Considerations for Successful Scale-Up To Tox Batches And Phase-API (Bulk Drugsubstance)

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Abstract

Practical Considerations in Pharmaceutical Production Scale-Up: This paper is meant to provide a high-level overview of the steps required to prepare the bulk drug substance API. From first-in-human and through each of the clinical trial stages and into commercialization, scale-up of formulation design is a natural part of pharmaceutical development. At each stage of process development, the batch size increases, from laboratory-scale batches that may be quite small to support preclinical and early clinical stages, to pilot batches that are used in process development, and finally to the production-scale batches needed to support commercialization.

Introduction

Since phase 1 studies are generally first in human studies, they are the initial baseline for establishing the safety of the product in people. Because changes to product quality could affect patient safety, this paper focused on establishing a controlled manufacturing process and a set of analytical assays to detect any changes to the product which could potentially impact patient safety. In addition, a specific set of studies have also been discussed that also help to ensure patient safety during the phase 1 clinical trial. If the points in the paper are followed, the elements for a strong IND bulk drug substance development package and robust manufacturing process should be in place. In the beginning, we don’t pay too much attention to yields as long as the conversion is relatively decent. Before we start doing experiments, we focus first on things like which reagents to use and how to make the process as efficient as possible. We see what tricks we can use that we learned from other projects. Efficiency is the key. The more efficient the chemistry, the easier to purify and to meet ICH guidelines.

As the life cycle of drug development unfolds, the demands on the synthetic process will change. In early development, the emphasis is very much on timely delivery of bulk supplies of the API using a safe process. Thus, most of the SELECT criteria can usually be satisfied when preparing the first few kilograms of the API or New Chemical entity (NCE) in bulk. In these early clinical trial stages, the most frequent issue encountered involves patient safety. However, we are also focusing our efforts on attaining the highest yield, the lowest number of impurities, the easiest purification process, the least amount of pressure and most moderate temperature. In other words – the most efficient process. By the time that a drug candidate reaches Phase III clinical trials, the CMO will need to manufacture perhaps hundreds of kilograms of API and the demands on the process become more acute across the full range of SELECT criteria.

The most important factors in developing “right-first-time” processes

a) Chemical yield
b) Cycle time
c) Number of chemical steps and convergence
d) Use of higher molecular weight protecting group and reagents
e) Number of energy-consuming operations.

Implementing this approach is key to reducing API development time as complexity grows and budgets shrink. As with any risk management plan, the goal is to be proactive in finding and mitigating sources of risk. This is accomplished by removing unwanted variability in each stage of a process. In clinical trials, the emphasis is on identifying, reducing, and monitoring risks to...
In order to prepare material of 98% purity for the tox batches, it is necessary to understand and control the isolation of the drug candidate. Once optimal isolation conditions have been identified, the batch may be isolated under slightly less than optimal conditions, for example, by cooling the crystallization slurry rapidly or by applying smaller volumes of washes to the wet cake on the filter. Another approach is to crystallize the product in the presence of additional typical process impurities; for instance, the product may be crystallized in the presence of impurities added as a portion of the mother liquor from a prior batch. Other impurities that need to be controlled in tox batches and subsequent batches include metals, such as palladium, Class 1 and Class 2 residual solvents (www.fda.gov), and any by-products known to be toxic.

Table 1

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Proposed acceptance criteria</th>
<th>Release testing</th>
<th>Internal testing*</th>
<th>Stability testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Identification by spectroscopic method</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Impurities/Degradation products</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chiral impurity*</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td></td>
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<tr>
<td>Residual solvents*</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td></td>
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<tr>
<td>Inorganic impurities</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td></td>
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<tr>
<td>Water content</td>
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<td>X</td>
<td>-</td>
<td></td>
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<tr>
<td>Solids form</td>
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<td>X</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Particle size</td>
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<td>X</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ROI</td>
<td>X</td>
<td>X</td>
<td>-</td>
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</tr>
</tbody>
</table>

*In addition to the acceptance criteria, internal targets may be used to trigger action at the proposed 3X QC identification (0.3%) or qualification (0.5%) limits. Table 2 provides qualification scenarios for individual impurities based on levels in the initial lot used for GLP safety studies versus lots produced for Phase 1 or 2a clinical trials. For a DS with two or more clinical centers, specific rotation may be used to monitor chiral purity in early development due to the complexity of the molecule. Chiral impurities may also be monitored and/or controlled elsewhere. *Solvents used in earlier steps of the synthetic process can be monitored as impurities after purification. Chiral impurities are monitored by two methods: either using a chiral liquid chromatography method or following the reference guidance (Ref. 13) until the chiral impurity is below the limit.

Challenging the Parameters
Although some scale-ups are easier than others by virtue of their manufacturing process, scale-up is always a meticulous process of trial and error. For each stage of the scale-up process, the product must be physically and analytically tested against approved physical and analytical specifications and the critical process parameters must be challenged in order to ensure the process can be validated. For example, with a wet granulation in the high-shear granulator, we may begin the rate at which the granulation solution is applied to the blend at 1000 grams per minute and then compare that to a batch in which the same amount of granulation solution is added at 3000 grams per minute. If there’s no change in the net result, a range is established for validation batches and we could improve process efficiency by adding granulation solution at three times the original rate. This type of process is carried out for every stage of production regardless of whether formula is being scaled up from two-kilo laboratory batches to 10-kilo study batches or 1000-kilo production batches. The process is also repeated for any scale-up of more than 10 times the original size. To scale up a 10-kilo batch to 1000 kilos, the entire scale-up process would have to be repeated first when we scale from 10 to 100 kilos and again when we scale from 100 to 1000 kilos according FDA Scale-Up and Post-Approval Changes (SUPAC) guidelines (Table 1).

Conclusion

Gaining Regulatory Approval

As with all stages of pharmaceutical production, scale-up requires careful planning and meticulous documentation of data. Working with the client, the technical transfer team develops a process development protocol and prepares batch manufacturing instructions. As the final step, a process development report is prepared as part of the submission package. Comparing data from each step in the process helps determine scalability requirements and identify critical process parameters at full scale. When successful physical and analytical testing at each stage is complete, the first full-scale feasibility batch can be produced and fine-tuned to maximize process efficiencies. When the technical transfer team is satisfied with the process development or feasibility batches, registration batches are produced for submission to regulatory agencies. If approved, validation batches are produced in order to establish that the process is valid, stable and able to reliably reproduce the product formulation performance, efficacy and safety as originally devised. Ideally all subsequent batches will be prepared by the route and process used for tox and/or Phase 1 batches, so that on-scale impurities and impurity profiles will meet the guidelines above of course, it is difficult to predict the final optimized process for a drug candidate. The best approach to control impurities is to determine the optimal starting materials, reagents, process, and final form (salt, polymorph) early (“freeze” the final step)

References

11. www.moneycontrol.com/india/news/business/themis_ventistechransferdeal/16/07/294996,