CHAPTER 46- NEW DRUG EVALUATION

SUBJECT: PRE-APPROVAL INSPECTIONS	IMPLEMENTATION DATE 5/12/2010 COMPLETION DATE 5/11/2012

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	46832 NDA Pre-Approval Inspections/Methods Validation 46832B NDA Forensic Sample Collection/Analysis 46832C NDA Biotest Sample Collection/Analysis 46832M Pre-License Inspections (BLA) 46832D PEPFAR – NDA Pre-Approval President's Emergency Plan for AIDS Relief 52832 ANDA Pre-Approval Inspections/Methods Validation 52832B ANDA Forensic Sample Collection/Analysis 52832C ANDA Biotest Sample Collection/Analysis 52832E PEPFAR – ANDA Pre-Approval President's Emergency Plan for AIDS Relief

FIELD REPORTING REQUIREMENTS

INSPECTIONAL

1. Appointment of Pre-Approval Manager

Each district office (district) will maintain a Pre-Approval Program Manager (PAM) and an alternate and report these names to ORA Division of Field Investigations (DFI, HFC-130) (see **Part 6 – CONTACT INFORMATION**). DFI maintains and disseminates the Master List of these names for agency use. PAM decisions are expected to have the concurrence of the district director.

2. Domestic Establishment Evaluation Requests (EERs)

Via the Establishment Evaluation System (EES), CDER/Division of Manufacturing and Product Quality (DMPQ) will issue an EER to the district PAM. The district should respond to the request with an evaluation of the firm within 10 business days of the request.

3. Reporting for Domestic Inspections (NDA/ANDA)

Approval Recommendation: If the inspection of the facility finds that the application is acceptable, reports the status in EES by the district goal date.[1] In the event that the district goal date has passed,[2] a recommendation should be entered no later than 5 calendar days after the inspection completion date. The establishment inspection report (EIR), FDA-483, and coversheet need to be forwarded to CDER/DMPQ/New and Generic Drug Manufacturing Team (NGDMT) within 30 business days, either electronically (CDERPAIPROGRAM), by fax, or by mail. In those cases where information is available through FACTS, TURBO EIR, MARCS, or any other electronic repository of official records, an email with a reference to the appropriate database(s) is acceptable.

Withhold Recommendation: If the inspection of the facility finds that the application is unacceptable, report the status of the application in EES as soon as the determination is made, and no later than the district goal date. In the event that the district goal date has passed,[3] the status of the application should be entered no later than 5 calendar days after the inspection completion date. The inspection results should be summarized in the EES "Comments" field.

For a withhold recommendation, the following information is to be forwarded electronically (CDERPAIPROGRAM), by fax, or by mail to DMPQ/NGDMT. In those cases where information is available through FACTS, TURBO EIR, MARCS, or any other electronic repository of official records, an email with a reference to the appropriate database(s) is acceptable.

- The FDA-483, as soon as it is issued[4] (CDERPAIPROGRAM)
- Finalized EIR with coversheet, attachments, and exhibits within 30 business days of the last day of the inspection
- If a concurrent CGMP inspection was performed for marketed product and enforcement action is recommended, send the completed case recommendation to DMPQ/Case Management Team (CMT) via MARCS-CMS
- Forward any response from the firm as soon as it is received. Include the application number and Firm Establishment Identification Number (FEI). Copies of responses should be sent by express mail, scanned, or facsimile (if less than 50 pages) to DMPQ/NGDMT. Alternatively, the district can request that the firm submit a copy of the response directly to NGDMT at the conclusion of the inspection. The district should promptly provide any comments on the firm's response to NGDMT. The district will also enter appropriate milestones into EES to document whether its follow-up activities have changed the withhold recommendation (i.e., FDA-483 response is found to be adequate, or satisfactory follow-up inspection)

[1] The district goal date is the date by which the district should complete the inspection process, including entering the site recommendation into EES.
[2] The district PAM should provide advance notification to NGDMT (New and Generic Drug Manufacturing Team) if the district will be sending a late recommendation, and provide current information on the inspection findings.
[3] See Footnote 1.
[4] PAMs provide domestic FDA-483s to CDER/DMPQ; investigators provide FDA-483s to CDER/DMPQ immediately upon completion of a foreign inspection.

For an inspection that might result in an OAI status, whether or not the inspection is associated with a pre-approval inspection, the PAM must enter a "Potential OAI Alert" into EES as soon as possible. **This includes any CGMP surveillance inspection**. Once the district decides on its case recommendation, the PAM must update the "Potential OAI Alert." Refer to the EES Instructions located in the Help section of EES.

