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Review

Challenges In Designing Anda For Parenteral Products

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Abstract

Pharmaceutical industry is one of the most regulated sectors as it deals with life of myriad patients. This paper discusses quality by design for generic drugs and presents a summary of the key terminology. Quality by design (QbD)-based product development involves the following elements: (a) identification of quality target product profiles (QTPPs) followed by critical quality attributes (CQAs) for various parenteral products, (b) process design and identification of critical process parameters (CPPs), (c) design space, and (d) control strategy and continuous improvement. The elements of quality by design are examined and a consistent nomenclature for quality by design, critical quality attribute, critical process parameter, critical material attribute, and control strategy is proposed. Agreement on these key concepts will allow discussion of the application of these concepts to abbreviated new drug applications to progress.

Keywords: QbD, QTPPs, CPPs, CQAs

INTRODUCTION

An Abbreviated New Drug Application (ANDA)

ANDA is an application for a U.S. generic drug approval for an existing licensed medication or approved drug. The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, which 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. Electronic submissions of ANDAs have grown by 70% since November 2008.[1] The Section IV challenge has been credited with suppressing new drug innovation.[2] A generic drug product is one that is comparable to a patented drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Generic drug applications are termed "abbreviated" because (in comparison with a New Drug Application) they are generally not required to include preclinical (animal and in vitro) and clinical (human) trial data to establish safety and

effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. In cases of topically active drugs, the bioequivalence of a drug can be demonstrated by comparing drugs dissolution or transdermal drug absorption is compared with the innovator drug. In cases of systemically active drugs, active drug blood concentration of that drug is compared with the innovator drug.

Using bioequivalence as the basis for approving generic copies of drug products was established by the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. This Act expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials. At the same time, the brand-name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.

"The Orange Book"

Approved Drug Products with Therapeutic Equivalence Evaluations

- Contains list of all FDA approved drug products (NDAs, ANDAs and OTCs)
- Therapeutic equivalence codes
  - "A" = Substitutable
  - "B" = NOT substitutable
- Patent and exclusivity expiration dates
- Reference Listed Drugs - A drug product identified by FDA for generic companies to compare their proposed products

Post-Approval Submissions

- Supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities.
  - Prior Approval Supplement (PAS) – major changes
  - Changes Being Effected (CBE) – moderate changes
- Annual report must be submitted each year within 60 days of the anniversary date of approval of the application.
  - May include some minor changes

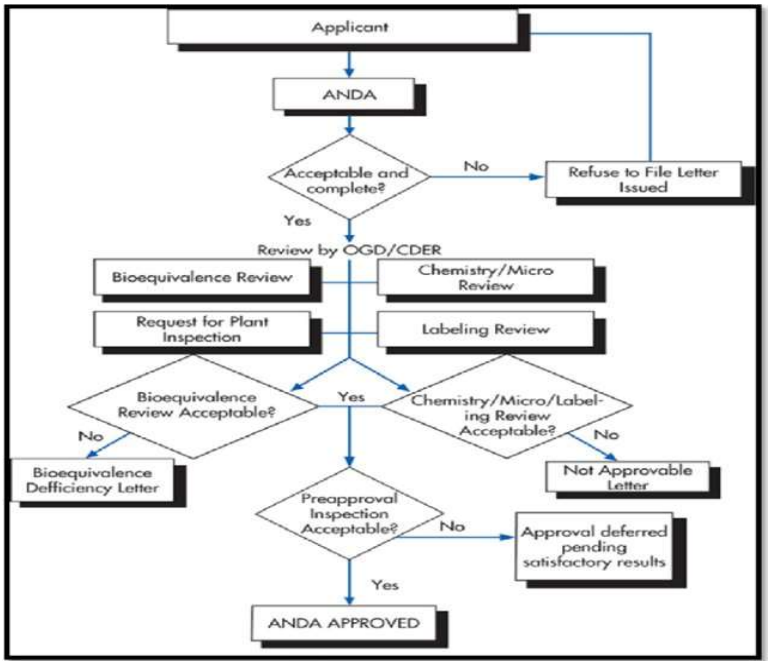

Fig 1: Flow chart of ANDA

New Drug Application (NDA)

