

Manufacturing Scale and Launch Site Considerations

Clinical manufacturing facilities, used for launch, would need to meet the same quality/GMP expectations as commercial manufacturing facilities. This will necessitate prioritization on gaining concurrence on comparability strategy/protocol for post-approval site changes in advance and may lend confidence to manufacturer's ability to ensure sustained supply post-launch, particularly when expediting launch upon initial approval.

Helping you get your product to market faster

Expedited clinical development programs for breakthrough therapy products will shorten the time available to optimize phase III and commercial manufacturing processes. This will necessitate prioritization of development efforts on process reliability over yield and cost of goods. As a result, process and formulation optimization may need to be deferred to post-approval; if it can be determined, there is no impact on patient safety or product availability



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

- Determine, as soon as possible, launch sites for DS and DP, clinical versus commercial
- Clinical manufacturing facilities, used for launch, would need to meet the same quality/GMP expectations as commercial manufacturing facilities
- Gaining concurrence on comparability strategy/protocol for post-approval site changes in advance may lend confidence to manufacturer's ability to ensure sustained supply post-launch, particularly when expediting launch upon initial approval
- If using a contract manufacturing organization (CMO) for DS/DP, ensuring there is capacity to allow rapid scale up and to support commercial volumes will be critical
- Consider decoupling drug substance and drug product qualification lots (e.g., using clinical DS for DP qualification), when feasible to save time on the critical path to licensure
- Pivotal clinical studies could 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)
- Scaling-up phase III clinical lots to commercial scale for launch with bridging comparability study

Use of Modelling to Facilitate Scale-up and Verification (small molecules and large molecules)

Scale-up Verification using process modelling techniques (for example multivariate analysis (MVA) or chemical reaction kinetics) can positively impact CMC development, in terms of delivering enhanced process understanding and accelerated scale-up and development. For drug substance and product processes designed at small scale, verification that they scale-up as predicted to intermediate and commercial scale can be achieved more rapidly and with greater confidence through the application of scientific principles, e.g. process kinetics and process modeling techniques such as MVA. This obviates the need for additional experiments at intermediate and commercial scale. The approach is aligned and supports plans to commercialize from pilot-scale facilities. It provides enhanced process understanding more rapidly than traditional qualification/verification approaches, giving confidence in predictions of how processes will run at larger scale.

Continuous Manufacturing (small molecules and 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 changed 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 type of CMC change, evaluate 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.

Cell line

A change of cell line is common during the development of a biotech product to ensure sufficient and robust commercial supply. However, it is considered a major change and is normally implemented as early as possible during development (prior to pivotal studies). It is therefore proposed that such cell line change may be performed during or post pivotal studies to enable early licensure under the accelerated access scheme for cases where there is convincing comparability evidence. In such a scenario, a comprehensive analytical comparability package would be required, ensuring that each potentially impacted CQA has been assessed. It may also be pertinent to include the use of established animal models in PK/ PD studies to support the analytical comparability where appropriate.

Process scale-up / Change of Site of Manufacture

A change of the process scale and/ or site of manufacture is usually considered a major CMC change. Within an accelerated clinical program, it may not be possible to perform the technical transfer into the commercial facilities and/ or manufacture at full scale for pivotal clinical studies. We consider it acceptable that manufacture for pivotal studies and initial launch could be performed at a smaller scale or a clinical manufacturing site (provided both adhere to cGMP), with analytical comparability data being presented at their earliest availability to support the switch to the commercial manufacturing site post launch. Process validation would then be provided post-approval based on data created at the commercial site.

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