Addressing Evidence Gaps in the Expedited Review Process:
Payer Perspectives

NOV. 18-19, 2021
Moderator Welcome

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Jennifer Graff, PharmD
Senior Director for Professional Affairs
AMCP Partnership Forums
Collaboration for Optimization

- Provide a voice for stakeholders
- Find common ground and gain consensus
- Identify actionable results
- Amplify to raise visibility
Goals of this Partnership Forum

• Identify the gaps between FDA accelerated approval requirements and treatment outcomes valued by payers.

• Explore opportunities for an evidence ecosystem to address gaps

• Develop policy recommendations to facilitate communication, reduce financial uncertainty, and potentially shorten the time to coverage decisions.
Thank You to Our Sponsors
How to Ask Questions
Audience Polling: How would you rate the need for accelerated drug approval?

1. Extremely necessary
2. Very necessary
3. Somewhat necessary
4. Not very necessary
5. Not at all necessary
Audience Polling: How confident are you to apply surrogate endpoints used for accelerated approvals to formulary decisions?

1. Extremely confident
2. Confident
3. Not very confident
4. Not all confident
5. Not applicable
Our Faculty

Vivien Chan, PharmD
General Manager
Director of Formulary & Contracting
Costco Health Solutions

Paula Eichenbrenner
MBA, CAE
Executive Director
AMCP Foundation

Lilian Ndehi-Rice,
PharmD, MBA, BCPS
Associate Vice President, Pharmacy Clinical and Specialty Strategies
Humana Inc.
Agenda

• Background on Accelerated Approval Pathway

• Managed Care Perspectives

• Forum Findings
  • Clarify Accelerated Approval Criteria
  • Correlate Surrogate Endpoints with Meaningful Outcomes
  • Bridge the Evidence Gaps with Enhanced Evidence Ecosystem
  • Advance Potential Policy and Practice Solutions to Reduce Financial Uncertainty

• What’s next?
History of ‘Expedited Programs’

• Tension of drug development/review timeline perceived as ‘too long’ by the patient community and ‘too short’ by others
  • HIV-AIDS in the early 1980s
    • Limited access to experimental drugs
    • Review standard largely ‘survival’
  • In the late 1980s
    • Increased access to experimental drugs
    • Institutionalization of Accelerated Approval
      • Allowing approval based on surrogate clinical endpoints transitioned from ‘survival’ to ‘reasonably likely to predict clinical benefits’

• Tension exists today
  • New goal for some: unfettered access to investigational drugs
  • Recent approval for new medications for ALS
Four Expedited Programs: Focus on Accelerated Approval

**Fast Track Designation**
- Section 506(b) of the FD&C Act 1988
- Features
  - Expedited development and FDA review
  - Can be rescinded

**Priority Review Designation**
- Prescription Drug User Fee Act of 1992
- Feature
  - Shorter clock for FDA review of marketing application

**Breakthrough Therapy Designation**
- Section 506(a) of the FD&C Act 2012
- Features
  - Intensive guidance from FDA
  - Rolling review
  - Can be rescinded

**Accelerated Approval Pathway**
- Section 506(c) of the FD&C Act of 1992
- 21 CFR part 314, subpart H
- 21 CFR part 601, subpart E
- Feature:
  - Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit
  - Confirmatory trials required
  - Approval may be withdrawn
Accelerated Approvals Based on Surrogate Endpoint is Common

Total Approvals (or ‘market access’): 269
> 85% of accelerated approvals in last 10 years are in oncology

Converted to full Approval: 132
Indication Withdrawn: 5
Application Withdrawn: 15
Not Yet Converted: 117
Payer Perspectives on Expedited Reviews
2021 Survey: What and Who

- Cross-sectional survey
- 22 questions
- Piloted to assess content and face validity
- Fielded Sept. 22-Oct. 4

### Respondents
- 178 respondents
- 159 qualified payer respondents

### Employer Types
- Payers
- Pharmacy benefit managers
- Specialty pharmacy

### Job Functions
- Pharmacy director
- Formulary management
- Operations
- Contracting

### Expertise
- Formulary
- Commercial or exchange plan management
Q: How impactful do you think accelerated drug approvals is to the future of healthcare? (1 = Not at all impactful; 5 = Extremely impactful)

Q: How would you rate the need for accelerated drug approval? (1 = Not at all necessary; 5 = Extremely necessary)

<table>
<thead>
<tr>
<th>Impact</th>
<th>Need</th>
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<tr>
<td></td>
<td>3.61</td>
</tr>
<tr>
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<td>3.17</td>
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Notes: Respondents that answered “Not sure/I don’t know” were removed from the analysis. All respondents that endorsed a work organization type of “other” were also removed. Averages are presented.
Q: How concerning are each of the following with respect to accelerated drug approval? (1 = Not at all concerning; 5 = Extremely concerning)

