Roundtable Session – Table 10 – Expedited Approvals of Medicines for Rare Diseases

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Abstract:

Millions of people worldwide live with rare diseases and most of these conditions lack approved treatments. Global Regulatory agencies are more commonly starting to use expedited pathways to facilitate initial approvals. However, rapid clinical development timelines combined with pressure to secure expedited global approvals can create significant pressure on the development of acceptable Quality and Regulatory CMC strategies. This roundtable discussion explores how to develop strategies which incorporate robust and flexible manufacturing approaches by sharing insights and experiences.

The session will examine the unique hurdles of licencing medicines for rare diseases. Participants will be free to direct the discussion but could discuss the challenges of keeping pace with clinical development, especially for global markets. We could also address the difficulties of validating processes with limited batch data and securing appropriate shelf-lifes with limited stability data. We could discuss how early analytical testing and advanced supply chain planning can prevent production bottlenecks. We could discuss opportunities to minimise the impact of local analytical testing and local GMP registration requirements. We could explore the use of reliance approaches focussing on initial licencing and discuss some of the challenges associated with registration of newer modalities.

The goal of this roundtable is to explore and share actionable solutions that can ensure reliable global approvals which facilitate future supply to market of high-quality therapies for rare diseases.

Discussion Questions:

1. It’s a medicine for a rare disease surely we don’t have to meet all local requirements? If it's good enough for major regulators other countries will accept it right?

2. What aspects of development might regulators be more willing to allow the sponsor to complete post-approval (e.g. as a commitment)?

3. Do I have to go for scientific advice to every agency before I file this product for a rare disease?

Notes:

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SUMMARY OF DISCUSSION: QUALITY, SUPPLY, AND REGULATORY STRATEGIES FOR RARE DISEASE PRODUCTS

The discussion covered a broad range of quality, supply, and regulatory considerations aimed at enabling expedited approvals of rare disease products worldwide. Strategies for both initial marketing applications and lifecycle management (LCM) activities were also explored.

The summary below highlights the key discussion points and is not intended to be exhaustive.

ADAPTED CMC STRATEGY FOR RARE DISEASE PRODUCTS

The discussion began with the challenges associated with manufacturing very small numbers of batches due to the limited patient populations typical of rare diseases. Consequently, reduced batch numbers may impact several key CMC elements.

Process Validation

Generating a traditional Process Performance Qualification (PPQ) package may be challenging. Alternative approaches may be acceptable, such as manufacturing two to three drug product (DP) PPQ batches supported by a single drug substance (DS) PPQ batch.

Specifications

A limited manufacturing history may result in a reduced understanding of the product at the time of the initial submission. Consequently, a broad set of specification parameters and tight acceptance criteria may be required by agencies for release testing.

In addition :

- Some countries require a comprehensive set of tests (e.g., heavy metal testing) and may not fully accept a control strategy-based approach.
- Certain health authorities may expect all release tests to be included in the stability programme.
- Overly broad or conservative specifications at launch can create a significant long-term regulatory burden, as post-approval specification widening may be difficult to achieve.

Shelf-Life and Stability

The amount of stability data available at the time of submission is likely to be limited.

Stability modelling is expected to become an important enabler in this area. However, its routine use remains limited to date, and acceptance may vary across agencies and countries. Early discussion with health authorities is therefore recommended.

PRIME Toolbox Principles

Application of the principles outlined in the PRIME Toolbox is encouraged. A platform approach could be used. However, acceptance may vary between health authorities, especially where products included in the platform have not been approved or marketed in all relevant countries.

Product Quality Benefit-Risk Considerations

As proposed in ICH M4Q(R2), Product Quality Benefit-Risk (PQBR) considerations may be used to support the overall benefit-risk assessment and demonstrate how anticipated patient benefits outweigh residual quality risks.

Analytical Testing

Local analytical testing can represent a significant operational burden. In certain circumstances, reduced testing strategies may be accepted.

Examples include:

- Use of Container Closure Integrity Testing (CCIT) instead of sterility testing at selected stability time points to conserve samples.
- Use of rapid sterility methods.

Acceptance of reduced testing programmes or alternative analytical methods varies substantially across countries. Furthermore, some countries expect all release tests to be performed throughout the stability programme.

OPERATIONAL COMPLEXITY, IMPLEMENTATION STRATEGY, AND PATIENT ACCESS

A key consideration is balancing operational complexity, global implementation constraints, and patient access objectives to ensure timely availability, efficient management of low-volume supply, and minimization of shortage risks.

Areas discussed included:

- Reduction of SKU complexity.
- Use of shared packs (multi-country packs).
- Multilingual and multinational packaging approaches.
- Electronic Patient Information Leaflets (ePIL) and electronic Product Information (ePI).
- Potential use of EU packs during shortages or other exceptional circumstances.

Licensing, Pricing, and Reimbursement

From a patient access perspective, it is important to assess whether obtaining a marketing authorization in every country is necessary. Given the very limited patient population involved, alternative access pathways may be available in some territories.

Pricing negotiations and reimbursement processes may also present significant challenges.

EARLY AND GLOBAL REGULATORY ALIGNMENT

Early engagement with health authorities and transparent communication are strongly encouraged, as they improve predictability and facilitate alignment on proposed development strategies.

It should not be overlooked that health authorities have experience in multiple products and companies and can suggest new approaches or alternative solutions that had not yet been considered by the industry.

Country-by-Country Regulatory Assessment

A comprehensive country-by-country assessment should be developed, covering:

- Rare disease-specific regulatory mechanisms
- Availability of expedited pathways
- Reliance procedure.
- CMC expectations and strategy
- Shared packaging and language requirements
- Post-approval commitments
- Post-approval variation timelines
- Lifecycle management activities (e.g., specification widening)
- Opportunities to leverage Post-Approval Change Management Protocols (PACMPs)

Country-Specific CMC Considerations

A detailed assessment of country-specific CMC requirements is recommended, as significant differences may exist regarding:

- Specifications
- Stability requirements
- Release and stability testing expectations
- Local packaging requirements

- Local analytical testing requirements

Examples discussed included :

- Batch strategies and manufacturing commitments, where traditional expectations for commercial-scale and PPQ batches may need to be adapted and agreed with health authorities.
- Limited acceptance and experience with stability modelling.
- Variable acceptance of platform approaches.

Reliance Pathways

When reliance pathways are used, inclusion of assessments from reference agencies/countries within the initial submission package may facilitate review and support the proposed approach.

Regulatory Interactions

For each product, requirements and expectations should be confirmed with all relevant countries (e.g., China, Brazil, Saudi Arabia).

The most appropriate type of regulatory interaction should also be defined as early (e.g., Scientific Advice procedures versus national consultation mechanisms).

Post-Approval Changes

The WHO *Guidelines on Procedures and Data Requirements for Changes to Approved Biological Products* can serve as a useful reference. The reporting categories and associated review timelines described in the guideline may improve predictability, which is particularly important for rare disease products.

Digital Submission Platforms

Cloud-based submission platforms such as Accumulus may facilitate information sharing by enabling participating health authorities to access questions and responses in real time, thereby increasing transparency and alignment.

CLOSING REMARKS

Thank you to all participants for the open discussion, valuable insights, and collaborative spirit. The exchange highlighted the importance of early planning, adapted CMC strategy considering requirements in all relevant countries, early and case-by- case engagement with health authorities and cross-functional collaboration in enabling timely patient access to rare disease therapies.