Examining Manufacturing Readiness for Breakthrough Drug Development

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Goal

The goal of this paper is to explore how sponsors and FDA may be able to expedite rate-limiting steps in Chemistry, Manufacturing, and Controls (CMC) and current Good Manufacturing Practice (cGMP) for products demonstrating high clinical benefits, and propose risk-based solutions that suit the expedited development timelines for breakthrough products, while ensuring an adequate supply of safe and efficacious product at the time of approval.

Introduction

In July 2012 Congress passed the Advancing Breakthrough Therapies for Patients Act as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 506(a) of FDASIA provides for designation of a drug as a breakthrough therapy "if the drug is intended alone or in combination with one or more other drugs, to treat serious or life-threatening diseases or conditions and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies." Breakthrough designation is a mechanism that the FDA can grant to sponsors to expedite the development of these promising therapies.

As part of the program, the FDA and sponsor collaborate in a dynamic, multi-disciplinary process to determine the most efficient path forward using an "all hands on deck approach" involving senior managers and experienced review staff and more frequent and interactive communications. The objective is to expedite design and review of the clinical development program so that trials are as efficient as possible and the number of patients exposed to potentially less efficacious treatment is minimized. As a consequence, clinical development timelines involving the traditional three distinct phases could be reduced from 7-10 years to 3-5 years.

These shorter clinical development programs will have significant impact on product and process development timelines requiring the manufacturing organization to reconsider traditional approaches to product and process development and undertake their own "all hands on deck approach" to ensure a sustained supply of safe and efficacious product at the time of approval. To ensure success the manufacturing organization should have good communications with the clinical organization to facilitate identification of potential candidates for breakthrough designation early and help gate or accelerate the appropriate CMC/GMP development activities. It is important to understand that breakthrough drug development programs are resource intensive; sponsors need to be selective about which programs to take forward and have management support. Moreover, a collaborative, cross-functional approach between development, commercial, and regulatory operations is needed to ensure successful development and launch of a breakthrough drug product.

This paper aims to explore options manufacturers have for front-loading certain critical product and process characterization activities, and working together with FDA to identify risk based approaches to mitigate the potential risk of having less CMC information at the time of launch versus the benefit of having these innovative new products available to patients sooner. The ultimate goal of both manufacturers and the FDA is to ensure an adequate supply of safe and efficacious product at the time of approval.

Breakthrough Development Programs may put CMC/GMP Activities on Critical Path

Timelines for completing CMC/GMP activities for a breakthrough product will be driven by the design of the clinical development program for the breakthrough product. Each breakthrough development program will vary depending on the knowledge and complexity of the product; timing of designation; how soon accelerated CMC development activities begin; availability of platform technology and relevant prior knowledge. If the breakthrough designation is granted at an early development stage

following promising preliminary clinical data, some of the Phase lll CMC enabling activities may need to be accelerated. On the other hand, if a breakthrough designation is granted to an already approved product or a product in late stage development, the challenges for manufacturing readiness will be less burdensome, but may need to be addressed in a more compressed time frame. This will necessitate risk-based approaches to product & process development, commercial readiness, launch and regulatory filings. It does not mean you can do less, but rather you will need to consider starting some activities sooner, completing some later and potentially deferring some activities including some process optimization to post-filing. The focus should be on a reliable supply of quality product at launch, not process optimization.

Manufacturing Considerations for Breakthrough Drug Development

Some critical product and process characterization activities that could be addressed earlier and facilitate manufacturing readiness for breakthrough products include:

In general

- Selection of the best molecular candidate for development (physical-chemical properties, pharmacokinetic (PK) profile) for small molecule drugs; screening for and engineering out (where possible) hot spots for degradation or undesired modifications for biologic drugs
- Checking candidate molecules for fit into a manufacturer's platform for drug substance and drug product and processes to improve speed and robustness
- Front loading activities to address non-platform behavior or unusual product and process characteristics
- Assessing Critical Quality Attributes (CQA) earlier and front loading method validation activities

