International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS™ | Volume 8 | Issue 4 | OCT-DEC | 2018 | 1254-1256
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

A REGULATORY STRATEGY AT THE TIME OF AN ANDA SUBMISSION FOR A SOLID ORAL DOSAGE FORM BY MANUFACTURING ONE SMALL SCALE BATCH AMONG THE THREE EXHIBIT BATCHES MAY BRING COST SAVINGS IN ADDITION TO PREVENTING POTENTIAL REFUSE TO RECEIVE FROM THE FDA

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ABSTRACT

Generic Drug Manufacturers (Applicants) submit an Abbreviated New Drug Application (ANDA) to the FDA based upon an innovator Drug or an RLD (Reference Listed Drug). [1] Many ANDAs get rejected without making it past the first obstacle (acceptance of the application). The Agency can refuse to receive (RTR) an ANDA based on one major deficiency or ten minor deficiencies. [2] The FDA refused to receive on average about 17% of all original ANDAs from 2013 through 2018 in accordance with the requirements outlined in the RTR Guidance. Among the many reasons for RTRs, the FDA will RTR an ANDA if the applicant does not package a minimum (threshold) amount of the finished drug product in the container/closure systems that are proposed for marketing, as discussed in FDA's guidance for industry ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers[3]. The threshold amount that should be packaged is governed by the specific dosage form. This article highlights "Batch Sizes and Packaging Amount Considerations for ANDA Submissions for solid oral dosage forms", since the requirements outlined in the guidance document present varying interpretations and may sometimes result in RTR if one of the three exhibit batches were not fully packaged. In this article, the author elaborates the advantages when the applicant proposes one small scale batch among the three primary batches to be manufactured for the original ANDA submissions.

KEYWORDS
FDA, ANDA, RLD, RTR

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, and low cost alternative to the brand-name drug it references.[4]The applicant should include the required information and documents in the applicable sections of the common

technical document (CTD) format for drug product applications in preparing the ANDA submissions. The data from three exhibit batches is one of the many requirements that should be included in the original ANDA submissions. The submitted ANDA will undergo an acceptance review followed by disciplines review and will be finally approved if the FDA concludes that complete information is presented in the ANDA.

DEFINITIONS:

Exhibit/Primary batch:

The batch should be manufactured and packaged with the similar production equipment utilized for the proposed commercial manufacturing. Data from three primary (exhibit/ submission) is required to be included in the ANDA. [3]

DISCUSSION:

A regulatory strategy by manufacturing one small scale batch among the three exhibit batches when filing an ANDA for solid oral dosage forms may bring cost savings in addition to preventing potential refuse to receive decision as outlined in this article. At face value, the suggested regulatory strategy will lower the overall manufacturing and packaging costs associated with the packaging of three exhibit batches required for the submission of an ANDA.

Batch Size and Packaging Amount considerations for Solid Oral dosage forms are:

one primary batch should be fully packaged, a minimum of 100,000 units in all proposed presentations is recommended, and representative samples from all three batches must be packaged in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166 (a) (1-5) and 211.166(b), and two of the three batches should be of at least 10 percent of the proposed production batch or 100,000 finished dosage units, whichever is greater (i.e., pilot scale batches), the third batch can be smaller than the 10 percent of the proposed production batch, but should not be less than 25 percent of the pilot scale batch and the stability data be generated for the three ANDA submission batches in the proposed marketing container. [3]

Since there are many requirements to be covered as presented above, it is possible that the industry may interpret the requirements and execute differently by the prospective ANDA applicants. Other than in special circumstances (orphan drugs or DEA products or low commercial volume drugs), the applicant manufactures three exhibit batches (pilot/primary) with a batch size of more than 100,000 units each of a solid oral dosage form. If the applicant packages each or a total of 100,000 units from the three exhibit batches, the ANDA will result into RTR decision. While it appears, the applicant might have met the batch size requirements outlined in the guidance documents, the reason for RTR decision is for not fully packaging one of the three exhibit batches in the proposed marketing container.

Regulatory Strategy:

To prevent the potential RTR from the FDA, the applicant may consider the suggested regulatory strategy as outlined below when filing an ANDA for a solid oral dosage form.

Manufacture two exhibit batches (pilot) with a batch size of at least 10 percent of the proposed commercial batch or 100,000 dosage units, whichever is greater and one small scale exhibit batch (third batch)with a batch size of not be less than 25 percent of the pilot scale batches or 25,000 dosage units, whichever is greater. The applicant must package the small-scale batch fully and the representative portions from the other two pilot scale batches in the proposed marketing container totaling to 100,000 dosage units. An example for batch size and amounts to be packaged is presented in table 1 below for an easy understanding, considering a tablet dosage form to be marketed in multiple pack/fill sizes (HDPE bottles).

Table 1: An example batch size and amounts to be packaged:

Batch Type/ Batch # / Drug Substance Lot #	Batch Size (units)	Pack sizes (Bracketing)	Notes
Pilot Scale/Batch 1/ Drug Substance Lot 1	120,000	30's fill – 15,000 Tablets 1000's fill – 20,000 Tablets	The bulk tablets to be used for the packaging should be representative. A portion of the remaining bulk may be used to establish bulk hold time study
Pilot Scale/Batch 2/ Drug Substance Lot 2	120,000	30's fill – 15,000 Tablets 1000's fill - 20,000 Tablets	The bulk tablets to be used for the packaging should be representative
Small Scale/Batch 3/ Drug Substance Lot 1 or 2 or 3 or combination of 1 and 2	35,000	30's fill – 15,000 Tablets 1000's fill – 20,000 Tablets	The batch should be packaged fully into the proposed marketing container. 100% yield is considered in the presentation.

CONCLUSION:

The regulatory strategy at the time of an ANDA submission for a solid oral dosage form by manufacturing one small scale batch among the three exhibit batches may bring cost savings in addition to preventing potential refuse to receive from the FDA. The suggested regulatory strategy requires manufacturing of one small scale batch and package fully followed by the packaging of representative portions from the other two pilot scale batches totaling to a minimum of 100,000 units in the proposed marketing container-closure system.

Received:04.08.18, Accepted: 07.09.18, Published:01.10.2018

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