NOTE: If a district recommends withholding approval and does not expect the EIR to be completed before the "user-fee" due date, the district is responsible for notifying and submitting written justification to the CDER/DMPQ contact for the EER as soon as possible. The justification should include the draft or final FDA-483 and a description of concerns related to the approvability of the application. "Withhold" recommendations based solely on a draft or final FDA-483 should be an atypical occurrence.

4. Reporting for International Inspections (NDA/ANDA)

The investigator will submit, via facsimile or email, the initial recommendation (including the FDA-483, if issued) and any other concerns related to the approvability of the application to DMPQ/International Compliance Branch (ICB) as soon as possible or within 24 hours after completing the inspection (fax: (301) 847-8742 or (301) 847-8738, email: CDERICB@fda.hhs.gov). ICB will send a copy of this recommendation and FDA-483, if issued, to ORA/Division of Field Investigations (DFI) within 5 business days.

At the close of the inspection, investigators will instruct firms to submit all communication to the International Compliance Branch (10903 New Hampshire Ave, White Oak 51, DMPQ/ICB, Silver Spring, MD 20993) and to copy the communication to the lead investigator. The lead investigator should promptly provide any comments on firm's response to DMPQ/ICB.

After completion of the EIR, the investigator will forward the following to ICB, either electronically (as email attachment or intranet weblink), by fax, or by mail:

- The final EIR, FACTS endorsement, attachments, and exhibits within 30 business days.
- Forward any communication from the firm, if it is received, as soon as possible.

ICB evaluates international pre-approval recommendations. After review, the ICB compliance officer will promptly update firm profile class codes in accordance with IOM Exhibit 5-14 for international PAIs. Note that profile class codes are only comprehensively updated after a CGMP surveillance inspection. For an inspection that *only* covers pre-approval issues, the profile class code covered during the pre-approval inspection should be updated. If an initial international inspection of a firm is classified OAI, no profile information should be entered. This assures the product cannot be marketed in the U.S. until a follow-up inspection verifies implementation of appropriate corrective actions or until corrections can be substantially verified through other appropriate means. When changing a profile status, the ICB compliance officer should explain in the "remarks" field of MARCS the basis for the change and include the date and description of applicable correspondence (e.g., mm/dd/yy Warning Letter Closeout Letter).

For an inspection that might result in an OAI status, whether or not the inspection is associated with a pre-approval inspection, ICB must enter a "Potential OAI Alert" into EES as soon as possible.

5. Reporting for Biologic Licensing Applications

For Biologic Licensing Applications (BLA), forward the firm's response, the final EIR with coversheet, attachments, and exhibits to DMPQ/MAPCB to coordinate assignment and evaluation, either electronically, by fax, or by mail. In those cases where information is available through FACTS, TURBO EIR, MARCS, or any other electronic repository of official records, an email with a reference to the appropriate database(s) is acceptable.

6. Reporting of Investigational New Drug Inspections

For Treatment Investigational New Drug (IND) inspections, districts and CDER/OC/DMPQ are to report the inspection findings within 10 calendar days of receipt of the EER into EES. See **Part 2 – Implementation** of this program for further instructions.

LABORATORY

Forward copies of all laboratory reports on the verification of NDA and ANDA analytical methods to the CDER review unit that requested the verification. Completed analytical worksheets will be maintained by the analyzing laboratory.

Drug samples connected with applications that are pending a decision may be collected for purposes other than methods validation. These samples may be analyzed by ORA laboratories or by CDER/DPA laboratories. All lab results that are classified lab class 2 or 3 samples[5] will be forwarded to the district compliance branch if the manufacturing facility is domestic, or to CDER/ICB, if the manufacturer is an international facility. Laboratories performing profile analysis should maintain remaining sample material and the worksheets for future retrieval.

[5] Refer to ORA Laboratory Manual, Volume 3 (Section 3).

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PART I - BACKGROUND

The Federal Food, Drug, and Cosmetic Act provides that FDA may approve a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), and a Biologic Licensing Application (BLA) if, among other requirements, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate, and ensure and preserve its identity, strength, quality, and purity.[6]

In 2002, the FDA announced a significant new initiative called Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. This initiative encourages implementation of risk-based and science-based approaches that focus agency attention on critical areas and promotes better and more consistent decisions among regulators. In accordance with the Pharmaceuticals CGMP for the 21st Century initiative, this compliance program includes scientific, risk-based approaches that incorporate inspection of the level of the firm's process and product understanding, an evaluation of the firm's manufacturing readiness, and verification of authenticity of submitted data.