Biologics

- Design and use host cell protein assays that are comprehensive in their coverage and can be used for multiple products (from the early stages of development and all the way through commercialization)
- Use cell line and vector constructs for which significant prior knowledge/platform knowledge is available (e.g., viral safety aspects) - ideally the clone selected for Phase l studies will carry through to commercialization, thus minimizing any comparability concerns arising from cell line changes; appropriate methods should be used to establish clonality
- Assurance of preliminary cell line stability for launch should be demonstrated (e.g., limit of *in vitro* cell age validation)
- Sequence variant analysis should be performed early in development and on aged cells

Small Molecule

- Incorporation of preliminary quality target product profile (QTPP) and bridging in the development of clinical service dosage forms for early clinical studies (i.e., Phase I) which may generate data to support a breakthrough designation (e.g., identification of whether enabling formulations are needed to support rapid development)
- Early identification of the most thermodynamically stable salt form
- Gain concurrence on final market image (color, shape, size and package for tablets) prior to formal stability batches or develop a bridging plan (i.e. color change)
- Early CMC risk assessments to support prioritization of experimental studies
- Evaluation of genotoxic impurities
- Impurities, impurity controls and the establishment of Regulatory Starting Materials (RSMs) are related elements of the drug substance manufacturing process. With less time to optimize the drug substance process as compared to a traditional development program, it may be

necessary to negotiate wider limits and provisional RSMs with the FDA. A commitment can be made to reevaluate these controls after launch when the process can be further optimized

Various CMC/GMP development strategies that might be employed to facilitate breakthrough drug development are discussed below. In addition, a table from the European Federation of Pharmaceutical Industries Association (EFPIA) Technical Development and Operations Committee (TDOC) Briefing Paper[1] (Annex 2) provides a comparison between traditional and accelerated CMC approaches for drug development and manufacturing to ensure early access to patients. These strategies will be supplemented with examples (Annex 1) of actual experiences that companies have had working with FDA to implement some of these approaches for expediting approval of breakthrough drug products.

Process and Formulation Development Considerations

In general:

- Phase lll and commercial process and formulation optimization will be truncated due to accelerated clinical development timelines. 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 commercial process with limited experience and optimize post-approval
- May need to use data from development material/clinical supplies to support material from initial commercial process lots
- Intermediate hold time studies may be delayed and straight through processing and scheduling of intermediates can be considered

Biologic drugs should focus on:

- Cell line and/or vector lock at Phase I
- Critical process attributes for consistent products
- Launch with Phase I/II formulation and optimize post-approval

Small molecule drugs should focus on:

- The Active Pharmaceutical Ingredient (API) and critical excipient attributes impacting formulation and drug product (DP) manufacturability and performance
- DP process impacting pharmacokinetics and patient safety
- If possible, lock clinical formulation to avoid bioequivalence (BE) studies prior to launch
- If efficacy is indicated in Phase I clinical studies (in oncology patients), companies may want to strive for a commercial dosage form to be used in the pivotal phase II clinical program
- Close alignment on linkages in control strategies (i.e. particle size distribution impact on dissolution) and overarching themes (moisture sensitive API) need to be maintained

Manufacturing Scale and Launch Site Considerations

In general:

- Determine as soon as possible launch sites for drug substance (DS) and drug product (DP) (clinical versus commercial)
- Clinical manufacturing facilities used for launch would need to meet the same quality/GMP expectations as commercial manufacturing facilities
    - Key differences for consideration are:

[1] EFPIA TDOC Briefing Paper on Medicines Adaptive Pathways to Patients Initiative (MAPPs) – CMC Challenges and Opportunities

- Cleaning verification versus cleaning validation
- Multi-product manufacturing, including investigational compounds with limited safety data
- It may be useful to consider dedicated product contact equipment and/or use of disposables to minimize concerns. Disposables may also assist with cleaning validation issues

- Gain concurrence on comparability strategy/protocol for post approval site changes in advance to lend confidence to Manufacturer's ability to ensure sustained supply post launch, particularly when expediting launch from a clinical site
- If using a contract manufacturing organization (CMO) for DS/DP ensure there is capacity to allow rapid scale up and to support commercial volumes

Biologic drugs should consider:

