INTRODUCTION
An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA’s Centre for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, and route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA’s Approved Drug Product with Therapeutic Equivalence Evaluations (Orange Book). Generic drug applications are termed “abbreviated” because they are generally not required to include preclinical and clinical data to establish safety and effectiveness. Instead, generic drug applicants must scientifically demonstrate that their product is bioequivalent. Using bioequivalence as the basis for approving generic copies of the drug products was established by the “Drug Price Competition and Patent Term Restoration Act of 1984”, also known as Waxman – Hatch Act.

ANDA Regulatory Approval Process
The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff processes the ANDA, assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA Checklist. Within the first 60 days following the submission of an ANDA, a filing review is completed. The Regulatory Support Branch (RSB) is responsible for the filing review. This group, organized under the Division of Labeling and Program Support (DLPS), consists of project managers and a support staff including technical information assistant(s), legal instruments examiner(s), and consumer safety technician(s). The branch chief who reports to the Division Director of DLPS supervises the branch.

COORDINATION OF THE GENERIC DRUG REVIEW
Once the ANDA is accepted for filing, the application enters the review queue. This means that the application is assigned to a bioequivalence reviewer, a chemist, and a labeling reviewer. Each chemistry team consists of a team leader, a project manager, and several reviewers. In this section, the emphasis will be placed on the chemistry project manager’s role in the generic drug review process. The chemistry project manager serves as the ‘Application’ Project Manager (APM). While APMs are located within the Chemistry review teams, they are actually a part of the Review Support Branch within the DLPS. Specifically, they plan, organize, and coordinate all of the review activities for the applications that they manage. This requires the coordination of all disciples. The APMs serve as co-leaders for the chemistry review teams. They assure timely resolution of scientific and regulatory conflicts to prevent delays in the review process. The APMs also make every effort...
Figure 1: Generic Drug Approval Process

BIOEQUIVALENCE REVIEW PROCESS
After an ANDA is accepted for filing by the RSB, the bioequivalence section is assigned to the Division of Bioequivalence to review. The Bioequivalence Project Managers (BPM) access a list of pending ANDAs and assign them to individual reviewers according to the first-in, first-reviewed policy. The BPMs also randomly assign other review documents such as Bio-INDs, protocols, and correspondence. The DBE’s responsibilities include the review of the bioequivalence section of ANDAs, supplemental ANDAs, Bio-Investigational New Drug Applications (Bio-INDs), protocols, and controlled correspondence. It is worth mentioning that more than half of all correspondence submitted to the OGD requests guidance from the DBE.

CHEMISTRY REVIEW PROCESS
After an ANDA has been accepted for filing by the RSB, the Chemistry, Manufacturing and Controls (CMC) section of the application is assigned to the appropriate Chemistry Division and Team, based on the therapeutic category of the drug product. Once the application is assigned to the team, the application is designated as “random” and placed on the team leader’s queue. The team leader assigns the application to a reviewer on his or her team according to the first-in, first-reviewed policy. The Chemistry Divisions review the CMC section of ANDAs, Drug Master Files, Supplemental ANDAs, Annual Reports, and Controlled Correspondence.

LABELING REVIEW PROCESS
After an ANDA has been accepted for filing by the RSB, the Labeling section of the application is assigned to the appropriate labeling reviewer based on the therapeutic category of the drug product. The Labeling Review Branch is part of the DLPS. A team leader oversees the work of 4-6 reviewers.

The basis for the labeling review is to ensure that the generic drug labeling is the “Same As” the RLD labeling. There are several exceptions to the “Same As” regulation. Exceptions are allowed for: differences due to changes in the manufacturer or distributor, unexpired patents, or exclusivities and other characteristics inherent to the generic drug product, such as tablet size, shape, or color. The labeling reviewer also identifies and resolves concerns that may contribute to medication errors. For example, the labeling reviewer may identify drug names that are similar or that sound alike. In addition, the labeling reviewer may address concerns associated with the prominence and legibility of drug names on a container label.

METHOD OF REVIEW
Chemistry and manufacturing and control determining the challenges around impurity profiling at the drug product Level:

The definition of the impurity profile of a new drug material is given in the guidelines of ICH, “a Description of the Identified and Unidentified Impurities” It is the common name of analytical activities with the aim of detecting, identifying, or elucidating the structure and quantitatively determining organic and inorganic impurities as well as residual solvents in the bulk drugs and pharmaceutical formulations.

TROUBLESHOOTING GENOTOXICITY
REGULATORY REQUIREMENTS AT THE DRUG SUBSTANCE LEVEL:
Compounds that can induce genetic mutations, chromosomal breaks, or chromosomal rearrangements are considered as genotoxicity impurities (GTIs) and have the potential to cause cancer in humans. ICH and EMEA guidelines provide the limits for impurities in drug substances and drug products. These limits are not acceptable for GTIs due to their adverse effects and hence it is necessary to set up limits based on daily dose of the drug substance. Even though this is desirable in quality point of view, it deploys the resources in process development.

a) USFDA Guidance:
USFDA released draft guidance for industry genotoxic and carcinogenic impurities in drug substance and products in 2008, to address GTI issues. This guidance describes a variety of ways to characterize and reduce the potential lifetime cancer risk associated with patient exposure to genotoxic and carcinogenic impurities.

The recommended approaches include:

(a) Prevention of genotoxic and carcinogenic impurity formation,
(b) Reduction of genotoxic and carcinogenic impurity levels (allowing a maximum daily exposure target of 1.5mg/day),
(c) Additional characterization of genotoxic and carcinogenic risk and
(d) Considerations for flexibility in approach to better support appropriate impurity specifications.

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The work done will provide a brief idea on the latest developments in the US ANDA filing and review process, as per CTD and eCTD submission, which will determine the most rapid route in gaining approval for Indian products.

CONFLICT OF INTEREST
Authors declare no Conflict of Interest.

REFERENCES