In 1992, Congress enacted the Prescription Drug User Fee Act (PDUFA). PDUFA was renewed in 1997 as PDUFA II, in 2002 as PDUFA III, and in 2007, as PDUFA IV. PDUFA establishes "User Fee Goals" to ensure that NDAs and BLAs are reviewed in a timely manner based on performance goals. It is an agency goal based on Congressional mandate that "user-fee" due dates be met. All agency components involved in the pre-approval program – CDER Office of Pharmaceutical Science; CDER Office of Compliance; ORA district offices; and FDA analyzing laboratories – will coordinate efforts to communicate and resolve outstanding application issues to assure PDUFA performance goals are met.

Generic drug applications also represent an important agency goal in providing greater availability of medicines to the American public. As a result of the generic drug manufacturing history and the Generic Drug Enforcement Act (GDEA) of 1989, this inspectional program was significantly revised to include more emphasis on data integrity.[7] More than 30 individuals and nine companies admitted or were found guilty of various fraud and corruption offenses involving generic drugs. Also, refer to the agency's application integrity policy (AIP) for a discussion of other regulatory enhancements.[8] Unlike NDAs and BLAs, ANDAs are funded exclusively through congressional appropriations.

FDA is committed to providing applicants with actions on submissions within the established time periods. Each CDER and ORA component with a role in the drug approval process is responsible for initiating and completing specific tasks, many of which with time frames established in this compliance program, in order to meeting these review time performance goals.

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[6] Federal Food, Drug, and Cosmetic Act §§ 505(d) and 505(j)(4)(A) *(21 U.S.C. §§ 355(d)(3) and 355(j)(4)(A))*

[7] Refer to *FDA Consumer magazine March 1997* for additional history about generic drug manufacturing (http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm139627.htm).

[8] See http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm

PART II – IMPLEMENTATION

2.1 SCOPE

A pre-approval inspection (PAI) is performed to contribute to FDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete. This program directs the ORA district office or DMPQ in the evaluation of establishments by on-site inspections and/or the establishment file review when the firm is named in the Chemistry, Manufacturing, and Controls (CMC) section of a New Drug Application (NDA), Abbreviated New Drug Application (ANDA) or Biological Licensing Application (BLA). This includes original submissions, CMC amendments to pending original submissions, and CMC supplements to approved drug applications. Domestic and international pre-approval inspections[9] are conducted for generic and innovator drug applications, and may cover all facilities associated with a submission, including drug component manufacturing (such as Active Pharmaceutical Ingredients (APIs), which are also known as drug substances), finished drug product manufacturing, and control testing laboratories.

The CMC section of an application includes analytical test methods for the drug product, specifications of the drug product and drug components, and a general description of the product's manufacturing and control procedures. [10] Multiple agency operating units collaborate in the evaluation of the general description of the product's manufacturing and control procedures. The assessment of a CMC section always includes a review by CDER application reviewers of information submitted in the application and frequently includes an on-site assessment (i.e., inspection of manufacturing operations by the district office).[11] This program has been designed to maximize the strengths of these FDA functions in evaluating submitted information.

This compliance program establishes the criteria for deciding whether inspections are to be conducted for a given application. In some cases, FDA may have sufficient current and pertinent information to arrive at a scientific decision on site acceptability without conducting a PAI. This program's risk-based decision criteria for performing an on-site inspection for an application ensure that inspection resources are directed to the greatest possible protection of public health. This program also provides risk-based strategies for the scope of inspectional coverage and clarifies roles in order to establish more efficient communication.

[9] The PAI inspection program also includes analytical method evaluations by FDA laboratories. See Part 4 and Appendix B.
[10] The requirements for the content of new drug applications are described in chapter 21 of the Code of Federal Regulations (CFR). For additional guidance, refer to "CTD" (Common Technical Document) at http://www.ich.org.
[11] The objectives of this program may be partly met by an Office of Compliance (or by CDER assignment to ORA) review of recent inspection reports (e.g., EIRs or reports from a counterpart foreign government regulatory agency, within established procedures).

2.2 STRATEGY

2.2.1 Assignment of Inspections – Decision Criteria

There are two types of pre-approval inspections performed: Priority and Discretionary. Refer to **Part 2.3, PROGRAM MANAGEMENT INSTRUCTIONS**, for the determination of a Discretionary PAI. If one or more of the following apply, the establishment meets the Priority criteria and an inspection is to be performed:

Priority Pre-Approval Inspection Criteria:[12]

1. Establishment is named in an application to FDA for the first time, including establishments that have never been inspected or have been inspected only for non-application drugs;
2. First application filed by applicant (for coverage of finished dosage manufacturing and testing);
3. First ANDA filed for an approved drug (for coverage of finished dosage manufacturing and testing);
4. Finished product contains a New Molecular Entity (NME) (does not apply to supplements);
5. Finished product content assay has a narrow range (e.g., 95-105% labeled strength for narrow therapeutic index drugs) or drug is expected to require titrated dosing (does not apply to supplements);
6. Finished product or API is manufactured by a substantially different manufacturing process or dosage form than previously covered at the establishment;
7. API derivation is high risk (e.g., API is derived from animal tissues) or the intended use has significantly changed (e.g., API previously used in non-sterile product is now intended for a sterile drug product);
8. Numerous application submissions or certain site/process/product changes that are expected to pose significant challenge to the state of control of the facility or process; and
9. Profile class status of application product or API is "unacceptable" or not updated via a site inspection within the past 2 years (3 years for control laboratories and 4 years for packaging and labeling), for original applications or significant pre-approval CMC supplements.

