Accelerated Development Programs for Innovative Therapies: Opportunities for Patients and Technical Challenges

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Outline

• Overview of Expedited Development Programs
  – US FDA
  – Other Countries

• Breakthrough Therapy Program

• Benefits and Challenges of Breakthrough Therapy Program
  – Technical Challenges for Breakthrough Development Programs

• Balancing Risk of Less CMC Data at Time of Filing vs Patient Benefit

• Summary and Conclusion
Expedited Programs for Serious Conditions
US FDA

- FDA final guidance issued in March 2014 defines each program, requirements, and benefits
  - Accelerated Approval
  - Fast Track
  - Priority Review
  - Breakthrough Therapy
Eligibility Requirements for Expedited Programs Based on Clinical Decision

• Serious Condition
  – Drug intended to treat a serious condition, defined as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning

• Available Therapy
  – Approved/licensed in the US for the same indication and relevant to US standard of care for the indication

• Unmet Medical Need
  – An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy
Fast Track

• Qualifying Criteria
  – Drug intended to treat serious or life-threatening disease or condition, and demonstrates the potential to address unmet medical needs
    • Based on non-clinical or clinical data
    • Can be submitted in an IND

• Expedites development and review
  – Frequent interaction with review team
  – Potential for Priority Review if supported by clinical data requirements
  – Opportunity for rolling BLA/NDA review
Accelerated Approval

• A drug that treats a serious condition and generally provides a meaningful advantage over available therapies

• Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., an intermediate clinical endpoint)

• Post approval confirmatory clinical trials required to verify the clinical benefit of the surrogate endpoint

• The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug
  – HIV (viral load)
  – Cancer (tumor progression)
Priority Review

- Drug that treats a **serious condition** and if approved would provide significant improvement in safety and effectiveness

- *Shortens the review timeline from 10 to 6 months*

- Sponsor can request priority review at time of submission of BLA/NDA

- FDA grants priority review within 60 days of submission at time of filing the application
Breakthrough Therapy

• To qualify for the designation, a drug must:
  – Treat a **serious or life threatening disease or condition**
  – Provide *preliminary clinical evidence* indicating a potential for substantial improvement over existing therapies on one or more clinically significant endpoints
  – Submit designation request during IND

• A drug with a breakthrough designation will have
  – Increased communication with FDA during development and review
  – FDA guidance to ensure that the design of clinical trials are as efficient as practicable
  – A cross-disciplinary project lead assigned to the FDA review team, and increased involvement of senior managers and experienced review staff
Expedited Programs Other Countries
Expedited Development Programs in EU

• EMA has a number of tools that could be used to support accelerated development of innovative medicines for life-threatening diseases
  – Conditional Marketing Authorization
  – Authorization Under Exceptional Circumstances
  – Compassionate Use

• To date these tools have not been widely used but could be considered in an adaptive licensing approach

• Legislative and reimbursement environment in EU more challenging for implementing a breakthrough approach like the US

• EMA and CHMP have been discussing “Progressive License” approach
  – Announced a Pilot Phase of “adaptive licensing” in March 2014
  – Since renamed “pathways” and referred to as Medicines Adaptive Pathways for Patients (MAPPs)
The aim of the pilot phase is to discuss with various stakeholders the earliest possible point at which patients can be given access to innovative medicines:

- Initial approval may be on a small sub-set of population
- Further submission and expansion of populations thereafter

Gain experience in a “safe harbour” context with regulatory authorities and experts, health technology assessment bodies, and patient groups in discussion of specific requirements for the benefit-risk assessment in early authorizations of these medicines.

