Regulatory Education for Industry (REdI):
GENERIC DRUGS FORUM

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Proper Regulatory Submission During the Lifecycle of Generic Drug Products: Drug Product Perspective

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Disclaimer

This speech reflects the views of the author and should not be construed to represent the U.S. Food and Drug Administration's views or policies.

Agenda

- Regulatory submissions during the lifecycle of generic drug products
- Part I: Controlled correspondence
- Part II: ANDA
- Part III: Supplemental ANDA

Three Main Types of Reg Submissions

R&D:
Controlled Correspondence

Pre-Marketing:
Abbreviated New Drug Application

Post-Marketing:
Supplemental ANDA

High Quality Submissions are critical to both the Agency and the applicants!

Lifecycle of a drug product: R&D → Discontinuation

Part I: Controlled Correspondence

GDUFA Commitments:

FY2015	70% in 4 months
FY2016	70% in 2 months
FY2017	90% in 2 months

Note: One additional month added if clinical input needed.

- Challenging questions
- Short review timeline
- High volume of submissions
- Good submission quality is badly needed

Definition:

A correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information for a specific element of generic drug product development.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm411478.pdf
http://www.fda.gov/AboutFDA/CentersOffices/officeofmedicalproductsandtobacco/CDER/ucm120610.htm

Part I: Controlled Correspondence

Facts

- ~1,200 submissions to the Agency/year (10 year average)
- Multiple disciplines involved: filing, BE, labeling, clinical, policy, DMF, Chemistry, biopharm, microbiology, etc.
- ~10% Chemistry related
- Loosely categorized into 11 categories: combination products, container closure system, dissolution, formulation, inactive ingredients, overage, stability, specifications, 505(j) eligibility, post-approval changes, and pre-approval changes
- GenericDrugs@fda.hhs.gov

