CONTROL STRATEGY CONSIDERATIONS

Expedited Control Strategy, based on limited manufacturing experience, but ensuring patient safety and efficacy.

Some activities that might be considered to speed development activities include the following:

- Launching with a provisional control system that ensures consistent product and upgrading the control system post-approval with more manufacturing experience and completion of process validation, such as

-Filing with an expanded monitoring program with more tests initially, more assay controls, and justify the elimination of some tests post-approval as more knowledge is accumulated

-Filing with broader in-process controls (IPC) and product specification acceptance criteria at launch and re-evaluating post-approval for specifications that are linked to process consistency

-Filing with preliminary critical process parameters (CPPs) and CQAs

- For small molecules, considering all available data, including dissolution profiles and other critical analytical results, i.e., impurities, solubility, disintegration, etc. during development, (2) ensuring stability specifications are justifiable if requested by the FDA, and (3) considering sunset specifications for some parameters (e.g., polymorphism)
- Utilizing enhanced modeling techniques, where possible to support conclusions
- Managing second-generation processes through a life cycle approach in the post-approval lifecycle management plan (PALM), which may contain a network of comparability protocols to facilitate life cycle 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

Control Strategy Impurity Fate Mapping - Purge Modelling (small molecules)

The ICH Guideline M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, advocates the use of in-silico structure-activity modeling to identify potential mutagenic impurities. M7 then allows for multiple approaches for the control of mutagenic impurities, including analytical testing, chemistry purge arguments, or a combination of the two. Many impurities are highly reactive, will not typically survive through the synthetic processes, and therefore present a negligible risk of carrying over into the drug substance. Despite this, the completion of spiking and purging experiments that demonstrate the purge of low levels of mutagenic impurities can be a time-limiting element in drug substance development, particularly the development and validation of the sensitive analytical procedures required.

Use of Prior Knowledge: Viral Clearance / Inactivation Steps (large molecule)

(Adopted from EBE Concept Paper on Platform Manufacturing of Biopharmaceuticals).

The viral clearance steps in a mammalian cell-derived biopharmaceutical manufacturing process are almost always considered when the use of platform process data/ knowledge is discussed. This is because typically the same virus clearance studies are executed multiple times under the same protocol on different protein molecules. The different proteins, especially those from the same 'family' of molecules, e.g. monoclonal antibodies, generally show similar behavior at the different clearance steps (filtration/ low pH or chemical inactivation/ chromatography) which are operated the same way (platform process) for each product. These repeated studies tend to yield consistent and similar results from product to product. Indeed, the CHMP Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products acknowledges that prior in-house experience and data may be used to support the reduction in virus clearance testing for investigational products. There is an opportunity to eliminate such repetitive internal testing of well-characterized viral clearance steps and save time in an accelerated development scenario. In addition, numerous other published studies have demonstrated the capability of established downstream process steps for viral clearance. FDA supports the possibility to reference to

peer-reviewed published viral clearance studies in an accelerated development project for a given viral reduction step/claim without repeating the same studies again in-house and gaining agreement to this approach early in the development.

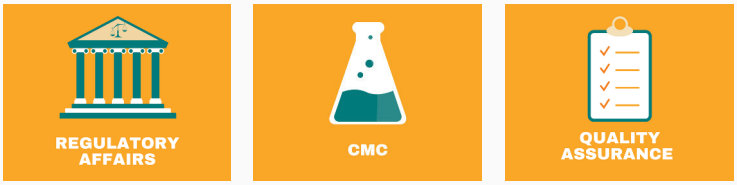
Manufacturing Changes to support Commercialization (large molecules)

Under an accelerated access scheme, it may not be feasible to perform pivotal clinical studies with the "to be marketed commercial process" thus necessitating further changes to the process that will be reflected by updating/ supplementing the initial Marketing application. The assessment of the changes and the supportive data to ensure the safety and efficacy of the changing process will be completed in a step-wise manner as would be done with other "non-accelerated" products (i.e. estimate product risk level, categorize the type of CMC change, evaluate the outcome of in-vitro/ex-vivo characterization and assess – if applicable - need/ type of in-vivo testing). In expedited schemes, where appropriate and justified, the use of prior knowledge/ platform knowledge will be leveraged for the comparability assessment. Three potential manufacturing changes are proposed below with proposed supportive data packages. This is not an exhaustive list.

Manufacturing Process Development Data / Control Strategy

For accelerated development, where appropriate and justified, the sponsor will leverage the platform or prior knowledge for the marketing authorization application under the expedited scheme. Further, the process control strategy will be refined and confirmed as more batches/ materials are manufactured. The initial manufacturing process may be based on preliminary ranges and specification acceptance criteria that might be broader than for products developed in a traditional setting and will be reassessed when a more comprehensive data set is available.

DSI Solutions



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