2.2.2 Inspections by Objective

There are three primary inspectional objectives of this PAI program, all of which require an informed strategy and careful on-site evaluation. These objectives are:

Objective 1: Readiness for Commercial Manufacturing
Objective 2: Conformance to Application
Objective 3: Data Integrity Audit

Specific coverage of these elements, as well as the recommended inspection and audit techniques for manufacturing and testing operations, are described in **Part 3 – Inspectional**.

[12] Priority PAI Criteria is assessed by both the CMC application reviewer and by DMPQ. The inspection coverage for each of these Priority inspection criteria is described in **Part 3** of this program.

2.2.3 Roles/Responsibilities of CDER and Field on Reviewing and Assessing A/NDA CMC Submissions

The FDA organizational levels involved are:

- ORA district offices and laboratories
- CDER Office of Compliance (OC), Division of Manufacturing and Product Quality (DMPQ)
    - Manufacturing Assessment and Pre-Approval Compliance Branch (MAPCB)
        - New and Generic Drug Manufacturing Team (NGDMT)
        - Biotechnology Manufacturing Team (BMT)
    - International Compliance Branch (ICB)
- CDER Office of Pharmaceutical Science (includes multiple CDER review offices)
    - Office of New Drug Quality Assessment (ONDQA)
    - Office of Generic Drugs (OGD)
    - Office of Biotechnology Products (OBP)
    - New Drug Microbiology Staff (NDMS)
    - Office of Testing and Research (OTR)

Part 6 – Program Contacts provides contact information for each of the offices that have a role in implementing this program. Each application entry in EES should list the assigned PAM, CDER application reviewer, and CDER compliance officer.

Although multiple offices collaborate in the evaluation of establishments named in applications, lead offices are established in CDER and ORA to accomplish pre-approval program requirements.

- ORA responds to inspection requests, inspects sites in accordance with this program, reports findings, and provides a recommendation on site acceptability to the Office of Compliance.
- CDER OC DMPQ evaluates establishments, determines if a PAI must be conducted, reviews inspection reports and recommendations, provides a site acceptability decision to other CDER offices, and assures uniform application of program decisions, CGMP policy, and adherence to this program. For international establishments, the International Compliance Branch (ICB) serves as the compliance office.
- CDER ONDQA, OGD, OBP, NDMS, OC/BMT, and other product review offices perform review of submitted information (e.g., test methods, manufacturing and control strategy) and establish specifications and other regulatory commitments where needed to support application approval decisions.
- CDER OND determines and issues the final decision on an application or licensure for NDAs and BLAs. CDER OGD performs this function for ANDAs.

The process to approve or withhold an NDA, ANDA, or BLA is an important FDA responsibility and is an important CDER function. The final decision is based on the contributions of multiple FDA sources of information, including the product's safety, efficacy, and quality. The effective implementation of this program requires coordination between: 1) CDER application reviewers; 2) Office of Regulatory Affairs; 3) CDER OC; and 4) FDA laboratories. The roles and responsibilities of ORA, the CDER application reviewers, and CDER OC in performing reviews and inspections are further described in **Part 7 - Center and Field Responsibilities**.

Specific roles and responsibilities for district and CDER review staff are set forth in the chart attached as **Attachment A** of this program. These are organized by topic area for ease of reference.

For analyzing laboratories, CDER OTR/Division of Pharmaceutical Analysis and ORA laboratories may be tasked with analyzing the drug product or the analytical method validation before approval.

2.3 PROGRAM MANAGEMENT INSTRUCTIONS

2.3.1 New Drug Application Inspection Assignments

2.3.1.1 Product Review Responsibilities for Establishment Evaluation

Establishments named in an application are electronically processed and tracked in the Establishment Evaluation System (EES).[13] **Each establishment** is assigned an Establishment Evaluation Request (EER) within a single submission. The EERs are then forwarded to the necessary offices for review.

Upon the receipt and filing of an application from the applicant, the CDER application reviewing office will enter the establishment information into EES and generate EERs for all establishments named as participating in the manufacturing[14] of the product. This information will include the type of submission, type of manufacturing or testing conducted, including specific intermediate step(s) or type of laboratory analyses (e.g., microbiology, chemistry), and any other relevant information of the facility's function.

