Table 24: Adapting CMC Activities for Accelerated Approvals: Challenges and Lessons Learned, Especially from Pandemics (Site Transfers, Scale Up, Comparability and Process Validation)

Facilitators –

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Scope:

CMC development activities are often gated by clinical data readouts and can become critical path if program timelines are compressed. We will discuss strategies for accelerating rate limiting CMC activities for submission, meeting logistical requirements, and mitigating impact to lifecycle maintenance. Come prepared to discuss experiences with or ideas for fast-to-market strategies, perhaps drawing from recent experiences with development of vaccines and neutralizing antibody therapies for COVID-19.

As this topic covers many quality aspects of accelerated product development, Table 24 will cover topics relating to manufacturing such as site transfers and scale ups, process and product comparability, and process validation (PV). In parallel, Table 23 will focus on control strategy concepts such as specifications setting, stability, and analytical methods.

Questions for Discussion:

1. Accelerating submissions:
    a. What approaches can be taken to compress the timing for site transfers and process validation (e.g. ADCs, mAbs)?
    b. What are ways to overcome challenges of limited lots for PV?
    c. How can comparability assessments justify provision of site transfer/scale up data during review and potentially launch with clinical supply?
    d. What happens when something goes wrong with manufacturing?
2. Logistics:
    a. The DP process is validated but the inputs for the DP PPQ runs are pre-PPQ; can these DP PPQ batches serve as launch material if their upstream inputs were not from validation runs?
    b. What are lessons learned from inspections during the pandemic?
    c. How can Sponsors balance fixed production schedules with pre-license inspections during accelerated reviews?

    d. How might Sponsors better plan for product launches immediately following early approvals?
    e. What are best practices for managing accelerated regulatory reviews, including pilot programs?
3. Lifecycle challenges:
    a. How do Sponsors balance global submission requirements (e.g. different PV data packages) if only a subset of countries agrees with the risk/benefit?
    b. What initial core dossier structure/content would support quicker access to global markets? Have you applied ICH Q12?

Discussion Notes:

January 26 and 28, February 1 and 3, *combined* –

- *What is needed in accelerated review scenario?*
    - Given that things are moving quickly, more avenues for rapid/ flexible meetings with the agency would be desirable
- *How to to be successful with (very) limited batch number for comparability?*
    - Leverage prior knowledge
    - For BLA, while initially some data might be pending, the full package has to be available at some point; what matters is totality of data
- *Comparability/ impurity challenges*
    - Analytical comparability between for Pre-PPQ to PPQ / Clinical to commercial involved release and characterization data, use of orthogonal methods, extent of the change, changes from process intensification and what it impacts the CQA, which batches are chosen for process and product comparability exercises, perform risk assessment and have a really good understanding of the process and product. Prior knowledge of platform may come in handy though there are product specific assays which need product specific data.
    - CHO and E. Coli strains well characterized. CHO K1, there are variants that behave differently, develop a platform, then scale up, 2L to 100L. Product specific activities need to start in PII and PIII. Have a comparability strategy early on, try not to make major changes in late stage, no change in scale.
    - Participants weighed in PV challenges, CMO management, flexible operations.
- *Comparability—special considerations?*

    - Stability (again EMA Toolbox Guidance): possible to move away from real-time data with proper justification
    - Q: what if something goes wrong with your primary stability batches? – might still be possible to leverage data for shelf-life (justification important, cf. "Cuno depth-filter issue" some years ago across biotech industry, with leachables causing yellowish off-colour in DS)
    - Minimum comparability package for an EUA product is case-by-case based on risk/benefit
- *How to accelerate novel modalities when platform data/ prior knowledge is missing?*
    - Engage with the regulators, they still need a solid package
    - Oligonucleotides and ADCs mentioned as example: bring chemical and biologics knowledge together
- *Insights on specific process validation challenges?*
    - Less than 3 batches is very challenging!
    - Some companies have been successful with concurrent validation (e.g. for orphan or oncology indications)
    - How to deal with non-sequential PV batches: consult agency, might be possible, although usually not planned

- *Use of prior knowledge*
    - See EMA workshop on prior knowledge: https://www.ema.europa.eu/en/events/joint-biologics-working-party-quality-working-party-workshop-stakeholders-relation-prior-knowledge
- *Considerations for CMC packages for accelerated products in international markets (eg. China)?*
    - Probably advisable to take a more "conservative" approach; generate standard validation packages
- *How can CMC development keep track with clinical development?*
    - Launch from R&D site
    - Co-development at R&D site and commercial site

- Challenge the dogma of "sequential" development, especially for process validation where it is possible to use non-PPQ inputs to validate the performance qualification (e.g. non-PPQ DS into PPQ DP)
- Useful CMC publications in PRIME/ Breakthrough context:
  - EFPIA: https://www.efpia.eu/media/554681/cmc-development-manufacture-and-supply-of-covid-19-therapies-and-vaccines.pdf
  - EMA: https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf
- Approaches can be taken to compress the timing for site transfers and process validation : consider scouting for CMOs early in the program, method validation performed earlier than Phase 3 if program gets BTD designation.
  - Specific example provided in which FDA agreement was obtained to perform both development and commercial process in parallel even prior to Phase 3 facility fit was locked in. This was for an Orphan drug with BTD designation in the US and Prime designation in EU.
  - Comparison of DP formulations (liquid to lyo) was done in parallel with the facility fit. Agency was open to it.
  - Question asked on whether the applicant gets a break in the stability package that has to be submitted for co-developing development and commercial processes at the same time. Response was that since most of the batches manufactured were in liquid formulation and shelf life was based on liquid, not the lyo then the applicant needed to submit with a minimum of 3 months of PPQ data for lyo, provide data during review and agree to a post approval commitment, immediately at approval got the shelf life extension.
  - The use of Q12-related control strategies and risk assessments was limited. Module 3 section were submitted in a rolling fashion; was both advantageous and disadvantageous as there is no breather; however review was intense and quick and approval obtained on time or prior to PDUFA date.