Several companies have already initiated pilot projects; a recent EMA report indicated that sixteen out of 58 applications have been selected to continue the pilot project:

- 5 orphan drugs
- 2 ATMPs
- 5 anti-cancer
SAKIGAKE Process in Japan

• Principles are broadly similar to US FDA Breakthrough Designation Process
  – Speed review of innovative new drugs

• “Saki” means “early” or “go beyond”, while “gake” means “run”; Sakigake translated into English means “forerunner review assignment”

• Sakigake fits in with Japan’s desire to be seen as a world class country for innovation and drug regulation

• Scheme will apply broadly to medical devices and regenerative medicines as well as conventional drugs and biologics

• Only products developed first in Japan, globally, or in parallel track with elsewhere will be eligible for the special treatment
Sakigake Process -- Practical Operation

- Sakigake products receive priority review with a target of six months from submission to approval (versus 12 month review for standard products)

- Waiting time for consultations with the regulator before the start of clinical trials cut from the standard 2 months to one month

- PMDA will assign a consistent “concierge” contact to shepherd Sakigake products through the regulatory process from consultations to approval

- Rolling submissions allowed to start reviews on available data before full submission of pivotal clinical results; may result in enhanced requirements for post-marketing surveillance and lengthened re-examination period
Art. 25 The company may submit, exceptionally, the clinical trials report containing completed phase II studies and initiated phase III studies in order to require the registration of new drug for the prevention or treatment of serious threat to life or highly debilitating diseases, since it is demonstrated for both cases as unmet medical need.

Sole paragraph. In specific cases where the phase III studies are not applicable and the phase II studies are enough for proving the efficacy and safety of the drug, the company may submit the application for registration after completing phase II studies.
Article 23 Exceptionally, the company may apply for registration of new biological product used in the treatment or prevention of severe diseases and/or high mortality, with phase II clinical studies already concluded and with ongoing phase III studies, provided a high therapeutic or preventive efficacy is demonstrated and/or there is no other comparable alternative therapy or drug for that stage of the disease.

Paragraph 1 If the registration is granted by Anvisa, the safety and efficacy must be monitored and evaluated continuously in Brazil, by the pharmacovigilance system of the owner company, meeting the legislation in effect.

Paragraph 2 In the cases foreseen in this article’s heading, in addition to the documentation described in Sections I and II of Chapter III of this Resolution, when filing the registration application, the applicant company must submit the following documents: I – schedule of conduction and conclusion of the phase III clinical studies; II – preliminary results of the phase III clinical studies, if available.

Paragraph 3 Results of the phase III clinical studies must be submitted to ANVISA as soon as they are available, as pointed out in the conduction schedule.
Breakthrough Therapy Program
Breakthrough Therapy Program

• On July 9, 2012 the FDA Safety and Innovation Act (FDASIA) was signed into law and included the Advancing Breakthrough Therapies for Patients Act

• For serious or life-threatening diseases; preliminary clinical evidence shows a substantial improvement over existing therapies

• Can leverage accelerated approval; priority review; and rolling submission

• Breakthrough Therapy Designation Process
  – Sponsor has clinical data
  – Sponsor submits breakthrough therapy request based on clinical data
  – FDA has 60 days to review and respond
    • Designation YES (“granted”) or NO (“denied”)
  – FDA decision-maker = Medical Policy Committee
    • FDA Senior Staff
Breakthrough Therapy Designation Criteria

• Breakthrough Therapy Designation Request (BTDR) decisions are complex and there is no one-size-fits-all characterization of a Breakthrough Therapy (BT) drug nor a definitive threshold for substantial improvement

• Some preliminary patterns suggest that FDA relies on three primary considerations:
  – Reliability of clinical evidence (trial design and analysis issues)
  – Magnitude of treatment effect shown (persuasiveness of the data)
  – Availability of therapies to which the drug is being compared

• Wide variation by therapeutic area in trial characteristics, patient populations and available therapies make it difficult based on existing grants and denials to determine a substantial improvement threshold
Breakthrough Therapy Designation Requests  
Denial “Themes”

• Lack of compelling benefit-risk for a subset population
• Clinical trial evidence may be compelling, but does not demonstrate substantial improvement in efficacy or safety over available therapy
• Single-center source of data limits credibility
• Safe and effective dose not identified
• Lack of heterogeneity in population
Breakthrough Therapy Designation Request (BTDR)