- Decoupling drug substance and drug product qualification lots (use clinical DS for DP qualification) when feasible to save time on the critical path to licensure
- Pivotal clinical studies may be performed with material from different scale and/or site than is intended for long term commercial production (e.g., studies originally expected to be Phase II studies could be used as pivotal studies)
- Scale-up Phase lll clinical lots to commercial scale for launch with bridging comparability study

Process Validation Considerations

- Likely to have limited manufacturing experience at commercial scale; the number of full-scale validation lots at the time of filing may be lower than a typical application
- Clinical DS used for DP Process Validation – need early alignment with FDA on starting materials (small molecule products)
- Leverage process and product platform knowledge (e.g., for monoclonal antibodies) with appropriate justification to speed development
- Leverage life-cycle validation principles, "continued verification"
    - Use development experience/smaller scale batches in Process Performance Qualification (PPQ) strategy
    - Some PC/PV studies could be deferred, such as process linkage studies or chromatographic resin re-use at full lifetime
- Consider concurrent validation approach based on a CDER Compliance Policy Guide CPG, Section 490.100[2], for orphan drugs to allow for product distribution concurrent with release of each conformance batch (batch specific release option). This would enable launch from a commercial site with limited number of batches, but is dependent on manufacturer ensuring trust:
    - Prior demonstration of manufacturing consistency for clinical process material
    - A validation protocol for commercial material and at least one executed batch record at time of filing
    - Robust Quality Systems able to effectively manage Corrective and Preventive Actions (CAPAs) and change management
- PC/PV studies impacting patient safety must be complete prior to filing, and a sufficient amount of process characterization data, successful clinical and pilot scale runs to assure product supply at launch

Analytical Development Considerations

[2] http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074411.htm

- Analytical method development
    - Partial or complete front-loading of analytical understanding to balance more limited process robustness and support future comparability exercises
    - Focus on high priority assays such as potency for biologics and content, impurities and dissolution for small molecules to ensure suitability for control system
    - Involve commercial QC in assay design during development and co-validate if possible
    - Use partially validated methods for internal release and stability testing of qualification lots and complete validation before commercial release
        - This approach presents a business risk if problems arise in validating a method and should be accompanied with a backup plan requiring retesting lots and or implementing alternative methods
    - Launch from clinical site and transfer to commercial site post-launch

Control Strategy Considerations

- Control strategy based on limited manufacturing experience but ensuring patient safety and efficacy
- 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, i.e.,
    - Filing with an expanded monitoring program with more tests initially, more assay controls, and justify elimination of some tests post-approval as more knowledge is accumulated
    - Filing with broader IPC and product specification acceptance criteria at launch and re-evaluating post-approval for specifications that are linked to process consistency
    - Filing with preliminary CPPs and CQAs
- For small molecules, it is important to consider all available data including dissolution profiles and other critical analytical results (i.e., impurities, solubility, disintegration etc.) during development and stability to be able to justify specifications if requested by the FDA; and consider sunset specification for some parameters (polymorphism for example)
- Utilize enhanced modeling techniques where possible to support conclusions
- Manage second generation processes through a life-cycle approach in post-approval lifecycle management plan (PALM) which may contain a network of comparability protocols to facilitate lifecycle improvements to the product and process
    - For critical aspects, consider submitting draft P.2 section (gaps in data sets) for early FDA review and concurrence

Stability Data Considerations

- Accelerated development timelines may limit availability of real time stability data
- Launch with reduced real time stability for commercial material
    - Leverage stability from early development and clinical batches when formulation remains unchanged and product comparability demonstrated
    - Use forced degradation and stress studies to provide additional supporting and comparability data
    - Provide stability protocol for commercial material
    - Gain FDA concurrence and commit to provide more real time confirmatory data during review and post-approval
- Enhanced temperature monitoring and control of the product during shipment may be considered until support for adequate expiration dating is attained

Pharmaceutical Quality System (PQS) Alignment with BT Product Development Considerations