2.3.1.2 OC/DMPQ and ORA Responsibilities for Establishment Evaluation

2.3.1.2.1 Determination of Priority or Discretionary Pre-Approval Inspection

OC/DMPQ

DMPQ will receive the EER from CDER Office of Pharmaceutical Science (ONDQA and OGD) for prompt evaluation. DMPQ will determine if any of the Priority Pre-Approval Inspection Criteria are met, as provided within **Part 2 – IMPLEMENTATION: Strategy**. The EER will be categorized into one of two categories and then forwarded to the district for review:

- Priority PAI: DMPQ strongly recommends that a pre-approval inspection be performed because one or more Priority PAI Criteria was met. If only Criteria #9 applies, in that the profile is unacceptable or has not been recently updated, DMPQ enters "GMP Inspection" request in EES. If any of the other criteria apply, DMPQ enters "Product Specific" inspection request in EES and forwards it to the district.
- Discretionary PAI: DMPQ recommends that no pre-approval inspection be performed because the Priority PAI Criteria were not applicable to the site or product. DMPQ enters a "10 Day Letter" request for evaluation into EES and forwards it to the district.

[13] CDER Review Division enters all facilities named in a drug application into EES. DMPQ then determines which facilities fall under the Priority PAI Criteria.
[14] Refer to 21 CFR 210.3(b)(12). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm

For international establishments, the EER is reviewed by OC/DMPQ and assignments are directly submitted to ORA/DFI.

ORA/District Office for Domestic Establishments

Districts have **10 calendar days** to respond to a Priority Pre-Approval Inspection request by entering one of the three recommendations into EES:

1. **Approval**
2. **Withhold Approval**, or
3. **Assigned to IB**

The first two of these are often decided using current information and without a new inspection. The third leads to initiation of an inspection.

Rationale for not conducting a Priority Pre-Approval Inspection

If a district (domestic and ICB) has determined that a Priority PAI is not warranted, the reason for not initiating the inspection will be entered into EES along with the district's recommendation within 10 calendar days. Examples of rationales for not conducting a Priority Pre-Approval Inspection include the following:

- A facility has an acceptable profile for a similar product with a higher manufacturing complexity. The EES entry may read: "*Inspection of ABC Drug Co. for subject application is not warranted based on a recently completed CGMP inspection that found the establishment compliant for a related product type (application is for non-sterile liquid; establishment has acceptable history in sterile liquids) and which also met the other objectives outlined in the program for this priority situation. This decision was submitted to CDER DMPQ on [insert date]*."
- The district is currently monitoring the commitments of an establishment with an unacceptable profile status and has determined that a withhold recommendation is appropriate without need for a follow-up inspection. The facility and profile status will be reviewed again before a decision is needed for the current application.
- For international facilities, ICB or BMT may consider another recognized regulatory authority's inspection report when determining the need for a pre-approval inspection, consistent with established agency policy regarding the use of such information.

For a new drug application or BLA, a district decision to inspect must take into account the application's user-fee date.[15] Districts must assure completion of the PAI and the district recommendation well in advance of the user-fee date to facilitate DMPQ's full review and final decision

[15] CDER's Good Review Management Practices program has implemented enhanced collaborative team functioning for NDA and BLA review, in which the responsibility for timely information by each discipline is emphasized. Under GRMPs, each discipline reports on the latest status of their evaluations throughout the review cycle. For example, Medical Officers discuss the clinical review status, product reviewers (ONDQA or OBP) discuss the CMC review status, and CGMP representatives (OC) discuss the GMP/Facility review status. More timely inputs to the process (significantly before the PDUFA date) will allow the Center sufficient time to make a well-rounded and deliberative decision considering all information before deciding on application approvability.

on the facility evaluation prior to the user-fee date. This careful management of inspection scheduling also permits consideration of the firm's FDA 483 response.

Rationale for Conducting a Discretionary Pre-Approval Inspection

If the district recommends **Assigned to IB** or **Withhold** for a Discretionary Inspection EER, the district will provide written rationale via EES to DMPQ within **10 calendar days**. The district will determine the objectives to be covered during the inspection (refer to **Part 3 – Inspection/Audit Strategy**), and may also include these objectives in EES. Situations that may justify performance of a Discretionary Inspection (district or CDER-initiated), include the following:

- Multiple applications filed in short period of time involving a single establishment for manufacture of the finished product;
- Significant deficiencies were found during the last pre-approval inspection or the firm has a history of non-compliant pre-approval inspections; and
- Additional potentially adverse information regarding the compliance status of an establishment not yet known to CDER, such as an expected enforcement action recommendation during an ongoing inspection, multiple recalls, or new firm management.

