Demonstrate Value</th>
<th>Commercial Use/ In Promotion</th>
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<tr>
<td>Regulatory submissions (approval, label expansion)</td>
<td>Class reviews</td>
<td>By sales force</td>
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<tr>
<td>Non promotional medical discussions</td>
<td>HTA submissions</td>
<td>Promotional speaker programs and training</td>
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<tr>
<td>Medical engagements (Advisory boards, roundtables)</td>
<td>Reimbursement negotiations</td>
<td>Patient Journey</td>
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<tr>
<td>Responded to unsolicited requests</td>
<td>Value proposition / value messaging</td>
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<td>Scientific data communications, congress activities (press release, abstract book)</td>
<td>Insights for future clinical trials</td>
<td></td>
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<tr>
<td>Hypothesis generation for future clinical trials</td>
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Considerations for the use of RWD to Support Appropriate Product Use

- Audience is individual Healthcare Providers (HCPs)
  - May not have the required expertise to evaluate data
  - RWD competitive noise
  - RWD to support treatment decision (is it sufficient?)
- Not “substantial evidence,” but could complement RCT evidence
- FDA Draft Guidance on communication consistent with label
- Presentations:
  - Prominence of RCT vs RWD
  - Clear separation
  - Overarching claims
  - Wording of claims
  - Disclaimers
- Disclosure of limitations
- Execution – clear training and guidance
Considerations for the use of RWD to Support Clinical Decision Making

- Publications and scientific conferences
  - Terms of use

- Proactive medical communications
  - RWD “Consistent with label”

- Responding to unsolicited medical information requests:
  - From HCPs
  - From Payers
  - Providing RWD may constitute a transfer of value

- Scientific exchange
Considerations for the use of RWD to Support Access and Reimbursement

• Audience include payers and healthcare decision makers
  • Have the required expertise to evaluate data
• Presentations:
  • Prominence of RCT vs RWD - what is the focus of the claim
  • Comparative claims
  • Wording of claims
  • Disclaimers
  • Disclosure of limitations
• Execution – clear training and guidance
• FDAMA114 as amended by the 21st Century Cures Act
• FDA Draft Guidance on communications with payers
21st Century Cures Act – Amendments to FDAMA 114

**Revised HCEI Definition:** "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug." **Such analyses may be comparative to the use of another drug, to another health care intervention, or to no intervention.**

**Beyond the label:** a communication must "relate to" an approved indication of the product and explicitly provides that HCEI that "relates only" to an unapproved indication is not protected. **Manufacturers can communicate HCEI that relate to an approved indication but may go beyond label.**

**Applicable Disclaimers:** HCEI, where applicable, must include a conspicuous and prominent statement describing any material differences between the HCEI and the labeling of the approved drug.
FDA Draft Guidance on Drug and Device Manufacturer Communications with Payors, Formulary Committees and Similar Entities—Questions and Answers

• FDA's first official document addressing FDAMA 114 (as amended by the 21st Century Cures Act). Considerations:
  • Practices for generating and substantiating HCEI consistent with authoritative health care economic research bodies and are robust enough to meet the CARSE standard.
  • Is the audience eligible for proactive HCEI? Does it has the requisite knowledge and expertise and is carrying out its responsibilities for the selection of drugs for coverage or reimbursement?
  • Does the HCEI that "relate to" a drug's FDA-approved indication? Provides examples
  • All component of HCEI, including inputs and assumptions related to economic consequences and clinical outcomes, are CARSE.
    • This standard is important to consider to ensure compliance when HCEI is comparative and there is no underlying head-to-head clinical studies
  • Ensure that all required information is submitted along with HCEI to allow for robust review and discussion
Considerations for the use of RWD to Support Access and Reimbursement (Cont’d)

• Process evaluation and considerations:
  • Is there a robust review process to evaluate promotional materials to confirm:
    • That underlying HCEI is consistent with authoritative health care economic research bodies and meet the CARSE standard.
    • That all components of HCEI, including inputs and assumptions related to both economic consequences and clinical outcomes, meet the CARSE standard.
    • That all information is included (for example, disclaimers, limitations, etc).
    • Audience eligibility for proactive HCEI communications (has relevant knowledge and expertise in the area of health care economic analysis).
  • Is the process for HCEI generation consistent with authoritative health care economic research bodies and meet the CARSE standard.
  • Conduct HCEI research with guidance in mind.
The FDA previously issued guidance on the inclusion of RWE for medical devices, but no similar guidance for drugs. Now the agency is required to do so.

According to the 21st Century Cures Act, RWE is defined as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials (RCT)”.

- This can be taken to mean any data that can be collected from real life medical practice settings, including electronic medical records and insurance claims, and also from patient registries.

With the FDA moving ahead to provide a framework for inclusion of RWE in approval decisions, there will be robust opportunities to demonstrate increased efficacy, safety, and economic value in settings beyond RCTs.

- FDA public workshop (Sept. 13) on developing a framework for regulatory use of real-world evidence
Enforcement

- FDA enforcement to date has focused on misleading economic comparisons that imply product interchangeability/superiority, for example:
  - Claims of greater cost savings than supported
  - Switch claims that are solely cost-base and do not take into account other important considerations such as safety
  - Implied claims of cost savings due to productivity/function
  - Misleading comparative claims of effectiveness, safety, or interchangeability
  - Cost comparisons based on non-comparable dosing regimens
  - Lack of disclosure of additional costs that impact cost savings
- No enforcement concerning FDAMA 114, but this may change given current interest and focus.
Considerations and Mitigation

• Ensuring appropriate x-functional engagement and sharing of insights between Commercial, Medical and HEOR
  • Decisions on whether to pursue a study, which study to pursue, and the study methodologies used rest solely HEOR/Medical, based on their independent scientific objectives and judgment

• Protect Patient Information
  • Requests to combine multiple data sources containing patient data may raise risks of de-identification of patient information. Any such request should be escalated for further review

• What output is being generated and by which functional team
  • Publications
  • Clinical studies
  • Pharmacoeconomic studies
  • Real world data studies

• How will the information and related claims be utilized externally/execution
  • Determine requirements / standards for external use
  • Permission to use data as contemplated
  • Confirm scope of claims and use
    • Limitations
    • Disclaimers
  • Watch out for comparative claims
  • Engage x-functional colleagues early and often to determine applicable review path and/or escalation needs
Questions?