- PQS requirements must be adhered to for BT products development

    - PQS must provide flexibility to accommodate accelerated activities for BT product development timeline products
- The accelerated development PQS strategy for each product will be unique since it depends on the timing of BT designation
    - Flexibility will be required based on molecule and available product and platform knowledge
    - Only PQS activities with no impact to patient safety or product supply can be deferred
    - A quality risk assessment must be applied to all activities that will be deferred, and the rationale, and controls needed to ensure deferred activities are completed documented
    - Some activities that are normally completed prior to license application may need to be deferred as
        - Post-submission, complete at inspection
        - Post inspection, prior to approval
        - Post market commitments
    - Any PQS deferrals must be documented in a manufacturing readiness plan and monitored to ensure completion
- The manufacturing readiness plan can be used for developing internal filing and inspection readiness checklists to ensure all deferred activities are completed or addressed in a PALM

Balancing Risk of Less CMC data at Time of Filing vs Patient Benefit

In spite of front-loading certain critical product and process characterization activities it may not be possible in the limited timeframes available to complete all CMC/GMP activities at the time of filing and launch of a breakthrough product. To address this possibility, manufacturers should develop a manufacturing readiness plan which aligns the timeline for completing the manufacturing activities with those of the clinical development program. This plan should address all manufacturing sites and their suitability and readiness for development and launch of the breakthrough product; the design and implementation of critical characterization tools; the validation approach for process and methods; stability data to support adequate expiration dating for the product; and delineation of responsibilities for the development and commercial teams in addressing these issues. 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.

Below are some examples of CMC/GMP activities that may be incomplete at the time of filing and launch of a breakthrough drug product.

- 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, though some level of assurance will still be necessary regarding transfer for biologics
- 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

A fundamental assumption is that risk assessments demonstrate that having less data at the time of filing and launch of a breakthrough product will not compromise patient safety or product supply.

Completion of any deferred CMC activities should be documented in a comprehensive post-approval life cycle management plan (PALM) that is part of the marketing application and contains detailed timelines, deliverables, and types of regulatory filing to be completed post-approval.

Flexibility in Type and Extent of Manufacturing Data for Marketing Approval of Breakthrough Drug

FDA approval standards for marketed drugs require demonstration of substantial evidence of effectiveness, safety and product quality. FDA's expectation for pharmaceutical quality is the same for all drugs. However, FDA regulations for orphan drugs do allow for flexibility and scientific judgment in applying approval standards, in terms of the amount and type of data needed for a particular drug to meet the statutory standards. This rationale is stated in FDA's final guidance on Expedited Programs for Serious Diseases[3] which states that The "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)." Open and transparent discussions with FDA on balancing (and mitigating) risk of less CMC/GMP information at the time of filing versus patient benefit should take place prior to filing the marketing application.

Sponsor/FDA Interactions during Development and Review of Breakthrough Drugs

In addition to a risk-based, front loaded development plan undertaken by the Manufacturer to expedite rate-limiting steps in CMC/GMP for break through drug products, the Agency can work with manufacturers on risk based solutions that facilitate expedited development and review timelines without compromising availability of an adequate supply of safe and effective products for patients. A few areas for consideration are as follows:

- The traditional and time consuming process of formal meeting requests, scheduling, briefing documents and written responses may not be appropriate in the environment of an accelerated breakthrough therapy drug development program. More flexible approaches to ensuring information exchange and understanding should be considered to facilitate expediting development and review. Formal meetings should be reserved for more comprehensive program discussions or critical review milestones
- Soon after receiving a breakthrough designation Manufacturers should work with FDA on a plan for early and active engagement to schedule and conduct meetings during development to reach agreement on best path forward
- Consider designating a CMC/GMP point of contact (both sponsor and FDA) to triage meeting requests and sponsor questions
- Set up secure email to facilitate information exchange
- Agree upon schedule of important review milestones and turnaround timeframes for information requests
- Discuss use of "negotiated amendment" approach to submit agreed upon data packages during the review, for example:
    - Submission of the dissolution method development report and dissolution specification setting strategy for early review by FDA Biopharmaceutics reviewers
    - Additional real time stability data on commercial product
    - Additional batch data to support validation
- Discuss rolling submission of Module 3 components to enable more rapid access to CMC and facility data to facilitate pre-approval inspection scheduling and conduct; Gain early and