- Less safety data (vs therapies approved via non-accelerated pathways)
  - Extremely concerning: 51%
  - Very concerning: 22%
  - Somewhat concerning: 21%
  - Not very concerning: 5%
  - Not at all concerning: 0%

- Less efficacy data (vs therapies approved via non-accelerated pathways)
  - Extremely concerning: 39%
  - Very concerning: 38%
  - Somewhat concerning: 20%
  - Not very concerning: 4%
  - Not at all concerning: 0%

- Off-label use for non-orphan/rare disease indications
  - Extremely concerning: 30%
  - Very concerning: 47%
  - Somewhat concerning: 19%
  - Not very concerning: 3%
  - Not at all concerning: 0%

Payers are consistently concerned about safety and efficacy data in expedited reviews.
Expedited Reviews and Formulary Decision-Making
Q: Does your organization have a separate and/or expedited review process for therapies receiving accelerated drug approval?

Payers were significantly more likely to have a separate review process for therapies receiving accelerated approval in 2021 compared to 2018 (p < .05)

Statistical test: $X^2 (1, 198) = 4.64; p = .03$

Notes: Respondents that answered “Not sure/I don’t know” were removed from the analysis. All respondents that endorsed a work organization type of “other” were also removed.
Q: When your organization applies surrogate endpoints to your formulary decision-making process, what is the most important consideration?

Payers seek correlation of surrogate endpoints to clinically meaningful outcomes for formulary decisions.

- Correlation to clinically meaningful outcome: 63%
- Clear plan for validation of surrogate endpoint: 17%
- Ability to measure impact on member pop.: 13%
- Generalizability to member pop.: 5%
- Other (please specify): 2%
Q: How confident are you in applying surrogate endpoint data to guide formulary coverage decisions? (1 = Not at all confident; 5 = Extremely confident)

Payers are not confident in applying surrogate endpoint data to formulary decisions.

- Extremely confident: 1%
- Very confident: 17%
- Somewhat confident: 44%
- Not very confident: 34%
- Not at all confident: 3%
1. Clarify Terminology for Accelerated Approval Pathway
1. Clarify Terminology

“designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need”

- Serious or life-threatening condition
- Unmet medical need
- Available treatments

1. Unmet Need and Outcome Certainty Differ for Accelerated Approval Pathway

### Traditional Approval

- Adequate and well-controlled studies
- As safe and effective *as existing therapies*
- Clinical benefit (e.g., “prolongation of life or an established surrogate”)

### Accelerated Approval

- Adequate and well-controlled studies
- Meaningful therapeutic benefit *over existing therapies*
- Surrogate endpoint “reasonably likely to predict clinical benefit” or an intermediate endpoint other than irreversible morbidity and mortality”
## 1. FDA Surrogate Endpoint Requirements

<table>
<thead>
<tr>
<th>Category</th>
<th>Requirement</th>
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<tbody>
<tr>
<td><strong>Causality</strong></td>
<td>• Is there a compelling case for surrogate being on the single direct causal</td>
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<td></td>
<td>pathway to disease outcome, so less need for evidence of universality?</td>
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<tr>
<td><strong>Biologic plausibility</strong></td>
<td>• Is the biology of the surrogate so compelling that it adds to the weight of</td>
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<tr>
<td></td>
<td>empirical evidence for acceptance?</td>
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<tr>
<td>**Specificity/potential for</td>
<td>• Other factors affecting disease outcome, including off-target effects of</td>
</tr>
<tr>
<td>complicating effects**</td>
<td>drugs</td>
</tr>
<tr>
<td><strong>Proportionality</strong></td>
<td>• To what extent does the magnitude of change in the surrogate explain the</td>
</tr>
<tr>
<td></td>
<td>disease or the magnitude of change in disease status or burden?</td>
</tr>
<tr>
<td><strong>Universality</strong></td>
<td>• To what extent is there evidence across drug mechanisms or across different</td>
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<td></td>
<td>populations?</td>
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## 1. Sample Surrogate Endpoints Used in Accelerated Approval