- NDA is submitted based on FD&C Act 505(b).
- NDAs are submitted for:
- New molecular entity
- New formulation of previously approved drug
- New combination of two or more drugs
- New indication (claim) for already marketed drug

Table 1: Patent for NDA vs. ANDA

NDA	ANDA
Patent information is required to be submitted with all new drug applications at the time of submission of the NDA**.**	A certification for each patent listed in the "Orange Book" for the RLD must state one of the following: (I) No Patent Filed (II) Patent Has Expired (III) Patent Will Expire (IV) Patent Challenge
FDA relies on the NDA applicant or patent owner's signed declaration stating that the patent covers an approved drug product's formulation, composition or use.	

Table 2: Review Process for NDA vs. ANDA

NDA	ANDA
- Lower volume (average 25 approvals/year)	-Higher volume (more than 500 approvals/year)
-Higher complexity (pre-clinical and/or clinical trials, etc.)	-Lower complexity (safety and efficacy already established)
-One drug one application	-One drug multiple applications
-Pre-submission face-to-face meetings (IND phases)	-User fee (GDUFA) from 2013
- User fee (PDUFA) from 1992	

Requirement for ANDAs

- Must have an approved reference product (RLD) and a patent certification
- Must be Therapeutic Equivalent to a reference product
- Meet the quality standards for chemistry and/or microbiology
- All related facilities have acceptable cGMP compliance[3]

Therapeutic Equivalence

Therapeutic Equivalence includes:

- Pharmaceutically Equivalent (PE)
  - Same active ingredient(s)
  - Same dosage form
  - Same route of administration
  - Identical in strength or concentration
  - May differ in characteristics such as shape, excipients, packaging...
- Bioequivalent (BE)
  - Two drugs demonstrate same rate and extent when they become available at the site of drug action

Filing Review

- Filing review is conducted to determine whether the application is sufficiently complete to permit a substantive review.
- Acceptance/Refuse to Receive (RTR) letter is issued based on completeness of the ANDA.
- Updating the regulatory filing checklist on a quarterly basis (calendar year) and on an as needed basis.

Bioequivalence Review

- Evaluate bioequivalence study acceptability
  - Clinical portion (subject treatment)
  - Analytical portion (biological fluid analysis)
  - Statistical portion (are products bioequivalent?)

- Select appropriate in vitro dissolution method (solid dosage forms only)
  - Stability and controls testing
- Grant biowaivers where appropriate
- Review bioequivalence protocols

Bioequivalence

- Generic products is compared, in studies to the reference listed drug (RLD)
- Most studies compare the blood levels of the active moiety or moieties
- The generic product must be equivalent within certain pre-specified limits:
  AUC and Cmax of T/R: 90% Confidence Intervals (CI) must fit between 80%-125%

Biowaivers

21 CFR Part 320 provides situations where in vivo bioequivalence studies can be waived:

- Solutions (parenteral, oral, etc.)
- Drug Efficacy Study Implementation (DESI)
- Biopharmaceutics Classification System (BCS)
- Usually lower strengths of a product line

Labeling Review

- Reviews for "Same" as brand name labeling (with exceptions)
  - Labeling text to reflect differences in excipients, specific pharmacokinetic data
  - How supplied information - packaging container
  - Pharmacy practice issues - to prevent medication errors
- May exclude portions of labeling protected by patent or exclusivity

Chemistry Review

Reviewing drug substance and drug product for:

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Product specifications
- Packaging
- Stability

Drug Substance Information

- Most generic drug product manufacturers rely on third parties for supplying drug substances.
- Drug substance suppliers submit Drug Master File (DMF) to FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

Question based Review (QbR)

- Implemented for generic drugs in 2007
- QbR is a general framework for a science and risk-based assessment of product quality
- QbR contains the important scientific and regulatory review questions to:
  - Comprehensively assess critical formulation and manufacturing process variables
  - Set regulatory specifications relevant to quality
  - Determine the level of risk associated with the manufacture and design of the product

QbR Example

Q) What are the unit operations in the drug product manufacturing process?