- *Points to consider when launching from a clinical facility?*
  - Check EMA Toolbox guidance (s. above)
  - Comparability to commercial might be challenging, hybrid approach is possible (timing crucial)

- Q: Has clinical facility to be reflected in the dossier? – Based on experience: yes

- *Experiences with virtual inspection during 2020 pandemic year:*
  - FDA could not support foreign PLI or PAI inspections, but domestic inspections were possible. One or two companies reported supporting FDA remote inspection (appears to be domestic and site readiness type of inspections).
  - EFPIA is talking about flexibility, virtual remote inspections play a key role. PhRMA and BIO had meetings with FDA on virtual inspections. Participants noted that flexibility is here to stay. Russian inspectors have been coming for virtual inspections as routine inspection in Russia is common and not related to pre-approval inspections. Risk based: EMA is fully convinced no preapproval, no findings.
  - A CMO reported that they heavily audit/maintain site, train the inspectors, 3x a year train FDA on inspections, all of which support a remote inspection.

- *How to do manufacturing site selection in view of pre-approval inspection?*
  - Evaluate site inspection performance history
  - Paper-based inspections allowed in some cases
  - Point on virtual inspections and their broader "validity" also came up; regulators have some experience now, e.g. for EUA products

- *What are special considerations for selection of a CMO for an accelerated program?*
  - Consider both near-term and long-term support needs
  - Experience of CMO, customer support, help with tech transfers, facility fit.
    - CMO has a well vetted development plan for process and facility fit for seamless process/method transfer, perform risk assessments and mitigation for facility fit and analytical method transfers.
    - Can advise on what data packages involved, robustness of data, how can it be leveraged with existing platform technologies.
  - Does CMO have experience with new technologies
  - Capacity is the biggest downside for using CMOs; sometimes their own in-house programs end up competing with customer programs.

- *General discussion around new technologies to speed up development*
  - Main applications are for modular manufacturing, continuous manufacturing, process intensification approaches to increase the antibody titer (need a robust cell

line with at least 5 g/L to start, for e.g. perfusion culture), very modular production, mobile filling truck, warehouse type GMP facilities with cubes in side for cell culture and down stream operations.

        - A CMO reported ETT conversations with FDA for continuous manufacture.

    - Need to consider scale up and transfers. Can leverage ICH Q12 and Q13.

        - Late stage is all about cost of goods, amount of gms Mab/sq feet , PII to PIII requirements that raises COGS is multi-fold, such as looking at buffer use, cleanability and molarity of caustic.

- *Any experience with ICH Q12 tools?*

    - PACMPs (hopefully) developing to global tool over the next years; most companies still evaluating how to implement and if regulatory relief is provided.

- *What will the "new normal" look like and how to specifically accelerate tech transfers even further?*

    - Leverage publications (in chronological order):

        - Friends of Cancer White Paper "Examining Manufacturing Readiness for Breakthrough Drug Development": https://link.springer.com/article/10.1208/s12249-015-0455-1

        - EFPIA White paper on expedited CMC development: https://www.efpia.eu/media/288657/efpia-ebe-white-paper-expedited-cmc-development-accelerated-access-for-medicines-of-unmet-medical-need-december-2017.pdf

        - EMA / FDA Stakeholder workshop on support to quality development in early access approaches – link to all materials (incl. video recording): https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough

        - Latest EMA "Toolbox" Guidance (2021 draft) to support the development and completion of Module 3 quality data packages for PRIME medicinal products: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime_en.pdf

    - "Compress" activities as much as possible (e.g. for ADCs look at intermediates/DS/DP inputs in non-sequential, independent manner)

    - For method transfers, conduct tech transfer and co-qualification / validation at the same time

- Comparability: increased focus on clinical material for highly similar processes/ facilities
- Increased deferral of activities/ data collection into post-approval space
- Similarities in Quality Systems (in-house vs. CMO) are helpful

- *What are lessons learned on inspections during the pandemic?*
  - Likely post-pandemic scenario: more virtual/ remote/ paper-based inspections
  - How do plan for an inspection with busy manufacturing schedules and the PDUFA date in mind? – Challenging in e.g. multi-product facility, you need to plan for the "unexpected"/ better have a "flexibility cushion"
  - Think global (divergent regulatory expectations, e.g. wet signatures…)
  - This year is the year where all the world is looking at pharmaceutical manufacturing!
  - IT/ technology might still be an issue for truly "virtual" plant tours (agencies have to come up to speed with new technologies)
  - Overall industry experience with virtual/ remote inspections seems to be positive, but sometimes F2F presence continues to be important (inspection issues are often "people issues")