The district will use EES to automatically generate an assignment.

2.3.1.2.2 Inspection and Post-Inspection

If the inspection may result in an OAI status, the PAM must enter a "Potential OAI Alert" into EES as soon as possible. The district should use EES to record inspectional information and final outcomes for both Priority and Discretionary inspections. Once the district determines a recommendation, the PAM must update the "Potential OAI Alert." Refer to EES instructions within the Help section of EES.

2.3.2 Investigational New Drug (IND) Applications (Including Treatment IND and Treatment IND Protocols)

An IND is an application for approval to test a drug in clinical trials for humans. Districts will only inspect clinical trial manufacturing establishments when specifically requested to do so by CDER. Such requests will be issued using EES. These sites are not generally required to register and are not subject to routine drug process inspections.

A Treatment IND is an original IND that contains a protocol providing for extensive use of a promising new drug, in patients with a serious or immediately life-threatening disease or condition, for which no comparable or satisfactory alternative drug or other therapy exists. A Treatment IND protocol provides for administration of the IND drug outside of clinical trials and before marketing of the commercial drug. This can include use of a drug for diagnostic purposes. Because a Treatment IND is submitted with a 30 day review period, any establishment inspection request is a top CDER priority. If decision is made to inspect such a facility, the district is to ensure completion of the inspection within 10 calendar days of receipt of the inspection request.

2.3.3 Biological Licensing Application (BLA) Inspection Assignments

During review of a BLA, DMPQ/MAPCB determines if a pre-license inspection[16] should be performed and what objectives should be covered. The inspection team consists, as needed, of an investigator qualified by training and experience in biotechnology inspections, a DMPQ investigator, and an OBP reviewer. For fill/finish manufacturing operations, an ORA investigator will generally lead the team. The team should frequently include a MAPCB reviewer and an OBP reviewer. The lead investigator is responsible for the inspectional strategy, ensuring adequate coverage, consolidation and final issuance of the 483, and completion of the EIR. All team members are responsible for writing their portions of the EIR within established time frames.

2.4 IMPORTANCE OF REVIEW INDEPENDENCE

FDA offices involved in the pre-approval inspection program are covered by an "equal voice" philosophy. Under equal voice, all appropriate expertise should be brought to bear in the important decisions we make about applications, and each FDA office assigned a role in reviewing and evaluating new drug applications is valuable. The review of an application requires the input of multiple disciplines in FDA, and involves difficult regulatory judgments which may result in differences of opinion. Therefore, achieving a science-based and ultimately defensible decision about each application demands that reviews and evaluations be independent and encourage well-informed critical evaluations by each involved organizational unit. Review independence is accomplished, in practice, when each organizational unit:

- Integrates each contribution to enhance the decision of the multidisciplinary team;
- Provides an environment where each member of the team has an opportunity to express his or her view for the area in which s/he has a recognized responsibility;
- Ensures an avenue for promptly raising unresolved differences of opinion through the management chain for prompt resolution; and
- Maintains transparency with a full and adequate record documenting its decisions, including any significantly differing views.

2.5 KNOWLEDGE TRANSFER PROGRAM

CDER has initiated a program to enhance the risk-based focus of drug pre-approval inspections. CDER's pre-market assignments and communications will now effectively transfer product and manufacturing knowledge from CDER to ORA inspections. Specifically, CDER staff will alert the inspection team to manufacturing and laboratory issues found during the pre-market application review. CDER/DMPQ will communicate these areas of concern via the Knowledge Transfer Memorandum (KTM) or by initiating other forms of communication, including meetings, telephone calls, or participation on inspections.

The pre-approval manager will be alerted in EES that a KTM will be or has been issued. The KTM will be issued along with the pre-approval assignment. The inspection should not be delayed pending the issuance of a KTM.

[16] For the purpose of this document, "pre-license" inspections relating to BLAs are referred to as "pre-approval" inspections.

PART III - INSPECTIONAL

3.1 INSPECTION SCHEDULING AND PREPARATION

A PAI should be performed at the earliest opportunity in order to meet the district goal date. It may be combined with other programs or for-cause inspections as necessary for efficient and effective inspection coverage. The timing decision should carefully weigh the need for the inspection to provide an early contribution to the application review process with the need for efficient scheduling by the district. The district goal date, which is included in EES, is the date by which the district should complete the inspection process. A systems-based CGMP surveillance inspection pursuant to CPGM 7356.002 will be added if due by work plan or if findings from the PAI raise concerns that indicate the need for coverage of marketed products, as determined by district management.