A)

- Detailed flow chart
  - unit operations (blending, drying, etc),
  - equipment,
  - point of material entry,
  - identification of critical steps (with process or other controls)
- Narrative summary of the manufacturing process
- Reprocessing/reworking statement

- Executed batch record and blank product batch record

Microbiology Review

Reviewing sterile drug products (parenteral, ophthalmic, and inhalation) for:

- Product Development (container/closure integrity validation and preservative effectiveness)
- Overall sterile manufacturing process design and process controls
- Terminal sterilization/aseptic fill process validation
- Drug product specifications
- Release and stability
- Studies to support labeling

Inspection - cGMP/Compliance

- All facilities used for manufacturing, testing, packaging/storing drug substance and drug product are subject for inspections and must be in compliance at the time of approval.
- Inspection program is also design to check data integrity. If data integrity is in question all reviews will stop.
- Type of inspection includes: pre-approval, post-approval, and for cause.

ANDA Approval

All review disciplines find the ANDA acceptable and all facilities are in satisfactory standing as reviewed and inspected.

- Full Approval - all valid patents and exclusivities for the RLD are expired or any legal issues that may block approval of the ANDA are settled.
- Tentative Approval – there exist unexpired patents and exclusivities for the RLD.

Economic Impact of Generic Drugs

- Generic Drugs account nearly 80 percent of the 4 billion prescriptions written in the U.S. in 2011.
- Generic Drugs cost 30% to 80% less than brand counterparts

Challenges in Generic Drug Review

- Complex products and dosage forms
- Growing workload
  - Receipt of applications continue to be greater than approvals
  - Increasing complexity of review process
- GDUFA review performance commitments

GDUFA Hiring

Additional resources are need to enable the FDA to reduce a current backlog of pending drug applications and cut the average review time required.

- Microbiologist
- Chemist
- Chemical Engineer
- Consumer Safety Officer
- Pharmacist
- Medical Officer
- Operations Research Analyst
- Interdisciplinary Scientist
- Regulatory Counsel

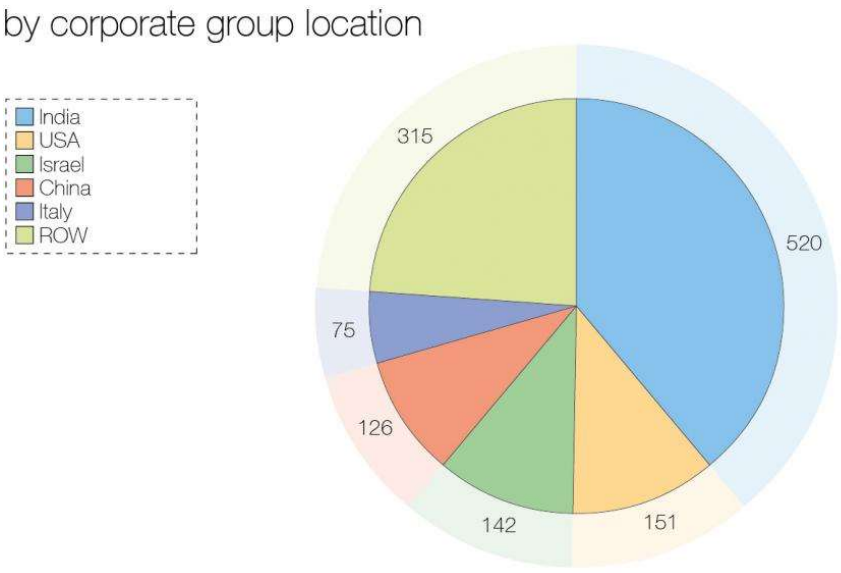

Fig 2: GDUFA's impact on API Industry

ANDA Stability Requirements[4]

The following existing ICH guidelines address stability for new drug substances and products:

Q1A(R2) Stability Testing of New drug sudstances and products.
Q1B Photo stability Testing of New drug sudstances and products
Q1C Stabilty Testing for New dosage forms.
Q1D Bracketing and Matrixing Designs for stability Testing of New drug substances and products.
Q1E Evaluation of stability data.

