

Abbreviated New Drug Application (ANDA) Approval Process

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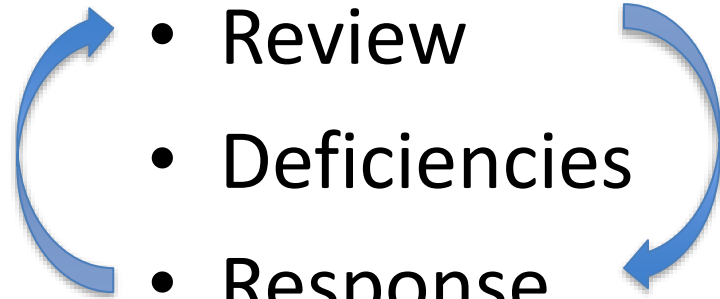
Definition of a Generic Drug

- A drug product that is generally the same as the Reference Listed Drug (RLD) with respect to their active ingredient(s), dosage form, route of administration, strength, conditions of use, and labeling (with certain exceptions). An application for a generic drug must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD and ensure the product's identity, strength, quality, and purity.

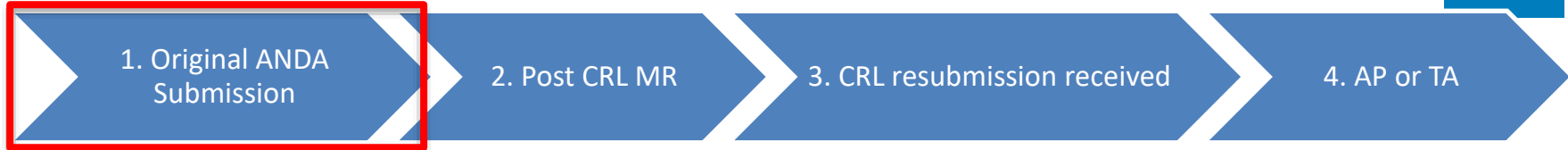
Overview of ANDA Approval Process



- Original Submission
- Review
- Deficiencies
- Response
- Approval or Tentative Approval
- Post-Approval Supplements



ANDA Review Lifecycle



- Division of Filing Review reviews the ANDA for acceptability
- Disciplines review
- Disciplines send Information Request (IR)/Discipline Review Letter (DRL)
- IR/DRL response received and reviewed
- Complete Response Letter (CRL) sent (if necessary)

- Post-Complete Response Letter Meeting Request (MR) may be submitted to clarify deficiencies sent in CRL

- Disciplines review the CRL response
- Disciplines send IR/DRL
- IR/DRL response received and reviewed
- Additional CRL sent (if necessary)

- AP = Final Approval – this action is taken if the ANDA meets all requirements for approval and there are no blocking patents or exclusivities
- TA = Tentative Approval – this action is taken if the ANDA meets all requirements for approval and there are patents or exclusivities that blocks the ANDA from Final Approval



Prioritization

- Prioritization of ANDAs is outlined in MAPP 5240.3 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*
- Examples of prioritization factors:
 - First Generics
 - Drug Shortages
 - President’s Emergency Plan for AIDS Relief (PEPFAR)
 - Public Health Emergency



NDA vs. ANDA Review Process

NDA Requirements	ANDA Requirements
1. Labeling	1. Labeling
2. Chemistry	2. Chemistry
3. Manufacturing	3. Manufacturing
4. Controls	4. Controls
5. Microbiology	5. Microbiology
6. Inspection	6. Inspection
7. Testing	7. Testing
8. Pharm/Tox	8. Pharm/Tox
9. Animal Studies	9. Bioequivalence
10. Clinical Studies	
11. Bioavailability	





Labeling

- ANDA product labeling must have the same labeling as the RLD, except for differences permitted under the FD&C Act (e.g., inactive ingredients and packaging configuration).
- In certain instances, the labeling for the generic drug may differ from the labeling for the RLD if FDA permits the ANDA applicant to omit (carve out) an indication or other aspect of the RLD's labeling protected by patent, or by exclusivity, and obtain approval for the remaining, non-protected conditions of use, provided the differences do not render the proposed product less safe or effective than the RLD for all remaining non-protected conditions of use.
 - Use codes in the Orange Book describe a general scope of a patent's method of use claim.
 - An ANDA applicant may not omit labeling that is not protected by a patent or exclusivity.

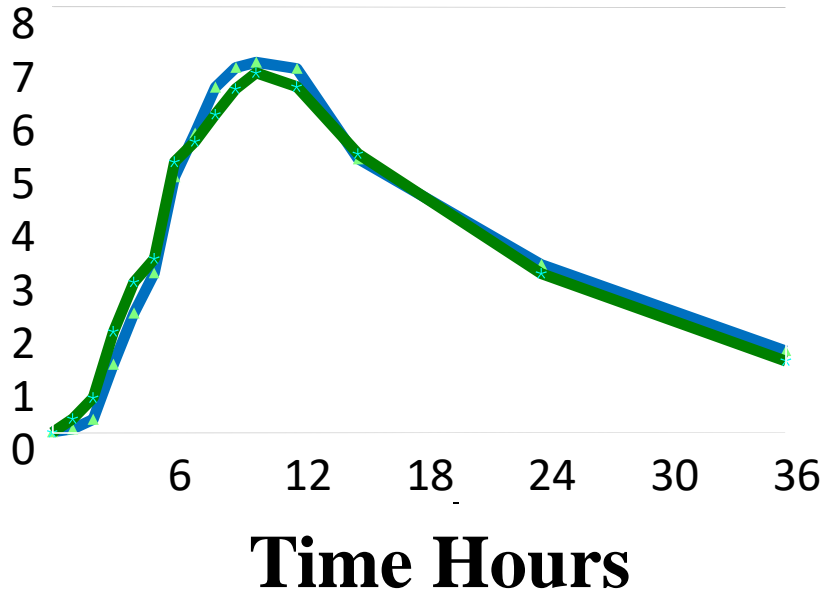
Bioequivalence

- The FD&C Act provides that a generic drug is bioequivalent to the listed drug if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug.
- For most products, the focus of Bioequivalence (BE) studies is on the release of the drug substance from the drug product into the systemic circulation. During such BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the RLD.