- As of May 2015, FDA has rendered decisions on 259 BTDRs during the first 4 years of the program granting 90 requests mostly through CDER
  - CDER received 258 requests and granted 78 (30%)
  - CBER received 50 requests and granted 12 (24%)
- Majority of BTDRs for oncology/hematology and antiviral drugs; antivirals highest proportion of grants
- 16 BT designated projects have been approved with an average of 5.7 months from submission of the BLA/NDA
- This year 4 Breakthrough Therapy Designations (BTD) rescinded because they no longer met criteria of substantial benefit over existing therapies
  - Sign of caution for sponsors in highly competitive areas
A Sponsor’s Perspective on Breakthrough

Genentech Roche Experience

- 8 Breakthrough Therapy Designations granted
  - 5 Oncology
  - 1 Ophthalmology
  - 1 Immunology
  - 1 Pulmonary

- Several denials

- One denial which upon resubmitting (with more data), designation was granted
Impact of Breakthrough Program on FDA Resources

• Significant resource commitment once Breakthrough Therapy (BT) granted to support “all hands on deck” approach for development and review of BT drugs
  – Congress did not allocate funding to cover costs
  – Concerns that program potentially impacting review of other applications
  – Congress may attach user fee for BT program to 2017 PDUFA

• Multi-functional review teams
  – Clinical
  – Pre-clinical tox
  – Clin Pharm
  – Statistics
  – CMC (DS, DP, assays, labeling, facility inspector, team leads)
BTD: Exploring the Qualifying Criteria
Brookings Meeting, April 2015

• Event Materials, Discussion Guide, Case Studies & Video:
  http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria

• Slides:
  http://www.brookings.edu/~/media/events/2015/04/24-fda-breakthrough-therapy-designation/breakthrough-therapy-slide-deck.pdf
Benefits and Challenges of Breakthrough Therapy Designation
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• FDA and sponsor collaborate in a dynamic, multi-disciplinary process to determine most efficient path forward so that clinical trials are as efficient as possible and number of patients exposed to a potentially less efficacious treatment is minimized
  – Clinical development timelines potentially reduced from 7-10 years to 3-5 years

• Shorter clinical development programs will have significant impact on manufacturing readiness to ensure a sufficient supply of safe and efficacious product

• Manufacturer will need “an all hands on deck” approach
  – Effective interface with clinical organization to identify BTD candidates early
  – Resource intensive; will need to be selective
  – Collaborative cross functional approach between development, commercial and regulatory operations needed for success
Expedited Clinical Development Programs will put CMC/GMP Issues on Critical Path

• Shorter clinical timelines for expedited pathways will necessitate new approaches to product & process development, commercial readiness, launch and regulatory filings

• Does not mean you can do less, will need to start some activities sooner
  – Focus on reliable supply of quality product at launch, not process optimization
  – Front-load critical product and process characterization activities earlier

• Develop manufacturing readiness plan to address timeline for development of the manufacturing capabilities with goals aligned to clinical development program

• Perform risk assessment regarding availability of less CMC information at the time of filing and product launch versus patient benefit; discuss mitigation approaches with Health Authorities early
Accelerated CMC Development Timelines for Breakthrough Products

• Cross functional technical team modeled accelerated timelines for large and small molecule products based on traditional phase dependent CMC/GMP activities

• Assumed 5 year clinical development program from initiation of phase I to launch based on:
  – Breakthrough designation granted after phase I studies, with pivotal study becoming expanded phase Ib or II
  – 1-2 years for sufficient preliminary clinical data to qualify for breakthrough therapy designation
  – 2-3 years to complete the pivotal study, file an application and launch the product

• Under this scenario some phase III activities will be on critical path and need to be accelerated; sufficient time to complete PC/PV activities available unless phase III timelines reduced
Key Considerations for Accelerated CMC/GMP Development Programs

• Leverage prior knowledge, platform data, and use of comparability protocols

• Prioritize development efforts on process reliability over yield and cost of goods. Optimize process and formulation post-approval, if no impact on patient safety or product availability

