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A Regulatory Strategy by Keeping the Same Batch Size for Commercial That of Exhibit Batches May Have Untold Advantages Over Traditional Approach When Filing an ANDA for an Immediate Release Tablet Dosage Form

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Abstract
Generic Drug Manufacturer (Applicant) submit Abbreviated New Drug Application (ANDA) to USFDA based upon an innovator Drug or an RLD (Reference Listed Drug) [1]. One of the critical documents to be included in the original ANDA is the master production batch record(s) for the largest intended production runs (i.e., commercial batch records) that is/are no more than 10 times the exhibit batch(es). Proposing any increased batch size than the exhibit batch scale in the Original ANDA may lead to unwarranted additional post approval commitments from the applicant. In this article, Author elaborates the advantages when the applicant proposes same batch sizes for exhibit and commercial scale i,e "No Scale Up" in the original ANDA submission.

Keywords
USFDA, ANDA, RLD.

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INTRODUCTION:
An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references. The applicant should submit complete information as required to be provided in each section of the common technical document (CTD) format for human pharmaceutical product applications in preparing their ANDA submission. Proposed commercial scale batch record is one of the many documents to be included in the

original ANDA submissions. The ANDA once submitted will undergo various disciplines review and finally if FDA believes that that adequate information including post approval commitments have been presented then accordingly the ANDA will be approved.

Definitions:

Exhibit batch:

It is the batch one which can be manufactured in production plant or even in pilot plant which have similar equipment such as in production facility. The manufacturing procedure is fully representative of and simulating that used for full manufacturing scale. For solid oral dosage forms this is generally taken to be, at a minimum, one-tenth that of full production, or 100,000 tablets or capsules, whichever is larger [2].

Proposed/ Commercial batch:

It is the batch manufactured in production facility after ANDA approval and during commercializing of the Drug product. Usually the size of proposed batch should be up to and including a factor of 10 times the size of the exhibit batch.

Scale-Up:

The process of increasing the batch size during the Commercialization of drug product [2].

DISCUSSION:

A regulatory strategy by keeping the same batch size for commercial that of exhibit batches presents several advantages over traditional approach (scale-up in proposed batch record) when filing an ANDA for an immediate release tablet dosage form as presented in this article. As a face value, the suggested regulatory strategy eliminates the need for two sets of batch records and opportunity to complete the process validation at the time of submission batches execution provided that the initial product launch quantities can support the suggested theme. However, the notable advantages associated with the suggested regulatory strategy are in the areas of 1) Post Approval Stability Protocol and Commitment and 2) Split Tablets Study on validation batches.

1)Post approval stability protocol and commitment:

The FDA may issue a deficiency and recommend the applicant to place first three commercial production batches on accelerated studies for 6 months per ICH Q1A(R2)-2.2.8 (3), if the applicant proposes larger size commercial batch record than the exhibit batches and do not include the post approval commitment to place three commercial production batches on accelerated studies.

From the industry standpoint, the purpose of accelerated stability studies is not to determine batch uniformity but rather to test for kinetic degradation. The kinetic degradation was studied and understood on 3 batches for 6 months at Accelerated Stability Conditions as submitted in the original application. The change in batch size from exhibit batch to production batch size is not expected to change the kinetic degradation of the product. Therefore, additional kinetic degradation study on 3 production batches may be considered repetitive and requires unwarranted resources.

To overcome the potential deficiency from the FDA recommending post approval commitment of 3 additional commercial batches on accelerated stability, the applicant may consider the suggested regulatory strategy by keeping the same batch size for commercial that of exhibit batches when filing an ANDA as presented in this article. However, the applicant may still retain the flexibility to increase the batch size under post-approval regulatory strategy as outlined below.

Post approval regulatory strategy:

Where required, once the ANDA is approved, the applicant may consider the increase in batch size up to and including a factor of 10 times the size of the pilot/biobatch under level 1 change and report in subsequent annual report. The FDA Guidance published in November 1995 ***"Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation"***, which states that the Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch is defined as level 1 change and requires only test data from long-term stability studies and to be reported in Annual Report.

2) Split Tablets Study for validation batches:

The FDA may issue a deficiency and recommend the applicant to perform Split Tablets Study for the validation batches, if the applicant proposes larger size commercial batch record than the exhibit batches for an immediate release tablet dosage form with a functional score.

From the industry standpoint, the applicant must have already included data from Split Tablet Study in the original ANDA for exhibit batches such as tablet splitability and the dissolution of the individual split tablet portions etc. The change in batch size from exhibit batch to production batch size is not expected to change the hardness limits and the tablet splitability, and dissolution of the individual split tablet portions. Therefore, additional Split Tablet Study on validation batches may be considered repetitive and requires unwarranted resources.

To overcome the potential deficiency from the FDA recommending post approval commitment of Split Tablets Study for validation batches, the applicant may consider the suggested regulatory strategy by keeping the same batch size for commercial that of exhibit batches when filing an ANDA as presented in this article. However, the applicant may still retain the flexibility to increase the batch size under post-approval regulatory strategy as outlined below.

Post approval regulatory strategy:

Where required, once the ANDA is approved, the applicant may consider the increase in batch size up to and including a factor of 10 times the size of the pilot/biobatch under level 1 change and report in subsequent annual report. The FDA guidance published in March 2013 on "Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation" states that an evaluation of the tablet splitability should be provided during the post approval period for any product changes at Level 2 and Level 3 as defined in the Agency's Scale-up and Post-Approval Changes (SUPAC) guidance. The change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch is defined as level 1 change and therefore an evaluation of the tablet splitability does not apply.

CONCLUSION:

The regulatory strategy at the time of ANDA submission for an immediate release tablet dosage form with functional score presents opportunity to consider exhibit batch size as proposed commercial batch. The suggested regulatory strategy eliminates the need for two sets of batch records and provides opportunity to complete the process validation at the time of submission batches execution if the initial product launch quantities can support the suggested theme. However, the notable advantages associated with the suggested strategy are in the areas of 1) post approval stability protocol and commitment and 2) Split Tablets Study on validation batches. The suggested regulatory strategy may help the applicant to secure approval of an ANDA for an immediate release tablet dosage form without post approval commitment to perform accelerated stability studies and split tablet study (functional score tablet) on the validation batches. Once the ANDA is approved, if the scale used during the exhibit batches does not support the initial commercial launch quantities, the applicant may still retain the opportunity and consider the increase in batch size up to and including a factor of 10 times the size of the pilot/biobatch under level 1 change and report in subsequent annual report.

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