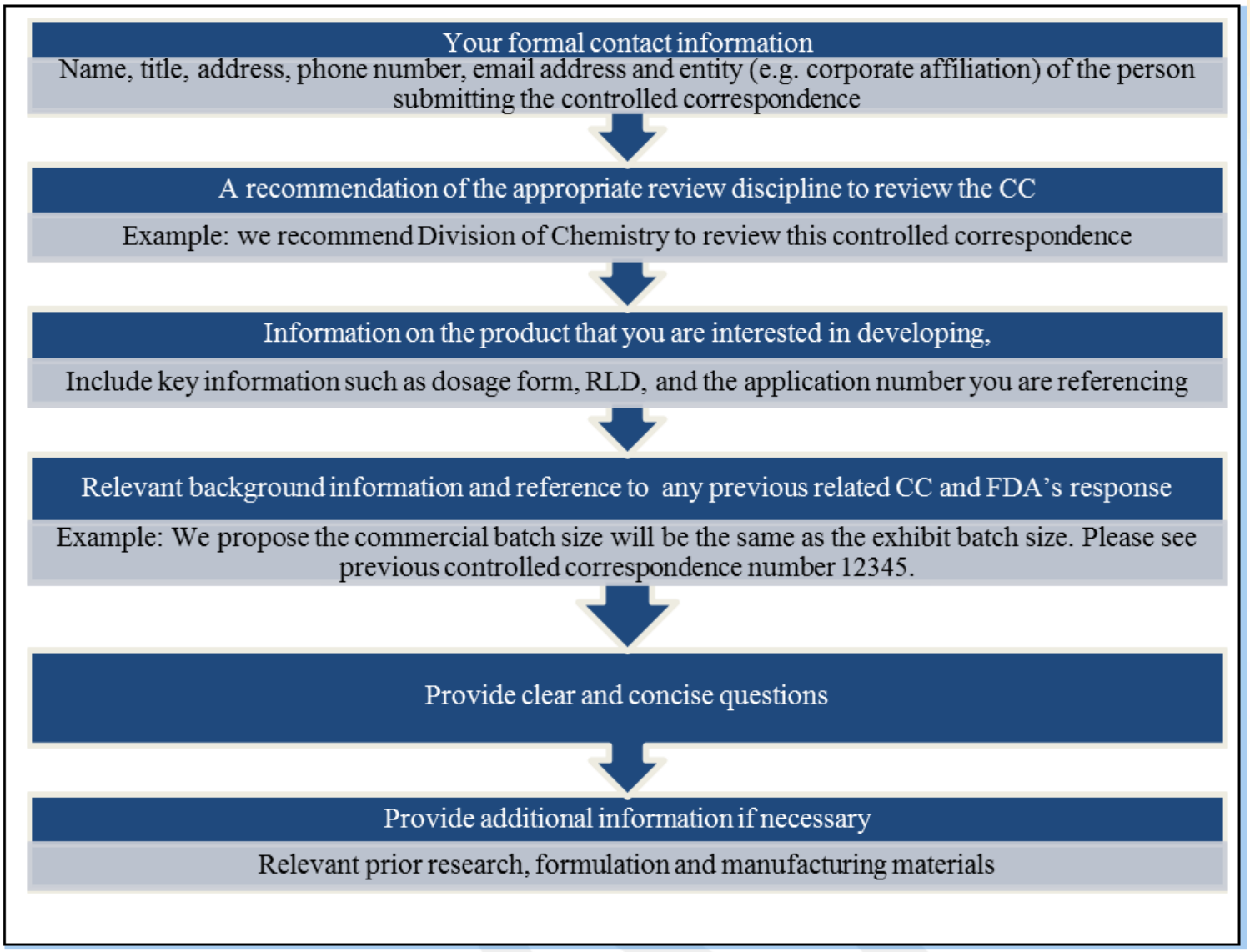
Part I: Controlled Correspondence

Commonly seen chemistry related inquires:

Category	Question	Answer
Stability	We fit the criteria; can we submit a reduced batch size?	Yes, please provide sufficient justification the batch size in your submission.
Formulation	What if there are 2 sources for the API?	Equivalency between the sources should be demonstrated in the application. For instance comparative stability and release data from one batch of the drug product manufactured using the API from alternate source(s) against the primary source are recommended.
Post-approval Changes	Should a (major) change be report as a PAS, CBE-30, CBE-0, or in the annual report?	Guidance was given on a case-by-case basis.
Overage	Is it acceptable to have an overage of the API?	In general, overage is discouraged and a review issue. In most cases, the firms were directed to include sufficient justification (if overage is used) in their ANDA submission for review. In rare cases, the Agency might concur based on the information available.
Formulation	Is it acceptable to submit a tablet or capsule size larger than that of the RLD?	This is not recommended; if it is deemed necessary, sufficient justification should be provided in the ANDA submission for review.

