A Framework for Critical Issues in Pre-approval Access

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The thoughts and opinions in this presentation are made by the speaker and not by or on behalf of Ultragenyx Pharmaceutical
Frameworks for understanding the issues

- The basics of pre-approval access
- Access to medicines
  - Mechanisms
  - Evidence vs breadth of access
- Different stakeholder perspectives
- Current trends
- Questions to consider when making pre-approval access decisions
Pre-approval access: the basics

• **Definition:** Use of an investigational medical product outside of a clinical trial

• **Confusing nomenclature:** compassionate use, expanded access, early access, named patient program, ATU, etc.

• **Main objective:** treatment rather than data

Expanded access to investigational drugs for treatment use – FDA June 2016
Questions and answers on the compassionate use of medicines in the European Union – EMA Jan 2010
Confusing Nomenclature

• Pre-approval access ≈ compassionate use ≈ expanded access ≈ early access
  – Compassionate use
    • In Europe refers to cohort programs
    • In US synonymous with expanded access (single or cohort)
  – Expanded access preferred term by FDA

• Named patient program
  – European term for single patient treatment
  – Can encompass named patient sales in certain countries

• ATU (Autorisations Temporaires d’Utilisation)
  – Specific to France
  – Can be nominative (single patient) or cohort
General criteria for pre-approval access

- Serious or life-threatening illness
- No comparable or satisfactory alternative therapy
- Potential benefit justifies potential risk and risks acceptable in context of disease
- Sufficient supply available
- Will not compromise drug development process

Expanded access to investigational drugs for treatment use – FDA June 2016
Questions and answers on the compassionate use of medicines in the European Union – EMA Jan 2010
Framework #1: mechanisms for access to medicines

**Clinical Trial**
- Gather data under protocol
- Necessary to enable marketing authorization

**Pre-approval Access**
- Main objective is treatment
- May be appropriate for access outside of clinical

**Marketing Authorization**
- Label defines efficacy, safety, dosage, and other information
- Access by prescription
- Enables payment for medicine
Access to medicines

- Investigational
- Approved

Level of available evidence

Breadth of patient access
Access to medicines

Level of available evidence

Investigational

Approved

Marketing authorization

Breadth of patient access

Phase 1 trial

Phase 2 trial

Phase 3 trial
Access to medicines

Level of available evidence

- Investigational
- Phase 3 trial
- Phase 2 trial
- Phase 1 trial

Approved

Marketing authorization

Pre-approval access: Where would you place it?

Breadth of patient access
Access to medicines: examples of pre-approval access

Investigational
Approved

Single Patient Access
Marketing authorization

Level of available evidence

Phase 3 trial
Phase 2 trial
Phase 1 trial

Breadth of patient access
Access to medicines: examples of pre-approval access

- Investigational
- Approved
- Marketing authorization

Level of available evidence:
- Single Patient Access
- Cohort Access
- Phase 3 trial
- Phase 2 trial
- Phase 1 trial

Breadth of patient access
Access to medicines: examples of pre-approval access

Level of available evidence

Investigational

Approved

Marketing authorization

Breadth of patient access

Single Patient Access

Cohort Access

Phase 3 trial

Phase 2 trial

Phase 1 trial

Supplementary Clinical Trials

Investigator Sponsored Trial

www.ultragenyx.com
Framework #2: Perspectives of different stakeholders

Patient
Physician
Regulator
Drug Developer
Different perspectives: the patient

- Access to promising treatment for serious or life-threatening condition
- Exhausted other treatment options
- Stressed out, crisis mode
- Seeking hope
- Willing to take risks
Different perspectives: the physician

- Find treatment for their patient
- Thinks one patient at a time
- Time constrained
- Variable understanding of investigational medicines and pre-approval access process
Different perspectives: the regulator

- Support development of new medicines that could advance public health
- Encourage generation of evidence necessary for marketing authorization
- Ensure patient safety
- Provide mechanism for pre-approval access under appropriate circumstances
Different perspectives: the drug developer

