International Harmonization of Expedited Programs: Challenges and Opportunities for Increasing Patient Access to Innovative Therapies

• Session I: Stakeholder experience with expedited programs: **process related issues**

  *Regulatory view from gene therapy company*
Introduction

• Harmonization vs Convergence:
  – Harmonization should be helpful for processes
  – Convergence more appropriate for scientific review
• Starting with process harmonization may help facilitate regulatory convergence when needed on scientific issues
• Process harmonization may influence mindset
• Harmonization could be leveraged to reduce potential existing complexity in regulatory processes
• Opportunity for collaborative approach with regulators on process harmonization
• Suggestions focused on US/EU

Identify areas where process harmonization would be of greatest value taking into account flexibility in existing frameworks
Existing expedited pathways regulatory processes

– FDA and EMA Orphan designations
– FDA Breakthrough Therapy designation
– EMA PRIME designation
– EMA Adaptive Pathways Pilot
– EMA/HTA Scientific Advice
– EMA/FDA Parallel Scientific Advice

• Additional considerations could include FDA fast-track, FDA priority review and EMA accelerated assessment, FDA BLA/NDA rolling submissions, EMA conditional approval, etc.
What is working well already

• **Orphan drugs**
  – Common application forms for orphan drug designation
  – Common annual reports for orphan drug designation

• **ICH:**
  – Development Safety Update Reports (DSURs) with regional appendices
  – Common Technical Document (CTD)
    • Would welcome a CTD for advanced therapy products

• **Clusters between EMA and FDA, as well as other agencies**
  – Orphan
  – Advanced Therapies
  – Oncology
  – Patient engagement
  – etc.

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Note: Parallel Scientific Advice relatively unpopular to date for unclear reasons:
- Either “too cumbersome/lengthy” or
- “Industry likes to play one agency against the other”
- There is opportunity for improvement
To what extent lack of harmonization adversely affects drug development?

Non-harmonized processes...
- ...create additional complexity, are more resource intensive and inefficient
- ...require significant experience to set global strategy; start-up/small company will default on US if other regions processes are too different or too complex to understand

- Lack of harmonization has not caused major delay, except for:
  - clinical trial applications in the EU take longer than in the US typically
  - processes specific to gene therapy (US RAC, EU GMO applications) are particularly cumbersome and create clear delays in initiating clinical trials
  - approach to pediatric development (EU can be more supportive in some instances)

- Process harmonization would help regulatory teams focus on scientific issues and increase chances of synchronized approval

- Joint or parallel processes will be helpful if very clear for all parties

Main impact is that new treatments are rarely available at the same time in all regions
Recommended Solutions for Processes

• **Clinical Trial Applications**
  – Harmonize clinical trial application requirements globally using CTD (similar to INDs)

• **Parallel Scientific Advice (PSA)**
  – **Templates:**
    - 1) Meeting Request; 2) Brief Pack, 3) Draft responses or “List of Issues” 4) Minutes 5) Final Advice
  – **Guideline with FAQs for criteria, process and timetable**
    - For serious or life-threatening condition with unmet medical need; priority for discussions on pivotal programs
    - For small companies with innovative products (support innovation and drive harmonization of regulatory science in parallel with advancement of science)
    - For rare diseases and specific disease areas
  – **Global tools for each product/indication:**
    - Evidence generation plan
    - Communication plan
    - Issue log

• **Expedited programs/pathways and designations:**
  [Orphan; Fast Track, Regenerative Advanced Therapy (RMAT); Breakthrough, PRIME, Sakigake, Adaptive Pathways]
  – **Single application form for BTD/PRIME/SAKIGAKE** (like for orphan drugs designation)
  – Designated products should be prioritized for PSAs

• **Registration**
  [Priority Review, Accelerated Approval, Under exceptional circumstances, Conditional Approval, Accelerated Assessment]
  – **Joint filings MAA/BLA and parallel review (ICH has helped with CTD format)**
Where is the added value?

• Source of innovation increasingly from small biotech companies
• Having different processes in the US, EU, and Japan certainly creates large hurdle for small/medium companies:
  – Most companies do not have required internal expertise to leverage existing mechanisms
  – Most companies would not have bandwidth to execute programs in 3 regions
  – And even less for rest of the world
  – Different processes complicate development; not always delay in first or second region, but certainly starting with 3rd region/country (sequential rather than parallel interactions)
  – What causes most delays are lengthy procedures; rather than how harmonized they are

• Harmonized regulatory processes:
  – Will be most helpful for small companies and exponentially more beneficial to support innovation
  – Will likely increase convergence within large companies & regulators
  – Will help reduce gap between regulatory science and advancement of science

• Convergence without harmonization may be more difficult
• Process harmonization and scientific convergence may make sense as a priority for rare diseases with similar standard of care and epidemiology across regions/countries, as well as specific disease areas identified as priority, particularly because of high unmet medical need