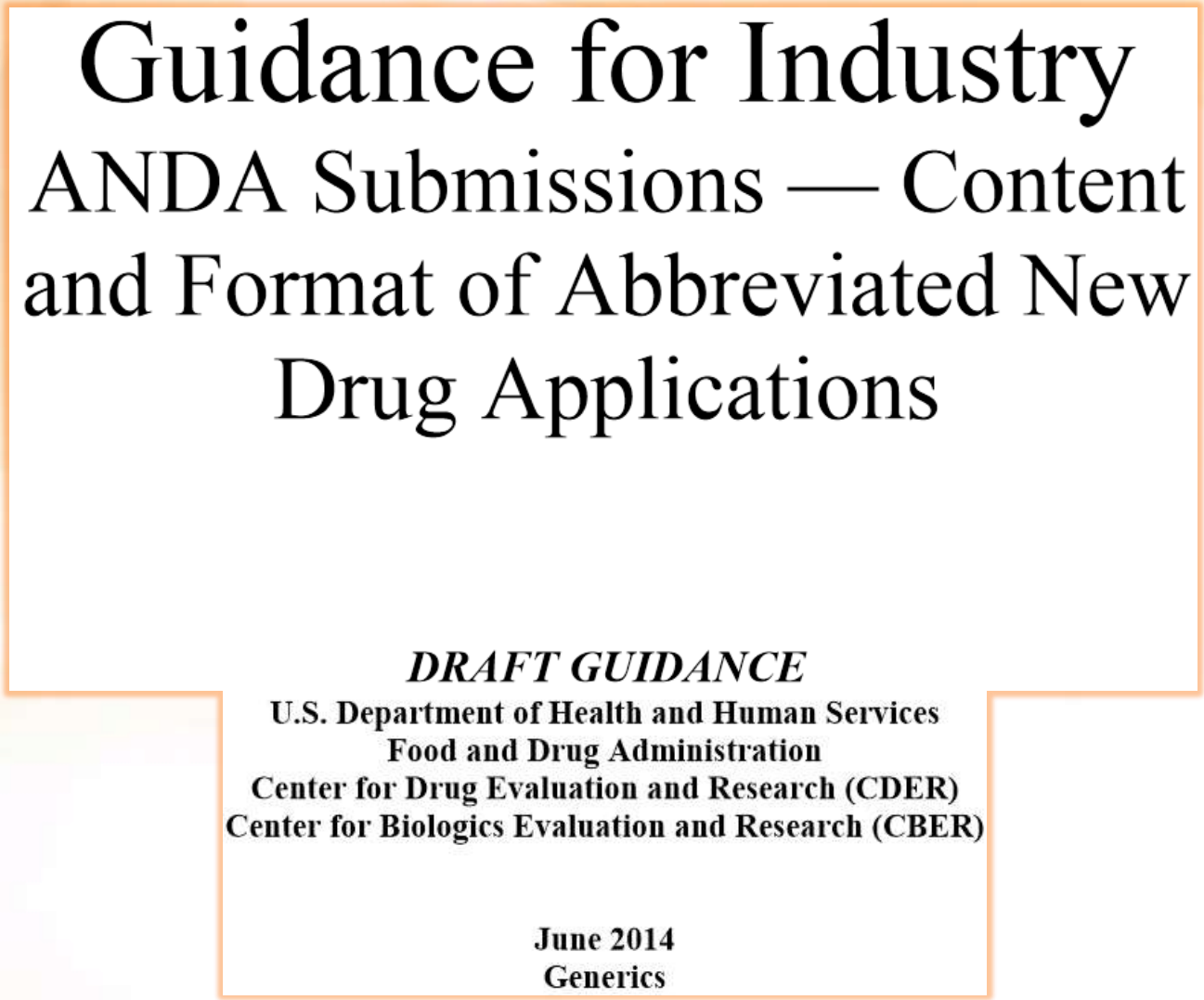
Part I: Controlled Correspondence

Submission recommendations:



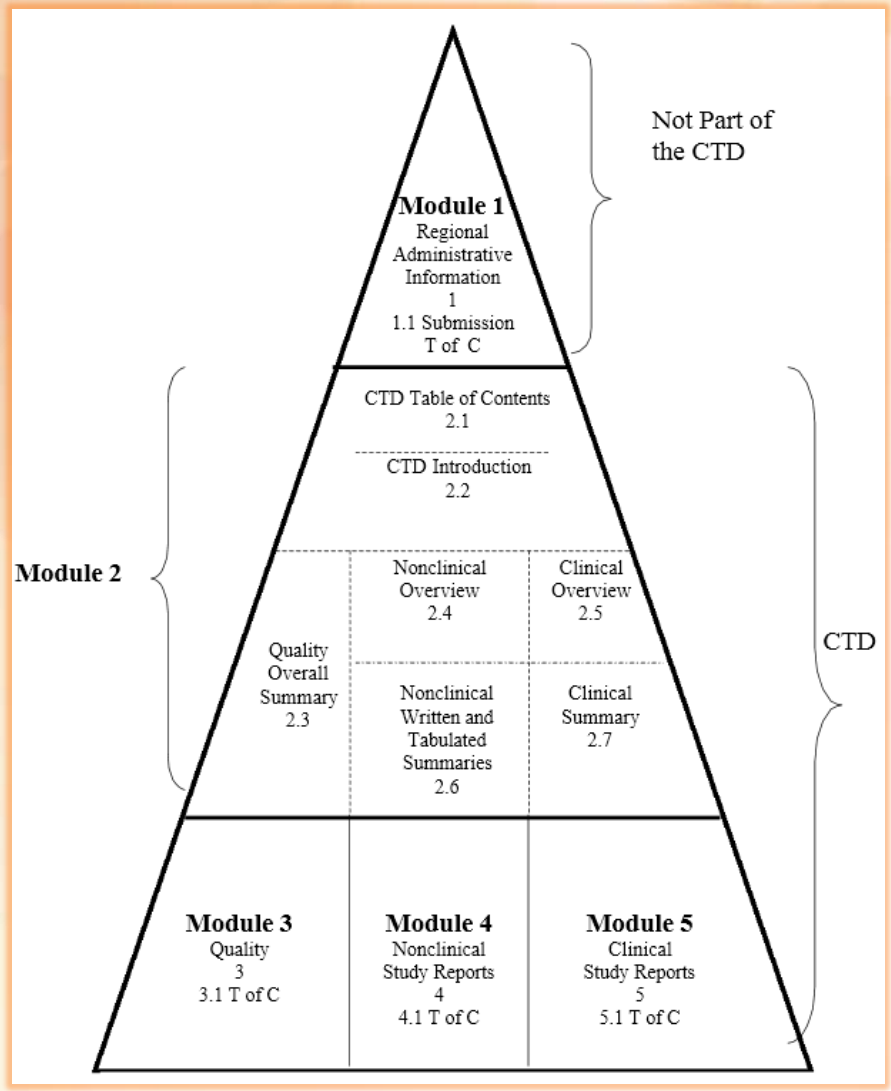
Part II: ANDA

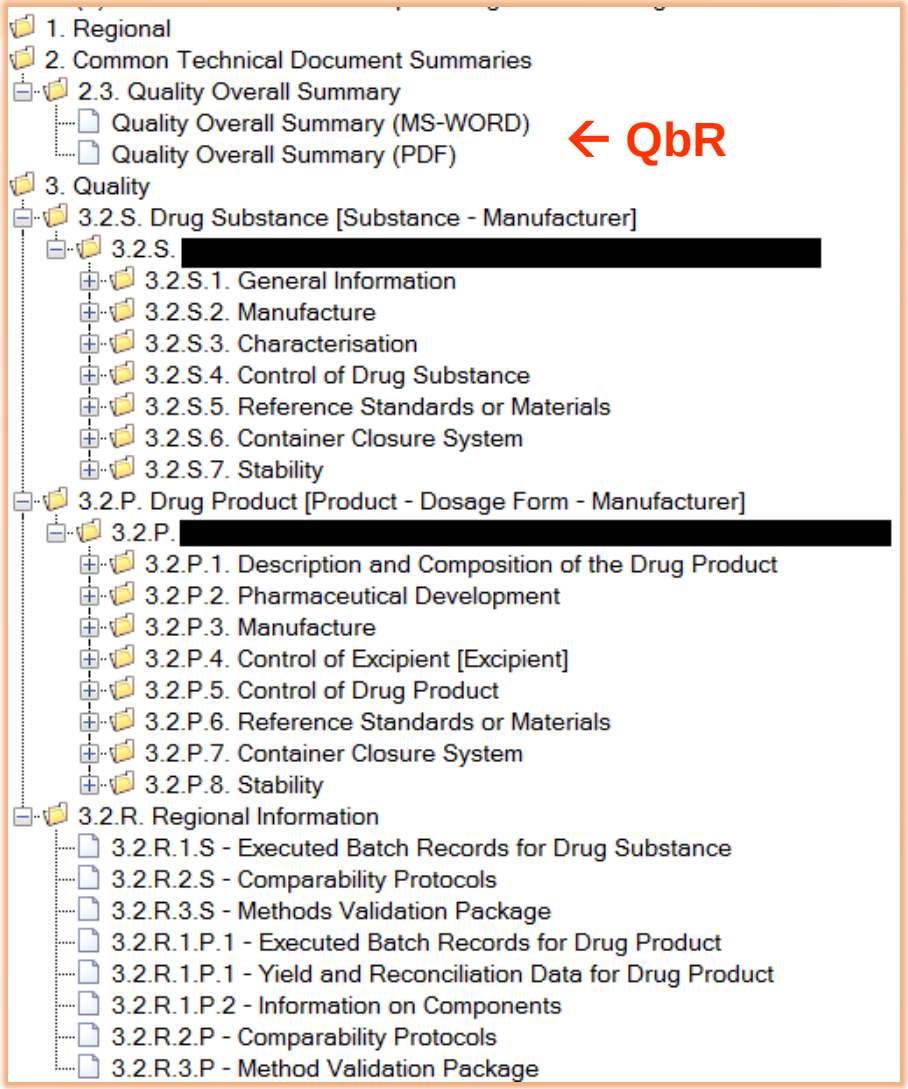
Agency's Current Thinking on ANDA Submissions