<table>
<thead>
<tr>
<th>Disease or Use</th>
<th>Surrogate Endpoint</th>
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<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Reduction in amyloid beta plaques</td>
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<tr>
<td>Chagas disease</td>
<td>Immunoglobulin G antibody negative or decrease in optical density</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Major hematologic response</td>
</tr>
<tr>
<td>Diffuse B-cell lymphoma</td>
<td>Durable complete response rate</td>
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<tr>
<td>Duchenne muscular dystrophy</td>
<td>Skeletal muscle dystrophin</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Reduction of GL-3 inclusion in renal capillaries</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Serum methemoglobin</td>
</tr>
<tr>
<td>Nonalcoholic steatohepatitis (NASH)</td>
<td>Histopathologic findings or improvement of fibrosis</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>Sputum culture conversion to negative</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Hemoglobin response rate</td>
</tr>
</tbody>
</table>

U.S. Food and Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. [https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure](https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure)
2. Correlate Surrogate Endpoints with Meaningful Outcomes to Payers
2. Improve Understanding of Surrogate Endpoints and Correlate with Meaningful Outcomes

- **What**
  - Understanding of scales norms

- **Who**
  - Ability to differentiate disease severity, response, adverse events

- **How much**
  - Clinically important differences

- **When**
  - Changes can be expected

- **Why**
  - Relationship to clinical or economic endpoints

<table>
<thead>
<tr>
<th>Overall Evidence</th>
<th>Surrogate Endpoints</th>
<th>Clinical Condition</th>
<th>Economic Implications</th>
</tr>
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</table>
| • More than 1 trial  
  • Randomized controlled vs. single arm trials  
  • Long-term follow up to assess durability of response | • Clinical context of surrogate endpoints  
  • Guidance on when change is anticipated  
  • Correlation of results across subpopulations (e.g., more or less severe disease)  
  • Validation with clinical outcomes | • Improved understanding of disease course and patient impact (especially for rare conditions)  
  • Information on subpopulations (e.g., genetic subtypes and disease impact) | • Resource use with worsening disease  
  • Number Needed to Treat  
  • Impact on total cost of care  
  • Budget impact for given plan membership |
3. Bridge the Evidence Gaps by Building an Evidence Ecosystem
3. Bridge Gaps in with Evidence Ecosystem
Data Networks, Analytics, and Infrastructure

- Claims Analysis
- Confirmatory Trials
- EHRs
- Patient Group Registries
- FDA Sentinel
3. Evidence Ecosystem Can Inform Payers

- Correlate surrogate endpoints to meaningful outcome measures
- Trust in surrogate markers
- Generalizability of benefits to sub-populations
- Treatment sequence
- Discontinuation criteria
- Patient Journey
# 4. Potential Policy and Practice Solutions Discussed

<table>
<thead>
<tr>
<th>Payment Solutions</th>
<th>CMS National Coverage Decisions</th>
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<tr>
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<td>CMS Coverage with Evidence Development</td>
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<td></td>
<td>Require value-based contracts for Accelerated Approval pathway</td>
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<tr>
<th>Streamline Coding</th>
<th>Allow biopharmaceutical companies to concurrently apply for HCPCS code with breakthrough designation</th>
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<th>Incentives for Confirmatory Trial Completion</th>
<th>Price at marginal cost until trial completed</th>
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<tr>
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<td>Create a differential rebate for AA products</td>
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| Communication | Voluntary payer advisory committee to aid surrogate endpoint considerations |
Coverage with Evidence Development

Considerations:
- Spillover effect beyond Medicare?
- Would additional legislative authority be needed?
- Evidence development requirements and status would need to be transparent to build trust
Apply Marginal Cost Pricing to Incentivize Confirmatory Trials

- Incentives for enrollment and study result disclosures
- Applicable to multiple lines of business
- Relative ease of administration
- Disincentives for innovation for small or rare conditions due to revenue at launch
- Limited long-term approach

Considerations:
- If marginal cost pricing is accepted, would coverage be mandatory?
Future of Accelerated Approval?

Increasing pressure to address:
1) ‘dangling indications’ and
2) incomplete confirmatory trials
3) product removal
4) FDA reforms?

Increasing pressure to provide:
1) direct access to investigational drugs, without any FDA involvement
2) access to medications with minimal evidence
3) expand approach within oncology
What’s Next?
Next Steps

https://www.amcp.org/Resource-Center/meeting-proceedings-findings/addressing-evidence-gaps-expedited-review-process-payer-perspectives
Key forum takeaways

1. Support Speed of Innovation but Balance Needed to Aid Timely Coverage Determinations
2. Clarify Accelerated Approval Criteria
3. Correlate Surrogate Endpoints with Meaningful Outcomes
4. Bridge the Evidence Gaps with Enhanced Evidence Ecosystem
5. Advance Potential Policy and Practice Solutions and Practices to Reduce Financial Uncertainty
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Mission
To improve patient health by ensuring access to high-quality, cost-effective medications and other therapies.