Table 1: Process Performance Qualification for Accelerated Products

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SCOPE:

Global regulatory convergence towards reduced development and approval time for potentially life-changing therapies is intended to enable earlier patient access. However, these reduced timelines also drive an urgent need to streamline pharmaceutical development and require increased flexibility from both manufacturers and regulators. One opportunity for shortening CMC development timelines is accelerating the Process Performance Qualification (PPQ) campaign earlier into development. Another opportunity is to reduce the scope of PPQ with a commitment to initiate comprehensive Continued Process Verification (CPV) at the outset of commercial manufacturing. This Table will discuss the impact of these accelerated development programs on manufacturing process development and regulatory requirements with a specific focus on the PPQ phase of validation. Table members will propose and consider mechanisms to condense development timelines, align on best practices for regulatory engagement, and identify key areas for industry advocacy.

QUESTIONS FOR DISCUSSION:

1. What is the table’s experience in accelerating CMC development specifically around the PPQ campaign?

2. Which specific areas have you been able to streamline for Accelerated Development programs as compared to traditional filings? Any validation requirements which were considered for deferral post BLA filing?

3. Have folks had success gaining approval with data from only 1 DS campaign at commercial scale prior to filing?

4. When are manufacturers beginning their ongoing process monitoring relative to PPQ? Is CPV for accelerated products more comprehensive than for routinely approved products? What expectations have regulators expressed regarding ongoing monitoring of accelerated products?

5. How can we best engage with the regulators with considering novel approaches to accelerated development?
NOTES:

- Our table was standing room only – clearly this is a hot topic! We had a great introduction to the topic from the last speaker before lunch from Genentech.
- Table’s experience in accelerated CMC development?
  - Some – similar to Genentech presentation. Only a finite number of things you can move around on the timeline, ended up in a similar place to Genentech. Biggest challenge was internally, doing a lot of things parallel, much different than doing things in series. Only way to do it even though it’s controversial internally. Quite a bit of talk with the agency and regulatory folks. Represented by John’s talk.
  - Causes a lot of churn, everyone’s excited for it, people want to do the right thing, don’t always agree what this is, risk profile, larger company with a portfolio becomes more difficult – sucks resources away from other things. Everyone wants to accelerate, but where do you put your resources? Feels a little bit like gambling. Attrition in portfolio, valuable resources, competing priorities, organization can’t be large enough to do everything or drugs become too expensive.
  - Really had to chance the vision because every single product can’t be breakthrough. Have to assume the selection for BD is a basis for prioritizing resources.
  - Human factor gets in, attaching your name and reputation to it, could hurt career.
  - When did clinical mfg made sure it was in a GMP facility to start with, made it so much easier. Changed the whole state of the program. Try to go into GMP facilities for a product that we think may get BD.
  - Other challenge is how fast you go – PC overlapping with PPQ – risk, CPPs turned up during the PPQ campaign. Can’t study every parameter in one round. Make sure criticality (CS) is identified in advance. Otherwise PPQ becomes PC.
  - How to handle analytical? Locked methods down but changed them later in lifecycle management under PAS. Not going to have full process understanding, full analytical understanding. Could have late CQAs breaking.
  - Analytical methods – can put off PPQ to the very end but I NEED stability to get shelf life. Locking down stability-indicating methods up front is on critical path. Up until PPQ to tweak and optimize remaining methods. At PPQ methods have to be validated (regulatory guideline).
  - Culture of the way we do things – acceleration = cultural change. “What do the regs actually say?” versus how we manage the business. Certain things FDA expects in a BLA, business has done other things to avoid costly failures @ PPQ. Can’t push off method validations after PPQ but FSS methods don’t have to be validated as long as they don’t change before validation (we think). What are the real “thou shalt nots?”
  - Methods – may not have the full ICH validation as long as methods do not change, is this acceptable? A couple of people have experience with post-market commitments on methods.
  - Need to choose the launch facility.
For some IP testing (maybe not CQAs) e.g. residual clearance, pull samples and go back to test when methods are validated. Have to evaluate all the risks. If CQA need to be more careful, methods were probably needed to develop the process, “it all depends…”

Changing method post-approval may work if method qualification done. Real-world application of method highlights more variability than you expected, have to change.

Meetings and briefing book are really important. Feedback on PPQ was essential. A lot of the questions will get responses during the ongoing communications.

So many release assays, make a strong story from other assays.

- What can be delayed for BLA?
  - Process-specific HCP versus a platform kit, may be opportunities to discuss, work towards full validation. Need full-scale process samples to lock down the process-specific HCP. Several examples of changing HCP assay post-approval.
  - Can’t put off cleaning validation – usually done early. Can that be done between BLA and PAI? Maybe… Usually try to get that out of the way early.
  - For shorter campaigns, membrane or column cleaning, could make sense to do it later (gets done all the time, even for none-BD).
  - DP PPQ – might be doing media fills on some sizes, put some lots on stability. DP stability data relies very heavily on clinical, may have 1 lot that’s DP at full scale, commit to putting other lots on stability in a protocol.
  - DP stability timepoints – it depends on what changes were made to DS, really DS that impacts how DP behaves, if change container closures or formulations you’re dead. Solid stability on DS goes a long way for DP stability. What about a scale change? May have limited stability at the large scale but expect to see some representative (at least 1 lot) stability data.
  - Comparability protocols for concurrent release of DS – have done that in drug shortages, very infrequent campaigns. Have to explain why. The less data you have, the more risk you have.
  - Most reviewers are reasonable, but you have to make a cogent story especially when you don’t have much data.
  - Many of the BD practices were being done before but it’s just becoming more common now.

