Industry Perspective: The Challenges and Benefits in using Expedited Regulatory Pathways

Alan Poirier, Pfizer Inc.
U.S. Regulatory Policy and Global Intelligence
Worldwide Safety and Regulatory

American Association of Pharmaceutical Scientists, Annual Meeting
November 14, 2016
Expedited Pathways Challenges and Benefits

• Accelerating Medicines to Patients

• Regulatory Flexibility

• Benefits of Expedited Pathways
  – How much time saved?
  – What works well?

• Challenges
Pfizer commitment to patients and support for Innovation

AAPS November 2016
It may take 12 - 14 years for a new drug to advance from research to approved product

12 - 14 years* for preclinical, clinical development, and regulatory review

* Source: Median new drug cycle times, KMR, Parexel Biopharmaceutical R&D Statistical Sourcebook (2013-2014)
Expedited pathways created for drugs which demonstrate potential to significantly improve lives, where the standard of care is inadequate

- Pathways have unique qualification criteria
  - Different by regulator and drug development stage (see references)

- Examples of qualification criteria
  - Significant improvement in safety and effectiveness, such as:
    - An effective treatment where none existed | Lack of a toxicity of another therapy
    - Reducing serious outcomes not mitigated by available Rx
    - Improving tolerability for people who do not respond well to available therapy
  - Therapeutic innovation that addresses a major interest in public health
Drugs may be designated as Breakthrough if they are directed at a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy.
## Different types of regulatory flexibility

<table>
<thead>
<tr>
<th>Examples of Flexibility</th>
<th>Examples: Expedited Regulatory Programs</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater Regulator involvement and guidance with development plan</td>
<td>✓ FDA Fast Track designation</td>
<td>✓ FDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>✓ FDA Breakthrough designation</td>
<td>✓ EMA Accelerated Assessment</td>
</tr>
<tr>
<td></td>
<td>✓ EMA PRIME</td>
<td>✓ PMDA Priority Review</td>
</tr>
<tr>
<td></td>
<td>✓ PMDA Sakigake</td>
<td></td>
</tr>
<tr>
<td>Faster Review (2 – 6 months faster)</td>
<td>✓ FDA Priority Review</td>
<td>✓ EMA Conditional Marketing Authorization</td>
</tr>
<tr>
<td></td>
<td>✓ EMA Accelerated Assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓ PMDA Priority Review</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓ Health Canada Priority Review</td>
<td></td>
</tr>
<tr>
<td>Approval based on surrogate endpoint or intermediate clinical endpoints*</td>
<td>✓ FDA Accelerated Approval – subject to confirmatory trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓ EMA Marketing Authorization under Exceptional Circumstances</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓ Health Canada Notice of Compliance with conditions (NOC/c)</td>
<td></td>
</tr>
<tr>
<td>Approval on limited data</td>
<td>✓ EMA Marketing Authorization under Exceptional Circumstances</td>
<td></td>
</tr>
<tr>
<td>Other tools: Waivers / Incentives/Vouchers</td>
<td>✓ Orphan designation (FDA, EMA, PMDA...)</td>
<td>✓ FDA priority review vouchers (PRV)</td>
</tr>
</tbody>
</table>

*with postapproval commitments

AAPS November 2016
How expedited pathways enable acceleration in Clinical Development / Review

(Based on Strong Early/Interim Data and High Unmet Need)

1. Approval with earlier/limited data (e.g. Phase 2, or Surrogate endpoints or Single pivotal trial)
2. Approval with earlier/limited data
3. Faster Review

Preclinical → Phase 1 → Phase 1B/2A → Phase 2B → Phase 3 → Review

1B – Proof of Mechanism
2A – Proof of Concept

Dosing
Pivotal Trials

Faster Review

AAPS November 2016
Expedited Regulatory Tools require more (and earlier) interactions with the regulator.

Preclinical development

Clinical development
Phase 1 | Phase 2 | Phase 3

Application Review

Post Approval studies

Early & Frequent Health Authority Interactions

Submission

Approval

Fast Track Process (US)

Breakthrough (US)

PRIME (EU)

Accelerated Approval (US)

Conditional MA (EU)

Priority Review (US)

Accelerated Assessment

Approval under Exceptional Circumstances

Strong collaboration between Agency and Sponsor to advance Regulatory Science

AAPS November 2016
Benefits from Agency interaction depends on timing

**Breakthrough Therapy Designation (BTD) examples**

- **BTD with pivotal data (submission in near future)** ➔ expedited review process
  - Agency may suggest a submission strategy or advise sponsor to seek a rolling submission
  - Agency may advise on methodology for bridging data between multiple studies
  - Agency may offer flexibility in the timing of pre-submission meetings and inspections
  - In some cases: waiver for Pediatric Study Plan requirements prior to approval
  - In some cases: submission of some data possible during the review cycle

- **BTD with early data (submission after more studies)** ➔ expedited development
  - Agency can offer design guidance on an efficient development program
  - Agency may influence study design | database size | end point selection
    - Sponsors have changed endpoints, and amended statistical analysis plans as a result
  - Agency and sponsor can also coordinate to expedite the manufacturing process.
Early Agency interaction can change sponsor thinking

Industry BTD examples

- Industry examples demonstrate the impact of FDA involvement and advantages of close regulator interactions

**Case A:** The FDA suggested that the pivotal trial should include an interim analysis of efficacy, so patients on placebo could be transferred to the treatment arm if preliminary results signaled a clinically significant treatment effect.