Districts may choose to contact firms prior to a PAI to determine their readiness for inspection. Any postponement of a scheduled inspection by the establishment or applicant that may impact on the agency's time frames for assessing an application should be reported to DMPQ/MAPCB promptly. Once scheduled, districts should make every effort not to postpone the inspection. Delays in gaining access to records and information maintained by an establishment during an inspection should be reported to DMPQ/MAPCB if the delay is expected to impact the agency's time frames.[17] For international and domestic facilities, if the inspection planning has started and the establishment is not ready for inspection, a written response should be obtained from the establishment[18] and include: (1) an explanation of the reason, and (2) when the facility expects to be available. A withhold recommendation should be entered in EES by the district.

Investigator preparation before a PAI should involve the following actions:

- Review the CMC section of application and any related DMFs for the establishment to be inspected (using the copy filed with home district of the application applicant, also known as the "field copy," or a copy obtained electronically). If possible, review the development report prior to initiating the inspection.
- Contact the chemistry and microbiology reviewer assigned to the application and discuss his/her findings, if any, and if available, obtain the Reviews from the PAM or chemistry reviewer. Determine if the reviewer(s) recommends special areas for data audit coverage during the inspection. Also, contact the reviewer(s) regarding questions on submitted information, such as test methods, data tables, raw material attributes, or justifications for finished specifications. This contact may also be made by the PAM or supervisor, depending on district policy. For a PAI in the Knowledge Transfer Program, the Knowledge Transfer Memorandum (KTM) will include specific areas of coverage (Refer to **Part 2.5 – Knowledge Transfer Program**).
- Contact a CGMP subject matter expert (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm) with any questions about the application of CGMP requirements with respect to the subject application or other broader deviations from the regulations. This contact may also be made by the PAM or supervisor, depending on district policy.

[17] Refusals of access to information should be referred to ORA/OE by existing procedures (e.g., IOM).
[18] Obtain the written response from the most responsible individual at the facility or designee.

- Develop, with other team members, if applicable, an inspection strategy specific to the establishment and product being inspected that is consistent with this program's objectives and inspection/audit techniques. Review the history of the firm and FDA-483 observations from previous inspections.
- Contact DMPQ/MAPCB and the PAM regarding any questions about this program.

The "field copy" of an application is to be an accurate reproduction of the CMC section of an original application (21 CFR 314.50(l)(3)). This information often contains trade secret or confidential commercial information and it is essential that the information be carefully protected to prevent its release outside the agency. Districts are expected to establish a controlled access filing system to prevent the unauthorized use or release of application information.

3.2 INSPECTION TEAM

PAI inspections should be, whenever possible, a team approach with at least one investigator and one analyst. Districts are to assign experienced investigators and analysts to perform PAIs. Investigators and analysts conducting these inspections will be qualified by appropriate training and experience.[19]

Districts are encouraged to request CDER application reviewers or a CDER CGMP subject matter expert to participate in PAIs, particularly those involving a new molecular entity, novel product formulation or dosage type, novel unit operation or processing method, and/or novel analytical methods or techniques. Districts are also encouraged to request support directly from other district offices, DFI national experts, or a member of the Pharmaceutical Inspectorate. Support from such additional sources may be especially valuable where local resource limitations impact a district's ability to perform the PAI.

The Center will be available to participate in certain PAIs. Requests and arrangements for CDER staff participation are facilitated by DMPQ, as follows:

- For NDA/ANDAs:[20] CDER staff, usually from the Office of Compliance or the Office of Pharmaceutical Science (i.e., ONDQA or OGD), send a request to DMPQ to participate as a supporting member of an inspection team. DMPQ then informs ORA of CDER's inspection team participants.
- For BLAs: PAIs are performed using a team approach by investigators and analysts with appropriate training and experience and one or more CDER representatives (i.e., MAPCB or OBP). DMPQ/MAPCB collaborates with OBP and the district to coordinate the inspection team participants and inspection timing. See **Part 2.3.3 – Biological Licensing Application (BLA) Inspection Assignments** for discussion of inspection team member roles.

[19] For an example of the training curriculum, refer to http://inside.fda.gov:9003/EmployeeResources/Training/ORAUCourses/default.htm.

[20] CDER Office of Compliance, in conjunction with CDER product reviewers and ORA, will schedule on-site method validation/verification (MV) inspections for selected applications. These MV inspections can be performed concurrently with the pre-approval inspection, but may be performed at any time.

3.3 INSPECTION/AUDIT STRATEGY

There are three primary inspectional objectives of this PAI program. These objectives are:

Objective 1: Readiness for Commercial Manufacturing
Objective 2: Conformance to Application
Objective 3: Data Integrity Audit

If one or more Priority Pre-Approval Inspection Criteria is met and the district recommends that a PAI should be performed, at least one objective must be addressed during the PAI. Based on the specific responsibilities of the establishment to be inspected and whether new profile classes are related[21] to inspected profile classes, the district determines the degree of coverage. The district should use Attachment C as a guide and apply additional coverage if there are overlaps.