Part II: ANDA

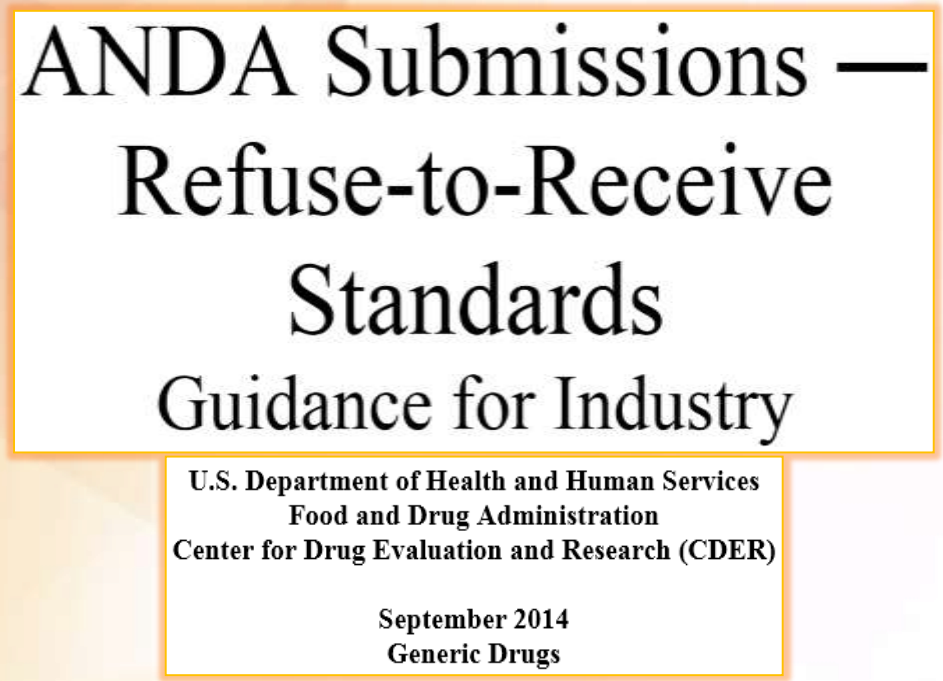
Common Technical Document (CTD)





Part II: ANDA

Filing: Received or RTR?


ANDA Submissions —
Refuse-to-Receive
Standards
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2014
Generic Drugs