**Case B:** The FDA recommended eliminating a comparator arm for planned phase III studies, reducing the study size by more than 100 patients.
Benefits from Expedited Programs

Agency maintains standards, but more engaged

- **Increased Communication**
  - Starts with seeking an expedited designation (e.g. Fast Track, Breakthrough, PRIME)
  - More design advice (endpoints, stat methods, etc)
  - Closer involvement of Agency management

- **Agency will be more engaged, may offer some flexibility**
  - Expect more guidance on program direction
  - Earliest interactions with Agency can “change the direction” (trial design)
  - Evidentiary requirements for S/E can be reduced vs original development plan
  - Use of post marketing commitments for additional data collection
Benefits: Review times are faster for expedited programs (2011-2015)

Figure 4: NAS median approval time by review type for six regulatory authorities in 2011-2015

*Expedited review’ refers to EMA ‘Accelerated Assessment’ and FDA/PMDA/Health Canada/Swissmedic ‘Priority Review’.
**The EMA approval time includes the EU Commission time.
***TGA does not currently have an expedited evaluation programme.

© 2016 CIRS- Centre for Innovation in Regulatory Science, Ltd
Expedited review:
different rates of use, different time savings

- Proportion of NMEs that qualify (11% - 51%)


AAPS November 2016
Benefits: Time savings range from several months to several years

**Early & Frequent Health Authority Interactions**

<table>
<thead>
<tr>
<th>Preclinical development</th>
<th>Clinical development</th>
<th>Application Review</th>
<th>Post Approval studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time Saved:**

- > 2 years \(^1\)
- 2-6 months \(^2\)

(1) References:

- Pfizer Trumenba Team experience with BTD and Accelerated Approval

The benefits of Expedited Pathways are clear

- Recognize the disease impact on patients
  - These procedures to expedite development and review are typically reserved for serious diseases and conditions

- Creates a shared urgency between Agency and Sponsor
  - Aligned incentives - neither party wants to “drop the ball”
    - Closer involvement of Agency management
  - More design advice (endpoints, stat methods, etc)
  - Trials that are efficient (more feasible) but still rigorous, and may result in reduced development costs.

- Patients have earlier access to new treatments
  - From 2 months to 2+ years time saved
Challenges with Expedited Pathways

Expedited Pathways are more resource intensive

• Early Success (good problem to have)
  – Early studies may become pivotal and trigger pre-submission discussion
  – Rapid turnaround for information requests
  – Review clock may be very brief (in some cases, a few months)

• At-risk investments may be required to prove you can make the product, have addressed nonclinical and other issues
  – Commercial mfg program must deliver quality product a time of approval
  – Toxicology study timing
  – Clinical: accommodate plans for DDI, statistical plan, programming

• Internal governance process may need to be condensed
  – Alignment decision criteria needed (when to add resources)
  – Expert project management very important
The benefits are clear…. but the challenges must be addressed in early planning

Regulators are responsive to medical needs and public health imperatives –

*Pathways are effective means to expedite products to patients*

Sponsor builds strategy into drug program before clinical testing

- **Agreed decision points** (& resourcing)
- **CMC** (process, stability, BE, facilities)
- **Toxicology** (chronic, repro, carci phase 4 commitment, rolling submission)
- **Clinical** (dose, endpoints, design)
- **Regulatory** (PIP, INN, companion diagnostics)
- **Market Access** (HTA/payer evidence needs)
- **Patient Views** and Preferences
Questions?
References for additional details

- FDA Fast Track: (details here)
- FDA Accelerated Approval: (details here).
- FDA Breakthrough Therapy Designation: (details here)
- FDA Priority Review: (details here)

- EMA Conditional Marketing Authorization: (details here).
- EMA Marketing Authorization under Exceptional Circumstances: (details here)
- EMA PRIME (PRIority MEdicines): (details here).
- EMA Accelerated Assessment Procedure: (details here)

- PMDA Sakigake: (details here)
- PMDA Priority Review: (details here)

- Health Canada Notice of Compliance with Conditions (NOC/c) approval (details here)
- Health Canada Priority Review: (details here)