GPhA 2011

Regulatory Recommendations for ANDAs

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October 4, 2011

Agenda

- Statistics
- Improving Submissions
- Updates to the Filing Review Checklist
- Refuse to Receive Issues
- Comments from RSB Reviewers

FY 2009

- 859 ANDAs submitted in FY 2009
- 263 PIV submissions
  - 409 eCTD submissions
  - 242 CTD submissions
  - 030 paper CTD submissions
  - 178 Gateway submissions
- 78 ANDAs RTR'd in FY 2009

FY 2010

- 813 ANDAs submitted in FY 2010
- 262 PIV submissions
  - 119 CTD submissions
  - 271 eCTD submissions
  - 012 paper CTD submissions
  - 411 Gateway submissions
- 113 ANDAs RTR'd in FY 2010

FY 2011

- 853 ANDAs submitted (as of 9/26/2011)
- 211 PIV submissions
  - 060 CTD submissions
  - 177 eCTD submissions
  - 005 paper CTD submissions
  - 611 Gateway submissions
- 148 ANDAs RTR'd (as of 9/26/2011)

Relevance of numbers

- 100% of Original ANDAs being submitted are in CTD format (eCTD+paper CTD+Gateway)

- Approximately 95% (or more) of original submissions are now electronic

  - Gateway submissions have continued to surge tremendously
    58=(2008) 178=(2009) 411=(2010) 611=(2011)

  - RTRs as a percent of submissions for 2011 is about 17% (data is incomplete as all of FY 2011 submissions have not been reviewed) FY 2008=15%, FY 2009=9%, FY 2010=14%

RSB timelines

- Currently at about 45 days for filing review of ANDAs
- PIV submissions usually prioritized during the filing review stage (to allow time for notices to be sent out)
- MaPP 5240.3 allows certain ANDAs to move to the front of the review queue - First generics with no blocking patents and exclusivities, PEPFAR Applications and Drugs intended to meet a Public Health and/or Agency Need

Improving Submissions

- **Follow the Filing Review Checklist**

  - This checklist will be updated quarterly and is posted on FDA.gov/Office of Generic Drugs website

  - Review your application and make sure that it contains all the applicable information listed on the checklist before sending it in

  - **Responses to filing deficiencies must be received by OGD within 10 business days**

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA:
APPLICANT:
RELATED APPLICATION(S):

DRUG NAME:
DOSAGE FORM:

LETTER DATE:
RECEIVED DATE:

☐ P-IV
☐ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST (Approved/Denied)
☐ PEPFAR

Electronic or Paper Submission: SELECT Type II DMF#

BASIS OF SUBMISSION:
NDA/ANDA:
FIRM:
RLD:

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: ☐ **Activity**	Bio Team: ☐ **Activity**
CHEM Team Leader: ☐ **No Assignment Needed in DARRTS**	Bio PM: ☐ **FYI**
CHEM RPM: ☐ **FYI**	Clinical Endpoint Team: **(No)** ☐ **Activity**
DMF Review Team Leader: **Aloka Srinivasan** ☐ **FYI**	
Labeling Reviewer: ☐ **Activity**	Micro Review: **(No)** ☐ **Activity**

Regulatory Reviewer: Date:	Recommendation: ☐ **FILE** ☐ **REFUSE to RECEIVE**

Comments:
Therapeutic Code:
On Cards:
Archival copy:
Sections:

- **For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd.htm**
- **For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf**
- **For more CTD and eCTD informational links see the final page of the ANDA Checklist**
- **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/**

Current Checklist Updates

- Section 1.1.2 (Establishment Information)
  - Should be submitted as an attachment to the 356h form and should contain the addresses of the ACTUAL manufacturing and testing facilities along with the details of their functions and the names, phone and fax numbers and email(s) of the responsible official(s) for the same. This information should **also** be included in sections 3.2.S.2.1 and 3.2.P.3.1. and must MATCH the version in section 1.1.2
- Section 1.2.1 (FDA Form 3674)
  - Should be submitted in the same folder with the cover letter and the applicable submissions are clearly spelled out at the top of the form. If this form is being submitted as part of a new strength amendment which does not contain a BE study then certification option A applies. It is up to the applicant to read the form and determine if Option B or C applies to submissions containing BE studies

Checklist Updates cont.

- Section 1.12.4 (Proprietary Name Request)
  - Requires the submission of a separate electronic amendment filed at the same time as the original ANDA – Refer to guidance document for proprietary names issued in February 2010
- Section 1.14.1.3 (PI and SPL Submissions)
  - Electronic Labeling (i.e. MS Word and PDF versions) and SPL should be submitted with the original ANDA – Refer to guidance document for providing content of labeling issued in April 2005
- Section 3.2.S.3 (Characterization of DS)
  - The name of the impurities, their structure and origin should be provided in a tabular format

Checklist Updates cont.

- Sections 3.2.S.4.3 & 3.2.P.5.3 (USP/DMF)
  - Verification of USP/DMF Procedures for the drug substance and/or drug product must be submitted in these sections
- Section 3.2.S.7 (DS Stability Information)
  - A retest date or the expiration date for the drug substance should be submitted in this section

Checklist Updates cont.

- Section 3.2.P.1 (DP Composition)
  - Elemental iron: calculation of max daily amount or statement of adherence to 21CFR73.1200 must be provided

- Parenteral Drugs: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the packaged configuration

Checklist Updates cont.

- Section 3.2.P.7 (Container/Closure Testing)
  - Recommended additional testing for all plastic containers
  - Solid Oral Drug Products: water permeation and light transmission tests
  - Oral Solution and Suspensions: tests to detect leachables, extractables, light transmission and the impact on the drug product – Refer to FDA guidance on container closures (1999)

Checklist Updates cont.

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

Checklist Updates cont.

- Section 3.2.P.8.3 (Stability Data)
  - Accelerated stability data

    a. four (4) time points 0,1,2,3

    -OR-

    b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data) - Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B)

Checklist Updates cont.

- Section 3.2.R.1.P.1 (Executed Batch Records)

➢ Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections:

a. Bulk Package Label (Section 1.14.1)

b. Bulk Package Stability (accelerated stability data) [0,1,2,3]

–OR-

Room temperature stability data [0,3,6]) (Section 3.2.P.8)

c. Bulk Package Container and Closure information (3.2.P.7)

Refuse to Receive Reasons

(63) Submission Format Inadequacies

(40) Bioequivalence Deficiencies

(27) Inactive Ingredient Issues

(23) Inadequate Stability Data

(19) Clinical Deficiencies

(15) Packaging Configuration Issues

RTR Reasons continued

(15) Multiple Minor Deficiencies

(07) Other CMC Deficiencies

(05) Not Q1/Q2 – Parenteral Products

(05) Not Q1/Q2 – Topical Products *

(03) Not Q1/Q2 – Nasal Products

(02) Wrong Basis of Submission

Comments from RSB

- Pictures of the Finished Product (for solid orals)
- Sample Statements – API and Finish Dosage Form - should be placed under Module 3.2.S.4.3 (API) and 3.2.P.5.3 (Finished Dosage Form)
- Supplier names and addresses for all excipients (preferred in tabular format on 1 or 2 pages)
- Reprocessing Statement should be placed under Module 3.2.P.3.3

Comments from RSB cont.

- DMF authorization letters
- Package insert in Word and PDF
- Spectra (IR and/or UV per USP) and chromatograms for all API batches and RS
- Components and Composition statement should list the quantities of all excipients using the same unit of measurement
- Detailed batch reconciliation