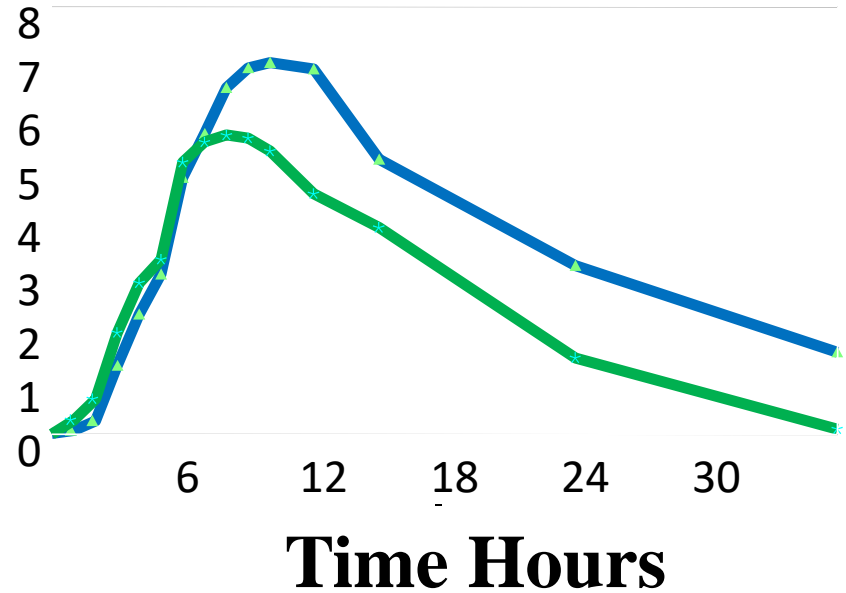
Bioequivalence



Bioequivalent



Not Bioequivalent



- Test drug product
- RLD



Complete Response Letters

- Complete Response Letters are a list of deficiencies provided to the applicant by the FDA when all disciplines have completed their review.
 - Deficiencies can be major or minor
 - The applicant must respond to all questions before submitting their response
 - Applicant has 1 year to respond to CRL, but they can request extensions if needed

Patents and Exclusivities for Generic Drug Products



- A **patent** is a property right granted by the United States Patent and Trademark Office (PTO) anytime during the development of a drug. Patents protect a drug manufacturer's invention (for example, a new drug or a new use for a drug) and prevent other manufacturers from marketing products covered by the patent, among other things.
- An **exclusivity**, provided by FDA, provides limited protection from new competition in the marketplace and precludes approval of certain ANDAs for prescribed periods of time. Certain exclusivities for qualifying brand name drugs and generic drugs were established in the Hatch-Waxman Amendments as part of the Drug Price Competition and Patent Term Restoration Act of 1984.

Patents and Exclusivities for Generic Drug Products (cont.)



- It is common for generic drug applicants to challenge a patent listed in the Orange Book.
- In many cases, the brand-name drug company/patent holder and the ANDA applicant reach a settlement agreement, resulting in dismissal of the litigation and lifting of the 30-month stay, if it is still in effect. The FDA is not involved in these court cases or in any settlement discussions.
- If an ANDA meets all requirements for approval but a patent or exclusivity still prevents final approval of the ANDA, the ANDA applicant may receive a tentative approval letter.



Approvals

- Final Approval of an ANDA is based on the following:
 - All disciplines deem the submission adequate
 - All facilities utilized are deemed adequate
 - There are no legal barriers to approval
 - Legal barriers to approval could include patents, exclusivities, or court injunctions.
 - Legal barriers to approval will result in FDA tentatively approving the ANDA.

Supplements



- Submitted after the approval of an ANDA to make changes from what was originally approved
- Types of supplements are CBE-0, CBE-30, and PAS
 - Changes Being Effected-0 (CBE-0) – certain moderate changes that allow distribution to occur as soon as FDA receives the supplement.
 - Changes Being Effected-30 (CBE-30) – certain moderate changes that require submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.
 - Prior Approval Supplement (PAS) - a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change such as this requires the submission of a PAS and approval by FDA before distribution of the drug product made using the change.



Supplements (cont.)

- Examples of Supplemental changes:
 - New Strength(s) added to an ANDA
 - New/Alternative Manufacturing Facility
 - Updating the Labeling of an ANDA to match updated labeling in the RLD
- Note that minor changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product may be submitted in the next annual report.

References

- *MAPP 5240.3 Prioritization of the Review of Original ANDAs, Amendments, and Supplements*
- *ANDA Submissions — Content and Format Guidance for Industry*
- *Post-Complete Response Letter Meetings Between FDA and ANDA Applicants Under GDUFA Guidance for Industry*
- *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA Guidance for Industry*



References (cont.)

- *ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs Guidance for Industry*
- *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA Guidance for Industry*
- *Information Requests and Discipline Review Letters Under GDUFA Guidance for Industry*
- *ANDA Submissions — Prior Approval Supplements Under GDUFA Guidance for Industry*