- Limited data sets – how do you overcome that in the BLA filing? Can 1 campaign support a BLA?
  - Sometimes just a few lots (not really just 1 lot…). Leveraging development and clinical data, and everything you have.
  - Specifications are always quirky, not just mathematical, have to include safety and efficacy considerations. Post-approval commitment to reevaluate specs. No one has huge numbers of lots at that point, have to use anything you have, make a comprehensive argument.
  - Could get a very tight spec with no raw material variability if specs basis is too narrow.
  - Anybody have a strategy for introducing variability in the clinic to support spec ranges? Make sure multiple lots of raw materials.
Need to consider that early clinical lots don’t have final assays. Keep retains! Want to go back to test clinical material, that’s critical. Build retains into your plan for accelerating.

- **Specifications – post-approval commitments?** Anybody have to update post-approval?
  - Is there any product that doesn’t?
  - Supposed to update process capability specs every year.
  - Issue of limited raw material variability in spec-setting lots is very problematic. Come in wide as credible, reassess to tighten.
  - Agency has pushed people to widen their specs when they’re too tight, pain in the neck to need a supplement to widen specs later. If reviewers can see the specs will be failed right away, they have pushed sponsors to widen them for the submission.
  - Use tolerance limits to widen the limits initially with small data.
  - Come in wider in the BLA, tighten later when data and experience support tighter specs.
  - Can’t always do a straight 3-sigma, tolerance limits may be so wide they’re not credible, have to find the sweet spot, compromise between data/statistics and science/clinical. Easier to justify tightening later than widening later. Widening specs later is very anxiety provoking for reviewers.
  - Have allowed sponsors to have different specs for commercial and clinical (wider for clinical material). Use clinical trial to study material that’s slightly wider. Frequently there are more clinical studies planned.
  - Have to be careful with the timing. Could limit supply if set limits too tight.
  - Clinical data rarely powered to show a difference.
  - Clinical mode of action, clinical experience, understanding of safety and efficacy profiles – specs should be based not just on statistical analysis.
  - Clinical experience for level of aggregates can demonstrate safety.
  - Zero success with asking clinical colleagues to include off-target materials in clinical trials. Have seen situations where a parameter that has potential to change on stability, can evaluate during clinical studies. During development, not post-licensure. Prospective plan to study materials at end of shelf life in clinical trials. Vary specific, clinicians may be reluctant. Usually a stability-indicating non-CQA that changed during shelf life. Was a study design, not thrown in as an afterthought. Proactive.
  - Say 10-60% deamidation, reviewers may ask sponsor to demonstrate that 60% is OK in the clinic.

- **CPV or ongoing process monitoring – how treating CPV for accelerated products?** Anything different?
  - Why would it be different? File robust process but with limited data, is there additional burden to monitor more closely post-approval?
  - One time had a strong justification to delete an attribute but health authorities wanted it monitored. Monitored first 50 lots, didn’t get added to specifications. Both US and EU (before BD).
  - May not have as much data, monitor more closely to establish control.
  - Reviewers haven’t seen that, not yet.
  - With BD, many changes in the first few years, start all over again with CPV?
IPCs, after n lots will delete those that aren’t meaningful. Once we have everything mapped well, we’ll determine what goes on the spec.

Common to reevaluate ranges and monitoring after some prespecified number of lots monitored. “Established conditions” may make this more common.

Risk of drug shortages is very important.

BD products, all products really, first 2 years many need a PAS. Post-marketing commitment may or may not result in supplements.

Before BD was official, people were doing these things, practices are becoming more common. Major PAS for new facility was planned as a way to accelerate by scaling up then transferring.

Nobody wants to launch without capacity, may launch with small scale and transfer early. Orphan drugs won’t have this issue.

Get product approved with PAS’s is probably worthwhile.

BLA for BD may get very complicated if too many comparability protocols (complicated to review, makes it very difficult to accelerate). What is a comparability protocol really buying you?

Only place they’re really worth it is moving a bunch of DP into the same facility. Probably need a PAS anyway for DS move.

Can file the PAS the day after approval, may not be worth including in submission. Have enough going on during the review (3-4 month clock), a lot of stress on the system. You’ll be arguing on ranges until you see the data. Reviewers may not have time during 3-4 month clock, may end up as PAS anyway.

Still CBE30 not AR. Buys you two months, is it worth it? Sometimes!

Other opportunities to engage regulators for feedback and dialogues?

WCBP networking and roundtables!

Could discuss accelerated strategy, but comes down to data for the specific product. Can only get so far talking about strategy in general terms.

Is EBE a pathway to Europe? Scientific advice prior to getting rapporteur may have limited value. Can backfire if too early. Meeting with rapporteur more helpful