• Launch with provisional control system that ensures consistent product, and upgrade the control system post-approval after more manufacturing experience and completion of process validation

• Leverage life-cycle validation principles, “continued verification” or concurrent validation

• Leverage use of stability data from representative pilot scale lots where formulation remains unchanged

• Consider broader product quality acceptance ranges for non-critical quality attributes until further manufacturing experience is gained post-approval

• Consider use of initial product supply from clinical manufacturing process if commercially viable

• Identify launch sites for drug substance (DS) and drug product (DP) early
Breakthrough Therapy

Balancing Risk of Less CMC data at Time of Filing vs Patient Benefit
Addressing Technical Risks vs Patient Benefit (1/2)

• In spite of front-loading certain critical product and process characterization activities it may not be possible to complete all CMC/GMP activities at the time of filing and launch of a breakthrough product.

• Manufacturers should develop a manufacturing readiness plan which aligns the timeline for completing the manufacturing activities with those of the clinical development program. Plan should address:
  – All manufacturing sites readiness to launch the breakthrough product;
  – Status of critical characterization tools;
  – Validation approach for process and methods;
  – Stability data to support adequate expiration dating for the product;
Addressing Technical Risks vs Benefit to Patients (2/2)

- Where gaps exist in completing certain activities a risk assessment should be performed addressing the availability of less CMC information at the time of filing and product launch versus patient benefit.

- This should be coupled with a risk mitigation plan to address these risks either prior to launch or through the use of a post approval life-cycle management plan.

- This manufacturing readiness plan and risk assessment should form the basis for discussion and agreement with FDA prior to filing the marketing application.
CMC Activities that May be Incomplete at Launch

Cannot Compromise Patient Safety or Product Supply

- Process validation (fewer than the standard number of full-scale manufacturing runs)

- Process characterization (e.g. long duration elements like resin reuse, validation of intermediate process hold times, or extending limit of *in vitro* cell age for lifecycle management of a biologic product)

- Available real time stability data on commercial product

- Validated transfer to commercial manufacturing site/scale,

- Provisional control system that ensures consistent product with need to upgrade post-approval

- Reliable process capable of meeting initial product demand with need to optimize process yield and performance post-approval

- Phase I-II formulation for launch with potential need to optimize post-approval
Risk Mitigation Approach for Less CMC Data

• PMCs & PMRs

• Well designed comparability protocols

• Post-approval lifecycle management plan
  – Include as part of the filing to support completion of deferred CMC activities post-approval
  – Provide detailed timelines, deliverables, and types of regulatory filings to complete activities

• Ensure appropriate flexibility in the Pharmaceutical Quality System to enable acceleration or deferral of certain manufacturing development activities for breakthrough drug development
  – QC reviewed and approved
  – Ensure PAI readiness
FDA Standards for Marketing Approval

- Substantial evidence of effectiveness, safety and product quality
  - Expectation for pharmaceutical quality is the same for all drugs

- FDA regulations for orphan drugs allow for flexibility and scientific judgment in applying approval standards, in terms of
  - Kind of data needed, and
  - Amount needed for a particular drug to meet the statutory standards

- FDA final guidance on Expedited Programs for Serious Diseases:
  - “FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability updates, validation strategies, inspection planning, manufacturing scale-up).”

- Need open and transparent discussions with FDA on balancing risk of less CMC information at the time of filing vs patient benefit; and means to mitigate risk
Summary

• Breakthrough Therapies offer significant patient benefits, but the reduced timelines introduce significant CMC challenges for product development

• Each case will have different risks and constraints so the specific CMC approaches will vary by product

• Key areas of opportunity include:
  – Leveraging prior knowledge and platform data,
  – Use of comparability protocols
  – Use of initial product supply from a clinical process or site;
  – Delaying certain process validation requirements not directly related to patient safety

• Expect these programs to generate significant post-approval CMC efforts and Phase IV commitments

• Key to success is open and transparent discussions with FDA
Doing now what patients need next