Draft Guidance for Industry: Controlled Correspondence Related to Generic Drug Development

Overview of Presentation

- GDUFA goals and definitions
- Inquiries that are considered/are not considered controlled correspondence
- Process for submitting and responding to controlled correspondence
- Process for submitting and responding to requests to clarify ambiguities

GDUFA II

- GDUFA II was signed into law on August 18, 2017 in order to facilitate timely access to high quality, affordable generic medicines
- FDA agreed to certain review goals and procedures for the review of controlled correspondence received both before, and on or after October 1, 2017
- In this presentation, the terms “control” and “controlled correspondence” are used interchangeably

GDUFA I v. GDUFA II Goals

Metric	GDUFA I	GDUFA II
Controlled correspondence	• FY 2015: respond to 70% in 4 months • FY 2016: respond to 70% in 2 months • FY 2017: respond to 90% in 2 months • If clinical division input required, add one month to goal	Standard control: review and respond to 90% within 60 calendar days Complex control: review and respond to 90% within 120 calendar days
If the controlled correspondence raises an issue related to a petition	If the control raises an issue that is related to the subject of one or more pending CPs, or petitions for stay or reconsideration, the goals will apply from the date FDA responds to the pending petitions	If the control raises an issue that relates to one or more pending CPs, the 60- or 120-calendar day time period starts on the date FDA responds to the petition or last pending petition
Request to clarify ambiguities	N/A	Review and respond to 90% within 14 calendar days

Controls Submitted During GDUFA I

- Commitment Letter: FDA will "[c]ontinue to review and act on…controlled correspondence submitted prior to October 1, 2017 that have been assigned GDUFA I goal dates pursuant to the GDUFA I review metrics applicable to those submissions."
- For any controlled correspondence submitted during GDUFA I for which FDA issued a response after October 1, 2017, and for which a submitter requests clarification of ambiguities in the controlled correspondence response, FDA will grant such a request for clarification, when possible, within the performance goal identified in the GDUFA II Commitment Letter.

Commitment Letter: Standard Controlled Correspondence

- As described in the September 2015 Guidance for Industry, *Controlled Correspondence Related to Generic Drug Development* (i.e., a correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development)
- Concerning post-approval submission requirements that are not covered by CDER post-approval changes guidance and are not specific to an ANDA

Commitment Letter: Complex Controlled Correspondence

- Controlled correspondence involving evaluation of clinical content
- Bioequivalence (BE) protocols for drugs that reference listed drugs with risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU)
- Requested evaluations of alternative BE approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical)

Guidance on Inquiries Inside of the Scope of a Control

- Commitment Letter: if a controlled correspondence raises an issue that relates to one or more pending citizen petitions (CPs), the 60- or 120- calendar day time period starts on the date FDA responds to the CP (if only one CP) or the last pending CP
- If a controlled correspondence raises an issue on a matter that is still under consideration by the Agency, the request will remain open until FDA issues a response

Guidance on Inquiries Outside of the Scope of a Control

- Requests more appropriately addressed through other mechanisms (e.g., pre-ANDA meetings, FDA's Regulatory Science Initiative)
  - The Agency will notify the requestor of the recommended alternative pathway and close the control

Guidance on Inquiries Outside of the Scope of a Control

- Exceptions to the definition of a control
  - BE guidance requests
  - Requests for review of BE clinical protocols if the reference listed drug is not subject to REMS ETASU
  - Pre-ANDA meeting requests
- In lieu of submitting a control, parties may submit these requests to GenericDrugs@fda.hhs.gov

Guidance on Inquiries Outside of the Scope of a Control

- Topics outside the scope of a control
  - Questions related to a specific pending or approved ANDA
    - Inquiry should be submitted to the ANDA
  - Inquiries not directly related to generic drug development
  - General or insufficiently detailed questions related to product development

Who Can Submit a Control?

- Generic drug manufacturers and related industry or their authorized representatives that have a question related to a potential ANDA submission to FDA's Office of Generic Drugs
  - Other parties (e.g., private citizens, financial firms, or public advocacy groups that are not directly involved in developing generic drugs) should submit inquiries to CDER's Division of Drug Information

How to Submit a Control

- Via email to GenericDrugs@fda.hhs.gov
- Submit the control on corporate letterhead, as an attachment to the email
- Send email from a corporate email address
  - To apply for a secure email pathway, contact: secureemail@fda.hhs.gov
  - Do not submit controls to individual FDA employees
  - Do not submit additional copies of a control in paper form, by courier, or fax
- If the control does not contain the information specified in section IV.B. of the guidance, the control will not be considered to be submitted for purposes of GDUFA II

