PROCESS VALIDATION CONSIDERATIONS

The following approaches could be considered for discussion and agreement with FDA:

The four expedited programs were developed by FDA to minimize the time spent on the development and review of new drug and biological products that address unmet medical needs in the treatment of a serious or life-threatening condition. These programs help ensure that therapy for a serious condition is approved and available to patients as soon as it has been proven to provide an adequate safety profile and clinically meaningful benefit.

- Due to the likelihood of having 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
- Determining if clinical DS could be used for DP process validation, through early alignment with FDA on starting materials (e.g., small molecule products) is critical
- Leveraging process and product platform knowledge (e.g., for monoclonal antibodies) with appropriate justification to speed development
- Leveraging life cycle validation principles continued verification

-Using development experience/smaller scale batches in Process Performance Qualification (PPQ) strategy
-Identifying whether some PC/PV studies could be deferred, such as process linkage studies or chromatographic resin reuse at full lifetime

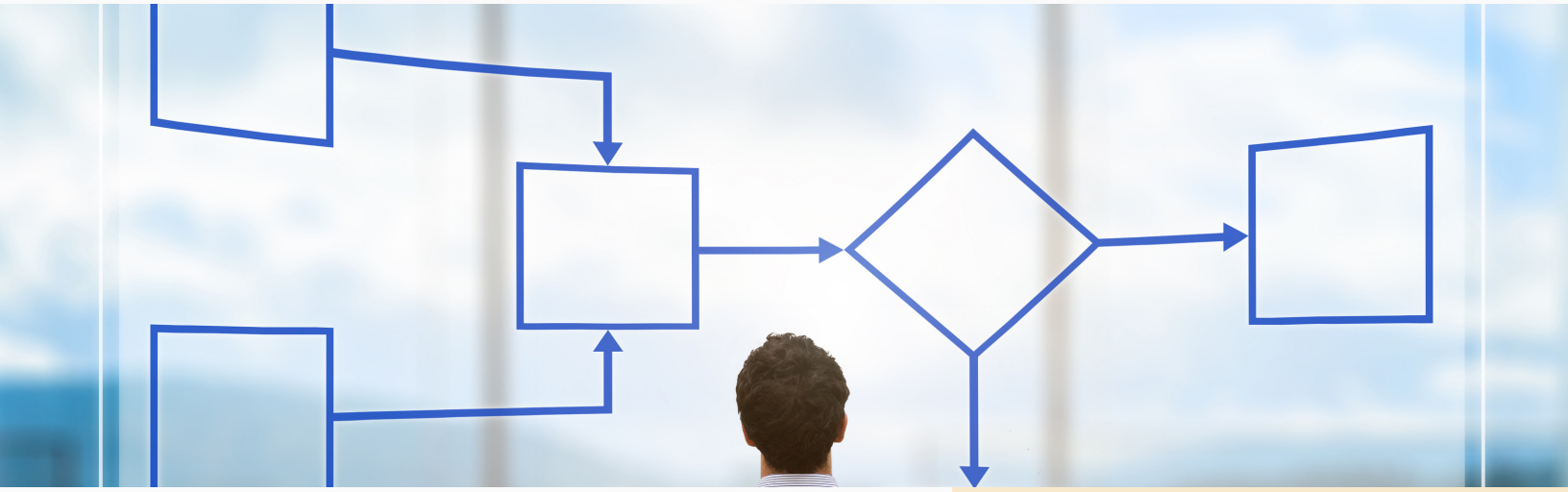
- Considering concurrent validation approaches, based on the FDA Compliance Policy Guide, CPG Section 490.100 (6), for orphan drugs to allow for product distribution concurrent with the release of each conformance batch (e.g., batch-specific release option). This could enable launch from a commercial site with a limited number of batches but is dependent on manufacturer end

-Prior demonstration of manufacturing consistency for clinical process material
-A validation protocol for commercial material and at least one executed batch record at the time of filing
-Robust Quality Systems able to effectively manage Corrective and Preventive Actions (CAPAs) and change management

Process Validation (small molecules)

In an accelerated development program, the period to gain extensive product and process knowledge before commercial manufacture will be significantly shortened. The extent to which a process may be run at a commercial scale may be limited and much of the process knowledge will be derived from small-scale experiments, platform knowledge, or in-silico modeling. This places increased emphasis on the process validation activities. The use of development and establishment batches as part of a more holistic process validation activity is one of the ways to accelerate this phase of the product lifecycle. In addition, there must be an acknowledgment of the need for increased use of concurrent validation to ensure that product specifically for process validation is not necessary.

Given the potential for limited process knowledge, acknowledgment by regulatory authorities that changes may occur during establishment and validation activities is critical, as long as these changes are critically evaluated for impact to product and other produced material. Data from early campaigns can be used to support validation when a detailed and robust monitoring and sampling plan should be



initiated as early as possible during development. Even after the completion of process validation, it is likely that there will be limited amounts of process data available. Therefore, the use of an enhanced monitoring period during commercial manufacture may be required. This will facilitate ongoing statistical analysis and trending of batches, providing data on the capability and stability of the process and product and facilitate process enhancements post-approval.

Process Validation (large molecules)
For all biotechnological products, there is a need to provide results of process verification studies on production-scale batches in the MA dossier at the initial filing. As these process evaluation studies are often on the critical path, it might delay the submission of the dossier and, therefore, could result in delayed access of products of unmet medical need to patients. It is therefore proposed for accelerated development programs (via an accelerated access scheme) to allow for the absence of process validation data in S.2.5 and P3.5 at the time of submission if mitigated by the inclusion of an appropriate protocol describing the process verification program and ongoing/continued process verification studies. Like for small molecules, the actual results of the process verification studies need to be made available for verification post-authorization by the supervisory authority.

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