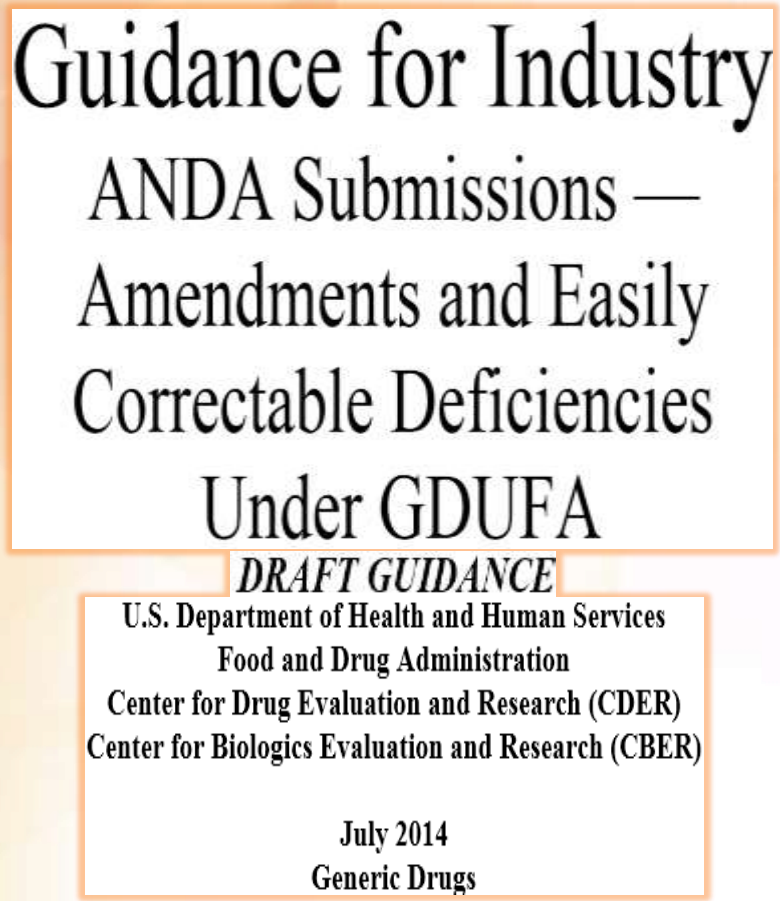
Quality (CMC) related RTR standards

- Excipients related
- Inadequate stability
- Insufficient packaging amount
- Missing batch records
- Missing validation/verification reports
- Special consideration for transdermals
- Inconsistent scoring, fill volumes, packaging/labeling vs. RLD
- etc.

An ANDA should be sufficiently complete to permit a substantive (scientific) review!

Part II: ANDA

Commonly Seen Deficiencies – Scientific Review


Guidance for Industry

ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2014
Generic Drugs

Chemistry MAJOR deficiencies:

- Unqualified impurity levels if tox studies required
- New source of API is needed
- New site of the FDF manufacture
- Unacceptable physical properties
- Need for full-term stability due to failing accelerated and intermediate data
- New packaging system
- New analytical methods
- CQA not identified or controlled
- Unacceptable overage
- Unrepresentative biobatch

Part II: ANDA

Commonly Seen Deficiencies – Scientific Review

Chemistry MINOR deficiencies:

- Unidentified or unacceptable impurity level
- Inadequate method validation
- Uncontrolled/unmeasured QA
- Insufficient in-process control
- Additional clarification for unexpected trends
- Modifications to CCS to increase protection
- etc.

Chemistry IR:

- Missing data sets, supporting documentation
- Lack of MFG process description
- Clarification for method validation
- Insufficient justification
- Content inconsistency
- etc.

References:

1. Bob Iser, et al., FDA Perspectives: Common Deficiencies in ANDA: Part 1 (DS), Part 2 (Description, Composition, & Excipients), Part 3 (DP Control & Stability), Part4 (DP MFG & CCS), Pharm Tech 2010-2011
2. Bob Iser, Commonly Observed CMC Deficiencies in ANDAs, AAPS webinar 2013

Part II: ANDA

Submission Expectations

- Electronic submission! (Paper submissions have no GDUFA goal dates!)
- Complete submission!
- In Module 2: hyperlinks to specific sessions in Module 3
- Hyperlinks within and among supporting documents in Module 3 are also appreciated!

Tip:

1. **Avoid all the commonly seen RTR standards and deficiencies – Complete and proper submission!**
2. **Use guidance/guidelines smartly!**

Part III: Supplemental ANDA

Overview

Figure 1: Number of supplements submitted between calendar years (CY) 2005-2012, based on the reporting categories identified by FDA. Blank: no designation given by FDA yet; Unknown: not reviewed by FDA yet; PAS: prior approval supplement; CBE 30: changes being effected in 30 days; CBE: changes being effected.