Content of a Control

- Contact information and letter of authorization that is dated within one year of the control
- FDA-assigned control number and submission date and copy of related control(s) and FDA's response(s)
- RLD(s) and accompanying information
- **A statement that the control is related to a potential ANDA submission to FDA's Office of Generic Drugs**
- A concise statement of the inquiry
- A recommendation of the FDA review discipline to review the control
- Relevant prior research and supporting materials

Additional Recommendations on Specific Types of Controls

- Requests concerning the acceptability of inactive ingredients
- Requests for Q1/Q2 formulation assessment
- Requests requiring review by more than one discipline (e.g., BE and Labeling should be submitted separately)

Additional Recommendations on Specific Types of Controls

- Requests related to product quality
  - Include prior research and supporting product quality information in the control. Typically, would include, as applicable:
    - A brief description of the proposed formulation
    - Manufacturing process
    - Container-closure system
    - Developmental studies

Additional Recommendations on Specific Types of Controls

- Requests concerning post-approval submission requirements
  - Defined as a standard controlled correspondence
  - The inquiry must: 1) not be covered by existing CDER post-approval changes guidance, and 2) not be related to a specific ANDA
  - Examples of post-approval submission requirement controls:
    - Specific questions related to a product site transfer that would impact more than one approved ANDA
    - Specific questions relating to modernizing a manufacturing facility that is approved for more than one ANDA

Additional Recommendations on Specific Types of Controls

- Complex controlled correspondence
  - Controls involving evaluation of clinical content
    - Includes, but is not limited to:
      - Requests that require input from the Division of Clinical Review
      - Clear, concrete questions related to the planning of a BE study with clinical endpoints
      - Questions related to adverse events that occur during the conduct of a BE study
    - FDA will consider, on a case-by-case basis, whether controls that require input from other offices in CDER and Centers includes the evaluation of clinical content

Additional Recommendations on Specific Types of Controls

- Complex controlled correspondence
  - BE protocols for drugs that reference listed drugs with REMS ETASU
    - Will be addressed consistent with the process described in the Agency's guidance for industry, *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD*
  - Requested evaluations of alternative BE approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical)
    - Will be considered complex controls when a product-specific BE guidance is available to industry

FDA's Response to Requestors

- Upon receipt, FDA will send an email that:
  1. Confirms inquiry is a control and provides FDA-assigned control number, or
  2. States that inquiry is not a control, or lacks sufficient information to make this determination
- Generally will confirm acceptance of control within 7 calendar days
- After reviewing the control, FDA's response will be sent via email to the email address from which the control originated
- FDA will not respond to status requests prior to the goal date

Clarification of FDA's Response

- Follow-up questions and requests for additional information are considered a new control
- FDA will respond to requests to clarify ambiguities in the Agency's controlled correspondence response
  - Commitment Letter: ambiguity in the controlled correspondence response "means the controlled correspondence response or a critical portion of it, in FDA's judgment, merits further clarification"

How to Submit a Request for Clarification

- Via email to GenericDrugs@fda.hhs.gov
- All clarification requests for a control should be included in a single submission to FDA:
  - Submit within seven calendar days from issuance of FDA's controlled correspondence response
  - Requests received after seven calendar days will be considered a new control
- If FDA determines that the clarification request does not contain the information specified in section V.B. of the guidance, the request will not be considered to be received for purposes of GDUFA II

What to Include in Request for Clarification

- Subject line of the email: Request to Clarify Ambiguities in a Controlled Correspondence Response
- Contact information and letter of authorization that is dated within one year of the clarification request
  - Where possible, the clarification request should be submitted by the person who submitted the control on which clarification is being sought
- FDA-assigned control number, submission date and copy of the control on which the requestor is seeking clarification, and FDA's response
- Clarifying questions and the corresponding section(s) of FDA's controlled correspondence response
  - The scope of the clarifying questions should be limited to the content of FDA's controlled correspondence response

FDA's Response to Requestors

- Commitment Letter: FDA will review and respond to 90 percent of requests to clarify ambiguities in the controlled correspondence response within 14 calendar days of the Agency's receipt of the request
- After reviewing the request for clarification, FDA, in its discretion, will either call the requestor or respond in written form via email to the email address from which the clarification request was sent
- FDA's response will either clarify the ambiguity or state that, in FDA's judgment, the controlled correspondence response does not merit further clarification

Resources

- *Federal Register,* Notice of Availability
- Draft Guidance for Industry, *Controlled Correspondence Related to Generic Drug Development*

Please contact CDERSBIA@fda.hhs.gov with any questions. Thank you.