[3] 21 CFR part 312

frequent access to reviewers via teleconferences to resolve questions, avoid delays, and provide clarity on specific concerns

- For small molecules, flexibility on the qualification of regulatory starting materials (RSMs), impurities and impurity controls, perhaps accepting something on an interim basis with a post-marketing commitment to reevaluate these controls after launch. Impurities and their associated controls, including RSMs, should be considered in light of the clinical indication and the potentially lifesaving nature of the drug. It may be necessary for drugs which have not been fully optimized at the time of launch to allow for wider initial controls which can be adjusted and refined as more experience is gained in commercial manufacturing provided product safety and quality will not be impacted

Conclusion

Breakthrough Therapies offer significant patient benefits, but the reduced timelines introduce significant CMC/GMP challenges for product development as well as resource commitments to align the development and commercial organizations. Each breakthrough drug development program will have different risks and constraints, so the specific CMC/GMP approaches will vary by product and timing of the breakthrough designation. Through careful planning and a thorough understanding, by all parties, of the requirements and timeframes, some activities may be optimized post-approval. Leveraging prior knowledge, platform data, and use of comparability protocols are key considerations for developing a breakthrough drug product. Additional considerations include the use of initial product supply from a clinical process or site; use of supportive stability data from representative pilot scale lots; delaying certain process validation requirements not directly related to patient safety; and consideration of broader product quality acceptance ranges for non-critical quality attributes until further manufacturing experience is gained. As a result, these programs will generate significant post-approval CMC efforts and Phase IV commitments to address control system updates, process optimization where needed and site transfers. The key to success is open and transparent communications with FDA to ensure the development program delivers an adequate supply of safe and efficacious product to patients.

Annex 1: Manufacturing Challenges in Developing a Breakthrough therapy Drug - Case Study Examples

Example #1: Genetech/Roche – Gazyva® (obinutuzumab), a humanized monoclonal antibody approved for the treatment of lymphoma. Acting as an immunomodulator, it targets CD20, killing B cells. Gazyva was the first FDA-approved Breakthrough Therapy approved by the US FDA in November of 2013.

- Breakthrough therapy designation was granted for Gazyva late in the development cycle, just prior to the BLA filing. Because of the late stage of designation as a Breakthrough Therapy for Gazyva, most CMC development activities had been completed
- However to allow for earlier launch FDA encouraged conversion of Phase 3 clinical material to launch material in order to allow an early launch (~1 month sooner)
- Detailed assessments of clinical material took place during PDUFA V mid-cycle and late-cycle meetings with FDA and during PAI at the Drug Substance manufacturing site
    - Same commercial manufacturing facilities and same scale of manufacture
    - Same manufacturing processes planned (very minor changes)
    - Transition from clinical to commercial CoA (met all commercial specifications)
    - Qualified Persons requested written endorsement from FDA to release
- Very supportive interaction with FDA regarding conversion of clinical material to commercial launch material to get this medicine to CLL patients quickly

Example #2: Merck & Co. – Keytruda® (pembrolizumab), the first PD-1 blocking drug approved by the US FDA, in September of 2014, for the treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. At the time breakthrough therapy status was granted to KEYTRUDA®, clinical supplies were only manufactured on a small clinical scale. Clinical development was in Phase I, and CMC development was stage appropriate, in early stages.