• Develop new medicines to address unmet medical needs
• Gather evidence for marketing authorization
• Limit risks to patients and to the investigational medicine
• Sustainable business model
• Typically the decision maker for pre-approval access
Typical conflicts that can arise from differing stakeholder perspectives

- Treatment for one patient vs. potential to benefit many patients
- Compassion for current sufferers vs. potential to help future sufferers
- Compassion for current sufferers vs. sustainable business model
- Potential for benefit vs. potential for harm or lost opportunity to benefit
Framework #3: Current trends to reconcile the different stakeholder perspectives

<table>
<thead>
<tr>
<th>Increased recognition of the issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased focus on the ethics</td>
</tr>
<tr>
<td>Renewed activity from patient advocacy orgs</td>
</tr>
<tr>
<td>Increased transparency from regulators and drug developers</td>
</tr>
<tr>
<td>Increased government action</td>
</tr>
<tr>
<td>Increased commitment from drug developers</td>
</tr>
</tbody>
</table>
Increased recognition of the issues

- Many industry conferences like this one devoted to pre-approval access
- CROs promoting pre-approval access services
- Regulatory and other government actions
- Numerous media stories
Complexities of pre-approval access in the news

Boston Globe, July 2015

Sick kids, desperate parents, and the battle for experimental drugs

The complex world of compassionate use drugs and who gets access to them.

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Young boy’s struggle to survive sparked widespread push for drugs for the terminally ill

Liz Szabo, Kaiser Health News

The dark side of ‘compassionate use’ of experimental drugs

By Arianna Eunjung Cha

Denying the Dying or Protecting the Vulnerable?

Compassionate Use of Experimental Drugs

Lynn Adams

Feb 1, 2016
Increased focus on ethics

- Breakout session in this conference
- Response to the Ebola virus outbreak
- Debate over right-to-try legislation
- CompAC: the Compassionate Use Advisory Committee
  - Partnership between NYU School of Medicine Division of Medical Ethics and Janssen

http://www.med.nyu.edu/pophealth/divisions/medical-ethics/compassionate-use-advisory-committee
Renewed activity from patient advocacy organizations

- Kids V Cancer Compassionate Use Navigator for the pediatric oncology community
- EveryLife Foundation workshop on compassionate use
- The Epilepsy Foundation support for removal of barriers to cannabis research
- The Abigail Alliance mission to create wider access to experimental medicines
Increased transparency

- FDA / HHS
  - New guidance documents for industry
  - Website for patients, physicians, and industry
  - Publication of FDA experience from 2005 - 2014
  - ClinicalTrials.gov requirement for posting expanded access programs

- Industry:
  - 21st Century Cures mandates industry to have publicly available policies and procedures
  - BIO encourages members to post policies
  - Companies are adding expanded access sections to their corporate websites
Increased government action

- 21st Century Cures act
- Right to try legislation
- FDA actions
Increased commitment from drug developers

• Posting policies
• More cohort pre-approval access schemes
• Incorporating pre-approval access plans early in the drug development process
• More engagement with other stakeholders
Framework #4: Considerations when managing pre-approval access decisions

• What is the nature of the disease?
  – Life threatening, irreversible outcomes, rapidity of progression?

• What is known about the patient?
  – Medical status, evidence for the disease in question, other treatment options?

• What is known about the investigational therapy?
  – Scientific rationale, evidence of potential benefit and risk?

• Potential impact on the drug development program?
  – Will effective development be harmed? Clinical trial option? Drug supply?

• What is the right thing to do?
Summary

• Multiple mechanisms for pre-approval access
• Marketing authorization provides broadest access
• Drug developers receive frequent requests for pre-approval access
• Differing stakeholder perspectives must be respected in pre-approval access decisions
• Landscape for pre-approval access is changing rapidly