An Abbreviated New Drug Application (ANDA) submission to US FDA

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Abstract: An Abbreviated New Drug Application (ANDA) is a written request to the United States Food and Drug Administration (USFDA) to manufacture and market a generic drug in the United States. Abbreviated New Drug Applications are "abbreviated" as they do not require the applicant to conduct clinical trials and require less information than a New Drug Application. In-vivo comparative bioavailability studies are required to be performed to establish the ANDA (generic medicine) is bioequivalent to the already approved product (called reference listed drug) in terms of safety and efficacy. The bioequivalence or therapeutic equivalence is proved in terms of pharmacokinetic or pharmacodynamics or efficacy and safety parameters which is evaluated by establishing the statistical significance between two products and comparison. Once the FDA has approved the submitted ANDA application, the applicant can manufacture and market the generic medicine. Small molecules can be approved by ANDA application. However, biologics and biosimilar products are not comes under generic medicine category as they are prepared by genetic engineering and it requires clinical trials to establish pharmacokinetics, safety, efficacy and immunogenicity of the product.

Introduction: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) created an abbreviated approval pathway for duplicates (generics) of a previously approved drug product in section 505(j) of the FD&C Act. An ANDA relies on the Agency's previous finding of safety and effectiveness for a reference listed drug (RLD) (it is the product of innovator) and as a result, may be approved without submission of the same type and extent of information that is requested for a stand-alone new drug application to establish the safety and effectiveness of the proposed product. Section 505(j) of the FD&C Act, together with its implementing regulations, generally requires that an ANDA must contain information to demonstrate that the proposed drug product and the applicable RLD are the same with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and, with certain exceptions, labelling. An ANDA must also include sufficient information (1) to demonstrate that the proposed product is bioequivalent to the RLD and (2) to ensure the product's identity, strength, quality, and purity. Consistent with any statutory provisions related to the exclusivity of and patents listed for the RLD, FDA must approve an ANDA unless there is insufficient evidence that these criteria are met or there is inadequate information to ensure the identity, strength, quality, and purity of the drug product.

Generic drugs cannot go on to the market until the branded patent has expired. Because branded drugs lose so much of their revenue when generic drugs are introduced, the Act provides them with patent extensions options, which now average about three years. Generic drugs are granted a 180-day period of exclusivity. Either the first drug to file an ANDA or the first group of drugs, is granted this period.

As generic drugs no longer require to prove their safety and efficacy. Under the bill, generic drug manufacturers need only submit an Abbreviated New Drug Application (ANDA) to prove their product's bioequivalence to the original branded drug. Hence, this is a cheaper process for manufacturers/sponsor companies, as the cost of conducting clinical and non-clinical studies or risking liability for patent infringement damages are not a part of the equation for the generic drug manufacturers. As a result, the generic products are being marketed at much lower price compare to innovator's products.

Common technical documents (CTD) requirements : The CTD format was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in an attempt to streamline the submission requirements for Japan, the European Union, and the United States. The CTD collects quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities. The electronic CTD (or eCTD) is the standard format for electronic regulatory submissions for ANDAs. As of May 5, 2017, ANDAs and submissions to ANDAs (which includes amendments, supplements, and reports) must be submitted to FDA electronically in eCTD format only.

There are specific guidance recommendations by FDA for all technical aspects of filing a CTD application and it should be reviewed thoroughly prior to submitting an ANDA. This guidance, also specifically addresses the content of the CTD for an ANDA.

The CTD is comprised of the following modules:

Module 1: Administrative Information and Prescribing Information

Module 2: Common technical document Summaries

Module	Content
2.1	Common technical document table of contents (Modules 2–5)
2.2	CTD introduction
2.3	Quality overall summary
2.4	Nonclinical overview
2.5	Clinical overview
2.6	Nonclinical written and tabulated summaries Pharmacology Pharmacokinetics Toxicology
2.7	Clinical summary Clinical pharmacology studies

	Clinical efficacy Clinical safety Literature references Synopses of individual studies

Module 3: Quality aspects

Module	Content
3.1	Module 3 table of contents
3.2	Body of data
3.3	Literature references

Module 4: Nonclinical aspects

Module	Content
4.1	Module 4 table of contents
4.2	Study reports
4.3	Literature references

Module 5: Clinical aspects

Module	Content
5.1	Module 5 table of contents
5.2	Tabular listing of all clinical studies
5.3	Clinical study reports
5.4	Literature references

In-vivo bioequivalence study: In-vivo bioequivalence studies are generally recommended for dosage forms intended for oral administration and to non-orally administered drug products in which reliance on systemic exposure measures is suitable for documenting BE (e.g., transdermal delivery systems and certain rectal and nasal drug products. Bio-waivers are considered as the waivers of clinical bioequivalence studies based on certain conditions. For most of parenteral products (including suspension, solutions etc.), bio-waiver can be applied where bioequivalence is self-evident. For immediate release products which are of class 1 (drug with high solubility – high permeability) or class 3 (drug with high solubility – low permeability) categories, bio-waiver can be applied based on FDA guidance recommendations.