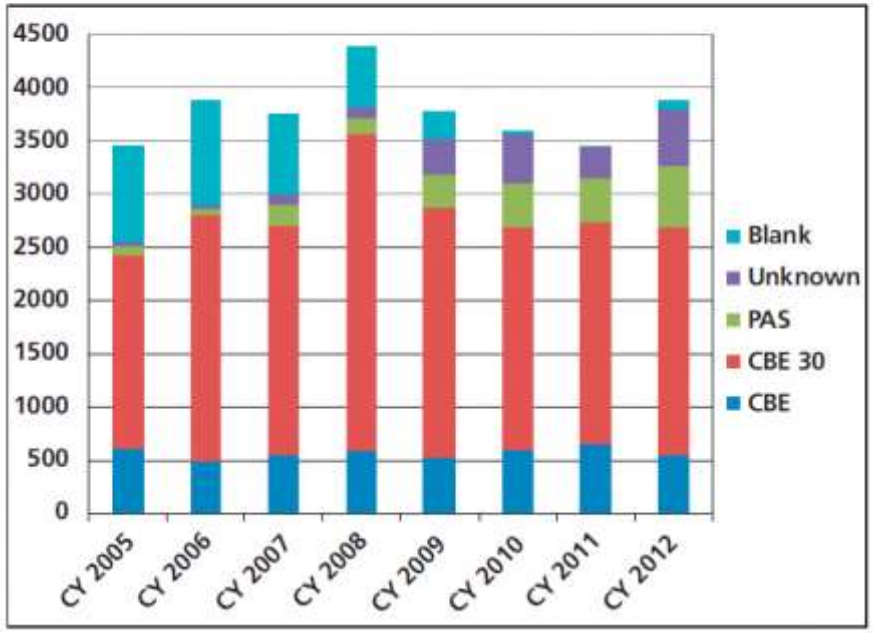
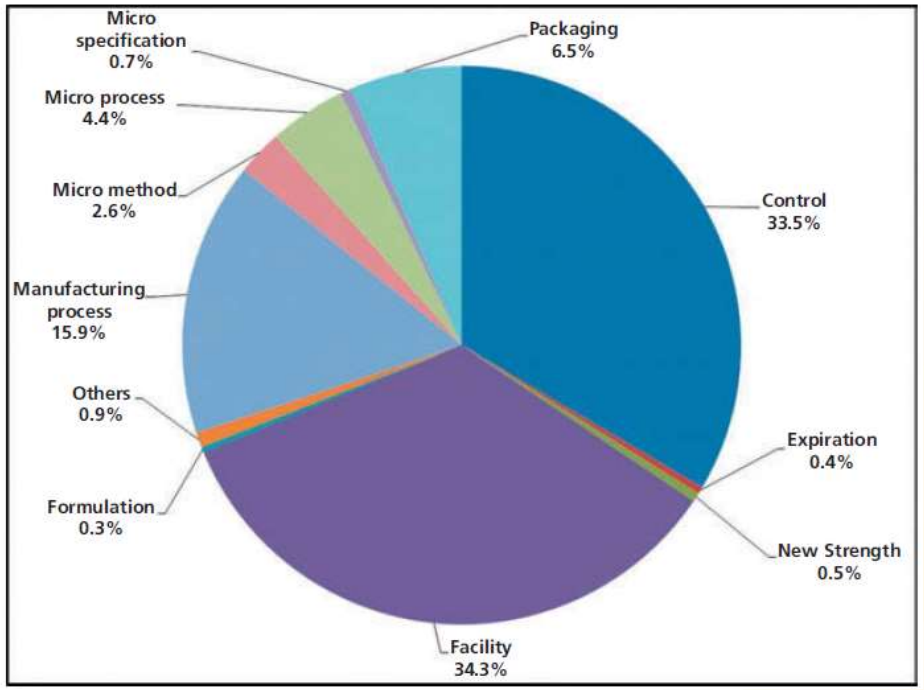


Figure 2: A representative distribution of postapproval chemistry, manufacturing and controls (CMC) changes to approved generic drug products, based on proposed changes reported in calendar year 2012.



Geoffrey Wu, et. al., A survey of postapproval CMC changes to generic drugs, Pharm Tech, March 2014

Part III: Supplements

Proper risk assessment of the proposed change(s) is critical to high submission quality and timely regulatory assessment!

Table I: Summary of the elevation of applicant claimed moderate risk changes to high risk reporting categories upon FDA's risk assessment.