The global market value for ophthalmic products was estimated around $15 billion in 2009 and is expected to increase to over $20 billion in 2014 (1, 2). An aging population worldwide coupled with higher occurrence of eye conditions and diseases such as diabetic retinopathy, dry eye, glaucoma, and age-related macular degeneration (AMD), have resulted in increased growth in the eye care market (2). The emergence of novel formulations like Restastis®, a cyclosporine oil-in-water emulsion formulation, sophisticated dispensing systems such as the Ophthalmic Squeeze Device, and ophthalmic injections such as Lucentis® will inevitably lead to higher expectations and scrutiny from the US Food and Drug Administration (FDA) to gain product approvals. Currently there are no Guidance Documents from the FDA for in-vitro testing of ophthalmic products. From a Chemistry, Manufacturing and Controls (CMC) standpoint, generics drug developers do not have formal FDA guidelines to successfully develop ophthalmic equivalents to support their Abbreviated New Drug Applications (ANDA). Yet, there seems to be an expectation from the FDA to request more information regarding the CMC attributes of ophthalmic drug products. In the absence of CMC guidelines, it is difficult for the NDA and ANDA applicants to navigate the regulatory process in ophthalmic product development. In addition, there is also a growing expectation for Extractables and Leachables (E&L) testing on ophthalmic products. PQRI plans to release guidelines for PODP (parenteral and ophthalmic drug products) this year, which is expected to increase the testing burden for all stakeholders.

To address the changing regulatory landscape in the ophthalmic area in an effective way, Next Breath proactively developed a comprehensive list of in-vitro analytical testing requirements. This analytical package was developed based on Next Breath regulatory expertise, close collaborations with leading ophthalmic device developers, and ongoing FDA interactions (workshops/conferences).

In this White Paper, Next Breath highlights key considerations and presents strategies to reduce risk and ultimately accelerate the process for gaining approval of an ophthalmic product. It presents a stepwise approach that Next Breath believes is critical in managing the complexities and the unknowns around the development of ophthalmic drug products. It also describes the efforts to support early stage development through registration stability and batch release. The process described below will assist both the NDA and ANDA applicants in developing robust regulatory packages to gain approval for ophthalmic products[5, 6].

GENERAL POLICY[7]

FDA considers the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA, in determining whether an ANDA is incomplete on its face. 13 During FDA's filing review of a submitted ANDA, FDA will determine if there are any major or minor deficiencies. Generally, a major deficiency is one that in FDA's judgment is significant in nature such as certain deficiencies found in 21 CFR 314.101(d) or 21 CFR 314.101(e);14 other major deficiencies are discussed in this and other guidances. Numerous minor deficiencies (discussed below) also constitute a major deficiency.

A major deficiency will result in a determination by FDA that the ANDA is incomplete on its face under 21 CFR 314.101(d)(3), and FDA will therefore RTR an ANDA containing a major deficiency A minor deficiency is one that in FDA's judgment is minor in nature and can be easily remedied.15 As a result, FDA will allow the applicant a prescribed time period (described below in this section) to provide a response to such deficiencies. In particular, if FDA determines that an ANDA contains fewer than ten minor deficiencies (i.e., nine deficiencies or fewer), FDA will notify the applicant of the deficiencies, by phone, fax, or through the primary method for communication, which is email. FDA, in its discretion, provides applicants with the opportunity to correct minor deficiencies or amend the ANDA, within seven (7) calendar days.16 If within 7 calendar days the requested information is not received, FDA will RTR the ANDA. However, if FDA determines that an ANDA contains ten or more minor deficiencies or one or more major deficiencies, FDA will not consider the ANDA to be a substantially complete application under 21 CFR 314.101(b)(1). In such cases, FDA will notify the applicant that FDA considers the ANDA not to have been "received." If the applicant decides to submit additional materials to correct the deficiencies, the resulting amended ANDA will be considered a new ANDA submission, received as of the date the amended ANDA is submitted (if deemed substantially complete), and the applicant will be required to pay a new ANDA fee. If an ANDA is not received and the applicant takes no action, FDA may consider the ANDA withdrawn after 1 year.17 An ANDA applicant's failure to take action after a refuse-to-receive decision on an ANDA may be considered a request by the applicant to withdraw the ANDA, unless the applicant requests an extension of time in which to resubmit the ANDA.18 There may be circumstances, however, under which an exception to, or a waiver of, a regulatory requirement may be granted. FDA will consider the merits of such circumstances on a case-by-case basis.19

The following sections discuss deficiencies that FDA considers to be major deficiencies. A selection of minor deficiencies is provided in Appendix A.