- Expediting CMC readiness to meet clinical timelines, meant decoupling drug substance (DP) Process Performance Qualification (PPQ) from drug product PPQ, enabling almost parallel execution and completion of DS and DP PPQ activities, both of which were rate limiting to the CMC file. This was enabled by ensuring no significant process changes were implemented between the clinical GMP DS batches used for DP PPQ, and the subsequent DS PPQ batches. 4-6 months were saved in the development timeline without incurring additional quality or patient safety/efficacy risk
- To meet the projected commercial and clinical demand, an additional drug substance manufacturing site was rapidly brought online prior to BLA filing. Through multiple interactions with the FDA, licensure was sought for 2 drug substance manufacturing facilities, one that was the initial clinical supply site, and, a second larger CMO site (licensure of this site was based on a strong analytical comparability package, the approach and content of which was discussed with the FDA via frequent interactions)
- The FDA partnership was critical to rapid resolution of multiple CMC issues, especially since this was Merck's first monoclonal antibody filing with the FDA. During the final stages of the review of the BLA application, the field office site inspections were not synchronized with early action by the review division – this resulted in removal of one of the manufacturing sites from the BLA, which was subsequently submitted for review and approved very rapidly
- In addition, the rapid pace of development of this molecule, along with multiple sites, the dosage form also transitioned from a lyophilized powder for solution for infusion to a liquid vial. This supply strategy was discussed and reviewed with FDA, in advance, resulting in the recent approval of the post-approval supplement for the liquid vial, based on analytical comparability in the previously agreed upon strategy
- A process/product specific Host Cell Protein (HCP) method for measurement of host cell impurities in the drug substance was not in place at the time of designation. Upon FDA review, a well characterized commercially available HCP assay, demonstrating appropriate coverage

and clearance in the process, was used for initial commercial release. During BLA review, a post-marketing commitment to develop a process/product specific HCP assay was agreed to. This allowed development, bridging and validation of this HCP method off critical path to initial approval, ensuring that the interim solution did not pose any patient safety/efficacy risk. Alternatively, inclusion of the process/product specific HCP assay in the BLA filing, would have resulted in a minimum of 6-9 month delay

- The importance of frequent and data-driven interactions with the FDA was critical to the success of CMC development for this drug

Example #3: Pfizer – Ibrance® (Palbociclib), granted accelerated approval, by the US FDA in early 2015, to treat postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer by inhibiting cyclin-dependent kinases (CDKs) 4 and 6. During commercial scale-up, the manufacturer identified a drop in dissolution performance at the end of each batch. This phenomenon did not occur at smaller scale of the drug.

- In order to continue uninterrupted supply to the clinical study while this issue was being investigated, a batch cut-off at 85% was instituted to throw away the final 15% of each batch
- The FDA was informed of the issue and agreement was obtained that the 85% cut-off was an appropriate interim measure until a permanent corrective action could be identified
- The applicant ultimately identified a set of successful modifications to the encapsulator hopper to improve powder flow and eliminate over-lubrication of the tail end of the batch. Stratified data across multiple batches and strengths confirmed the corrective action was successful
- The 85% cut-off was successfully been eliminated for the commercial process and for all future clinical batches

Example #4: Bristol-Myers Squibb – Opdivo® (Nivolumab), approved in December of 2014, Opdivo works by inhibiting the PD-1 protein and is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express BRAF V600, for use after treatment with ipilimumab and a BRAF inhibitor. The following flexibilities allowed for development of a complete package:

- Final Cell-based Bioassay not available until after PPQ batches
    - Used frozen samples (release and stability) to allow testing following method validation to justify acceptance criteria
- Drug Substance process changes allowed for improved robustness and facilitated future transfers to additional sites
    - Introduced modifications to downstream or purification processing steps prior to manufacture of commercial supplies. No change in cell line or upstream process
    - Type B and Type C meeting to align on strategy. Provided preliminary comparability data, including
        - Comparison of release and extended characterization analytical data
        - Side-by-side degradation profile at stress conditions
        - Full scale in-process control data comparison
    - Able to bridge stability data to allow expiry to be based on studies performed using material from the clinical process
- Endotoxin
    - Low endotoxin recovery observed with original (kinetic) method used for Drug Substance
    - Type B meeting to align on proposed strategy
    - Changed to gel clot method during BLA review
- Addition of 40 mg/vial presentation with limited formal stability data
    - Same formulation and glass vial as used for 100 mg/vial presentation
    - Type C meeting to align on stability strategy to support proposed expiry

Annex 2[4]: Illustrative Examples of Adaptations of Traditional CMC Development and Manufacturing Approaches for APIs and Drug Products to Ensure Early Access

The following table illustrates some approaches which a company may take to ensure early access of medicines.
N.B. this table is not intended to be comprehensive. Most aspects of the proposals are valid for small molecules/ NCEs as well as large molecules/ biotech products.