Calendar Year	CBE elevated to PAS	CBE 30 elevated to PAS
2005	25	30
2006	8	62
2007	77	279
2008	19	132
2009	3	109
2010	12	118
2011	18	134
2012	24	126

Guidance: SUPAC (IR, MR, SS, ATLS), 2004 Change Guidance, 2014 ARable CMC changes
Geoffrey Wu, et. al., A survey of postapproval CMC changes to generic drugs, Pharm Tech, March 2014

Part III: Supplements

Recommended Filing Strategies

- **A summary pertinent to the proposed change(s) is helpful!**
- **Assess the risk of each proposed change → highest level decides the filing category (AR, CBE 0/30, PAS)**
- **Grouping: if the same change is made to several ANDAs AND using the same supporting data package**
- **Make reference to other ANDAs to which same/similar change(s) was made, if submitted separately**

Adapted from Andrew Langowski's slides @ 2014 GPhA CMC Workshop

Part III: Supplements

356h Form

- #6 Provide authorized U.S. agent contact info (if applicable)
- #13 List all strengths, not just the affected strength(s)
- #20 Provide the RLD number
- #29 Include current address and contact info of all establishments

Part III: Supplements

Cover Letter

- **Describe/List all proposed changes within the first 2 paragraphs**
- **State the regulatory basis for each change: risk level and filing category – proper risk assessment is critical!**
- **Identify potential disciplines to be affected by the change(s)**
- **List any other ANDAs that the same or similar change(s) was made to (even not grouped)**

Adapted from Andrew Langowski's slides @ 2014 GPhA CMC Workshop

Part III: Supplements

Cover Letter (cont'd)

- Rational for proposed change(s) (e.g., OOS, equipment change, unavailable CCS materials, compendial update)
- For change(s) in specifications, provide the current and the proposed specifications for comparison
- Relevant supporting data in the CTD quality module(s): Do not include changes that are not listed in the cover letter!

Adapted from Andrew Langowski's slides @ 2014 GPhA CMC Workshop

Part III: Supplements

DMF Related Changes

- **Provide letter of authorization (LOA) and DMF #**
- **Provide date of the DMF amendment, describing the change(s)**
- **Provide copy of COA generated by in-house testing (in case of new API source or MFG process changes)**

Adapted from Andrew Langowski's slides @ 2014 GPhA CMC Workshop

Part III: Supplements

Facility Related Changes

- Withdrawal request of a facility should be submitted to the submission in which it was approved (original or supplement)
- Scenario I: Facility approved in the original ANDA:
  - “Quality Correspondence/Facility Withdrawal Request/Original” – no ACK letter
  - When adding a facility via supplement, it is helpful to reference the withdrawal request
- Scenario II: Facility approved in a supplement
  - Single-site supplement: “Supplement Withdrawal Request, SUPPL-XXX”
  - Multiple-site supplement: “Quality Correspondence/Facility Withdrawal Request, SUPPL-XXX” to withdraw part of the facilities
  - Combo supplement: “Quality Correspondence/Facility Withdrawal Request, SUPPL-XXX” to withdraw site(s) but retain other changes
- Withdrawal and addition of a replacement site cannot be conducted in the same submission.

Geoffrey Wu, et al. Proper submission of chemistry related post-approval changes to ANDAs. Manuscript in preparation.

Part III: Supplements

Other Considerations/Recommendations

- Relevant supporting data in the CTD quality module(s): Do not include changes that are not listed in the cover letter!
- Owner transfer is typically a PAS; exception can be granted especially when the new owner has experience with the particular product.
- Expedite review request may be included (for instance) due to drug shortage or loss of an API source leading to cessation of supply – sufficient background info needed.

Adapted from Andrew Langowski's slides @ 2014 GPhA CMC Workshop

Summary

- **Multiple types of regulatory submission during the lifecycle of a generic drug product**
- **Secret to success: high submission quality!**
- **Concise, specific and necessary info**
- **Charts and tables preferred**
- **Justified, justified, justified…**
- **Risk- and science-based thinking and writing**

Acknowledgements

- Susan Rosencrance
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- Bob Iser
- Andrew Langowski
- Chemistry Control Team
- Others

Questions?

Evaluation: surveymonkey.com/s/GDF-D1S8