A. Form FDA 356h (356h)

An ANDA must contain a completed application form (i.e., Form FDA 356h). If this form is not included, or is not signed, which indicates that the applicant is not attesting to the material contained in the application, FDA will RTR the ANDA.20

B. Submission, Format, and Organization

The ANDA should be formatted according to the eCTD format, and it should be submitted electronically for GDUFA metric goals to apply to the ANDA.21 Under Section 745A(a) of the FD&C Act, electronic submissions of applications to FDA will be required at least 24 months after the issuance of the final guidance for industry, Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (the eCTD guidance), which published on May 5, 2015. Accordingly, the electronic submission of ANDAs in a format specified by FDA is required as of May 5, 2017. 22

C. Non-Payment of GDUFA Obligation

FDA will RTR an ANDA in certain cases if there are outstanding user fee obligations23:

- If an applicant fails to pay the GDUFA ANDA or PAS fee within 20 calendar days of submitting the application 24.
- If an ANDA references a Type II active pharmaceutical ingredient (API) Drug Master File (DMF) that is not on the public available for reference list because of non-payment of the GDUFA DMF fee 25
- If an ANDA references a facility that is on the facility arrears list for failure to pay the GDUFA facility fee(s)26
- If the applicant is the owner of or is affiliated with the owner of a facility on the facility arrears list27
- If the applicant is listed on the backlog arrears list28
- If the applicant is affiliated with an applicant on the backlog arrears list. 29

In all of these cases, FDA will RTR an ANDA for nonpayment of GDUFA user fee obligations. Upon satisfaction of all applicable user fee obligations, CDER's Office of Management will issue a formal correspondence to the applicant indicating the adjusted receipt date (i.e., the date on which all outstanding user fee obligations were satisfied in full) for which the ANDA is eligible.

D. Lack of a Designated U.S. Agent for a Foreign Applicant

FDA will RTR an ANDA if a foreign applicant does not designate a U.S. agent. If the person signing the application form (i.e., Form FDA 356h) does not reside or have a place of business within the United States, the application form is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.30

E. Citing a Pending Suitability Petition as a Basis of Submission

If an applicant submits a copy of, or refers to, a pending suitability petition, FDA will RTR the ANDA because it lacks a legal basis for the submission.31 An ANDA can rely on a suitability petition as a basis of submission only after the petition has been approved by FDA. ANDAs can be submitted for drug products that differ from the listed drug, provided that a suitability petition requesting a change is submitted pursuant to section 505(j)(2)(C) of the FD&C Act and in accordance with 21 CFR 314.93 and 10.30, and the suitability petition is approved by FDA. The changes (from the RLD) that can be requested in a suitability petition are: • Change in route of administration • Change in dosage form • Change in strength • One active ingredient is substituted for one of the active ingredients in a listed combination drug An applicant who wishes to rely on an approved suitability petition as the basis of submission for an ANDA can do so by identifying the listed drug cited in the approved petition as the basis for the ANDA, subject to the limitation described in 21 CFR 314.93(f)(2). 32 In addition, the docket number and a copy of FDA's correspondence approving the petition must be included in the ANDA submission.

CONCLUSION

Parenteral preparations are sterile and pyrogen-free preparations that are designed to be administered directly into the systemic circulation of humans or animals. They should meet the pharmaceutical quality standards described in various pharmacopoeias and ANDA Stability guidance to enhance the quality of generic drugs by reducing stability failures, Clarifying stability expectations for OGD, Consistent stability expectations within FDA and by Standardizing stability expectations to benefit both industry and the FDA ensure clinical tolerance and be safe for their intended purpose of use.

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13. Decision trees for the selection of sterilization methods (CPMP/QWP/054/98)

14. See FY 2015 Performance Report to Congress for the Generic Drug User Fee Amendments, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/U CM493026.pdf. 13 21 CFR 314.101(d)(3).
15. Pursuant to 21 CFR 314.101(d), FDA "may" not consider an ANDA to be received if any of the deficiencies under that regulation applies. FDA will determine on a case-by-case basis whether a deficiency under certain provisions of § 314.101(d) is a major or minor deficiency, in accordance with the principles described in this guidance.