Topic	Traditional approach	MAPPs aligned approach
Formulation	Commercial formulation developed and optimised; comparability to pivotal clinical formulation demonstrated in dossier.	Use of clinical formulation, or limited optimisation of selected market form. Where relevant, comparability of launch formulation to pivotal clinical formulation demonstrated in dossier. Where relevant/known, planned commercial formulation described and a PACM Protocol to demonstrate comparability to pivotal clinical formulation in the dossier.
Packaging	Optimised, based on minimum requirements for protection.	Potential for use of "maximum protection pack" to mitigate limited shelf-life.
Analytical methods	Developed and validated.	Developed and validated.
Specification	Established and documented. Supported by extensive dataset.	Established and documented; possibly broader specifications as little data are available. May include more elements than traditional specification due to limited data set, and/or some parameters where the data will be reported but acceptance criteria not defined. Commitment to update (rationalise) after x time or y batches, based on pre-defined criteria and to reassess the control strategy.
Impurity assessment	Impurities identified, risk assessed and controlled. Controlled mainly by process knowledge rather than specification testing.	Impurities identified, risk assessed and controlled. Higher level of control by specification testing (could include intermediates) may be needed until sufficient data available to support greater reliance on process control.
Shelf-life	Shelf-life at launch based upon defined length of stability data on defined batch types/sizes (ICH Q1A). Post-approval extension as further data emerges.	Launch product will be supported by (ongoing) stability studies, but ICH-conform data may be limited. Negotiate employment of lean stability strategies (including stress conditions), use of stability models, and extrapolation for supporting shelf-life with Competent Authorities, enhanced use of scientifically relevant supporting data from earlier batches, and possibly more than one batch annually in ongoing stability. Support of adequate shelf-life with use of highly protective packaging/restrictive storage conditions as appropriate to the elicited degradation mechanisms.

[4] EFPIA TDOC Briefing Paper on Medicines Adaptive Pathways to Patients Initiative (MAPPs) – CMC Challenges and Opportunities

Topic	Traditional approach	MAPPs aligned approach
		Post-approval strategies will depend on formulation strategy and may also involve novel approaches.
Process development	Complete package at filing. Process supported by extensive development studies	Partly based on platform knowledge, to be refined as more batches/materials are investigated. May be based on Proven Acceptable Ranges (or set-points) until data set complete; more reliance on end-testing for product release.
Process validation	Prospective or Continued Process Verification.	Seek regulators' agreement to a concurrent validation approach, including extended monitoring.
Scale of production	Commercial scale	Small commercial scale. Scale-up protocol defined.
Sites of production	Commercial manufacturing site. Existing cGMP clearance or Inspection–ready. Multiple sites may be included.	May be clinical manufacturing site. Existing cGMP clearance (possibly only MIA-IMP). Inspection–ready; product history available to support approval of clinical site for commercial launch. Site addition PACM Protocol defined.
Viral Clearance Validation	Validated in small scale.	If appropriate platform data are available: include such data in dossier, validate in small scale prior to launch, and agree mechanism for provision of data to Competent Authorities.
Inspection of facility	GMP certificate available for commercial use of the facility.	Acceptance of GMP certificate for IMP manufacture or, where facilities are outside the EU, the acceptance of QP Declaration for imported API/product.
Cleaning method	Established	Established
Cleaning validation	Validated	Appropriate analyses on batch-wise basis, and and/or concurrent validation.
DMFs (where used)	Submitted in close conjunction with MAA	Negotiate early submission/pre-assessment to mitigate risk of landing on critical review path.

Annex 3: Acronyms

API	Active Pharmaceutical Ingredient
CAPA	Corrective and Preventative Actions
CMC	Chemistry, Manufacturing and Control
CQA	Critical quality Attributes
DP	Drug Product
GMP	Good Manufacturing Practices
IPC	In-Process Control
PAI	Pre-Approval Inspection
PALM	Post-Approval Lifecycle Management plan
PC/PV	Process Characterization/Process Validation
PK	Pharmacokinetic
PPQ	Process Performance Qualification
PQS	Pharmaceutical Quality Systems
RSM	Regulatory Starting Materials
QC	Quality Control
QTTP	Quality Target Product Profile