Reference listed drug (RLD): It is basically the innovator's product which is already marketed in the

country. The generic product is compared with RLD in terms of bioequivalence studies. The RLD detail is available in orange book including the RLD name, marketed by/innovator, patent expiry etc.

The statutory definition of bioequivalence (BE) is expressed in terms of rate and extent of absorption of the active ingredient or moiety, emphasizes the use of pharmacokinetic endpoints in an accessible biological matrix, such as blood, plasma, and/or serum, to indicate release of the drug substance from the drug product into the systemic circulation. BE frequently relies on pharmacokinetic endpoints such as Cmax (peak plasma concentration) and AUC (area under the plasma concentration time curve) that are reflective of rate and extent of absorption, respectively.

If serial measurements of the drug or its metabolites in plasma, serum, or blood cannot be accomplished, measurement of urinary excretion can be used to demonstrate BE.

Study design: FDA recommends use of a two-period, two-sequence, two-treatment, single-dose, crossover study design, a single-dose parallel study design, or a replicate study design for BE studies. For most dosage forms that release drug intended to be systemically available, FDA recommend that applicants perform a two-period, two-sequence, two-treatment, single-dose, crossover study using healthy subjects. In this design, each study subject should receive each treatment (generic (test) and RLD) in random order.

If the drug is not tolerable to healthy subjects, then the bioequivalence study can be performed in patient population as either single dose crossover study or multiple dose studies.

In bioequivalence studies, to establish the pharmacokinetic parameters, the blood samples are to be collected at various time-points. Collection of blood samples at an early time point, between 5 and 15 minutes after dosing, followed by additional sample collections (e.g., two to five) in the first hour after dosing is usually sufficient to assess peak drug concentrations. Failure to include early (5-15 minute) sampling times leading to first time-point Cmax values may result in FDA not considering the data for affected subjects from the analysis.

The statistical analysis of the pharmacokinetic parameters (ex. Cmax, AUC etc.) is performed using suitable program to establish the bioequivalence. The 90 percent Confidence intervals of pharmacokinetic parameters value should be at least 80.00 percent and not more than 125.00 percent for most of the generics.

Standardization of all procedures is specified in the FDA guidance that are required to be followed during the study conduct. Standardization includes fasting/fed requirements before and after dosing, posture restrictions after dosing, alcohol and other prohibited product's restrictions for specific duration before and during the study period, safety examinations, water restrictions etc.

For most of the drugs, FDA has published the product specific guidance for generic drug development. The product specific guidance recommends the bioequivalence study designs, analyte(s) to be measured in plasma or blood or serum, the pharmacokinetic parameters to be considered for bioequivalence assessment, safety etc.

The protocol need to be prepared which describes detail about the study design, population to be enrolled, inclusion, exclusion criteria, blood sample collection time-points, analyte(s) to be measured, bioanaytical techniques, statistical considerations, bioequivalence criteria etc. based on requirements of ICH GCP E6(R2), US FDA regulatory requirements and other applicable regulatory requirements. The study should be

conducted after written approval from the ethics committee on protocol and other important documents such as informed consent form, case report forms etc. The study should be conducted considering the ethical aspects as per ICH GCP requirements and GLP requirements.

Detailed study report will be prepared which describes all the aspects of the study conduct includes clinical, bio-analytical process, pharmacokinetic, statistical and safety aspects according to ICH GCP E3 guidance, FDA and other applicable requirements.

Clinical Data Interchange Standards Consortium (CDISC): Clinical Data Interchange Standards Consortium (CDISC) is an open, multidisciplinary, neutral, non-profit standards development organization (SDO) that has been working through consensus-based collaborative teams to develop global data standards for clinical and nonclinical research. All the bioequivalence studies for US FDA submission need to be submitted as per CDISC requirements.

Data format specifications for the tabulation datasets of clinical and nonclinical toxicology studies are provided by Study Data Tabulation Model (SDTM) and Standard for Exchange of Nonclinical Data (SEND), respectively, while data format specifications for the analysis datasets of clinical studies are provided by Analysis Data Model (ADaM).

FDA Inspections: US FDA can inspect the site where the bioequivalence study is conducted to assess the data obtained for the ANDA application. The inspection can be due to routine inspection, directed (e.g. for caused) inspection or follow-up inspection (e.g. warning letters, 483s). The site of inspection can be the contract research organization if the study conducted on healthy subjects or the investigators (hospital) sites if the study is conducted in patient population.

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