During the PAI, significant issues may be uncovered. This program allows for adjustments to the inspectional strategy based on inspectional findings.

Some examples of related profiles[21] include:

- *The establishment has a history of manufacturing immediate release tablets with a high API content, and the new application product is an immediate release capsule with a high API content. The API in both instances is highly soluble. In this case, the profiles would be considered **related**.*
- *The establishment has a history of manufacturing an extended release tablet product with low API content, and the new product is an immediate release tablet with high API content. In this case, the profiles would be considered **related**.*
- *The establishment has a history of manufacturing non-sterile API used in solid oral dosage drug products, and the new drug application names this site as manufacturer of a sterile API. In this case, the profiles would be considered **not related**.*
- *The establishment has a history of manufacturing immediate release tablet products with a high API content and the application product is an immediate release tablet with a lower API content. In this case, the profiles would be considered **not related**.*
- *The establishment has a history of manufacturing low dose, highly soluble immediate release tablets and the application product is a low dose, low solubility immediate release tablet. In this case, the profiles would be considered **not related.***

3.4 INSPECTION/AUDIT COVERAGE, OBJECTIVES, AND TECHNIQUES

The type and depth of inspection/audit coverage needed to address each PAI objective is described in this section, along with appropriate regulatory citations.

[21] A "related profile" refers to a manufacturing process or dosage form that is not substantially different from that previously covered at the establishment. Also see Priority Inspection Criteria (**Part 2.2 – Assignment of Inspection – Decision Criteria**).

3.4.1 Summary and Detailed Description of Objectives

Summary of Objectives

Objective 1: Readiness for Commercial Manufacturing
Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

a. Manufacturing and laboratory changes, deviations, and trends relating to the development of new drug substance and product manufacturing have been adequately evaluated.
b. A sound and appropriate program for sampling, testing, and evaluation of components, in-process materials, finished products, containers and closures for the purpose of releasing materials or products has been established, including a robust supplier qualification program.
c. The establishment has sufficient facility and equipment controls in place to prevent contamination of and by the application product (or API).
d. Adequate procedures exist for batch release, change control, investigating failures, deviations, complaints, and adverse events; and for reporting this information to FDA, such as field alert reporting.
e. The feasibility of the proposed commercial process and manufacturing batch record, including instructions, processing parameters and process control measures, are scientifically and objectively justified. This objective is linked to the firm's process validation program.

Objective 2: Conformance to Application
Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the biobatch (and other pivotal clinical batches, when applicable), the proposed commercial scale batch, and the API(s).

Objective 3: Data Integrity Audit
Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section such that CDER product reviewers can rely on the submitted data as complete and accurate.

Detailed Description of Objectives:

Objective 1: Readiness for Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

Objective 1(a): Manufacturing and laboratory changes, investigations, and trends relating to the development of new drug substance and product manufacturing demonstrate that the establishment has appropriately assessed related issues.

Assess that investigations related to the proposed manufacture of the commercial batch have been appropriately evaluated, including related laboratory investigations, equipment maintenance investigations, and related manufacturing (e.g., development batch) investigations. Investigative reports or resultant change control reports for development issues may not always be as comprehensive as required for marketed finished drug products. Nonetheless, the firm should appropriately document, record, and objectively assess all development data and information, including but not limited to data submitted in or generated after the filing of an application. Examples of deviations related to the application include:

- Laboratory issues which occurred during or after method validation, such as:
  - Unexpected laboratory events, including out-of-specification results and during current stability testing, in-process testing, and final product testing for the biobatch(es) or process validation batches
  - Discrepancies found while conducting the method validation (particularly issues that may have occurred in its final stages) or technical transfer
  - Changes in an analytical method after completion of the method validation or technical transfer due to an inability to use the method as written
- Related equipment maintenance and equipment performance issues which could affect the proposed commercial batch manufacture, such as:
  - Recent equipment maintenance issues, such as calibration failures, associated with commercial equipment planned for use in the proposed commercial batch record, to ensure that equipment is appropriately maintained
  - CGMP investigations and trending associated with the performance and capability of the same commercial equipment planned for use in the proposed commercial batch record
  - CGMP manufacturing investigations (e.g., significant deviations, rejects, complaints/returns) and trending associated with similarly manufactured marketed drug product at the establishment

Evaluate these investigations to determine if the establishment is prepared for the proposed commercial manufacturing process at commercial scale and has the controls in place to detect and/or mitigate the most likely and significant problems.

Related Regulations for Finished Pharmaceuticals: 211.67(a) addresses equipment maintenance, cleaning, and sanitization. For the validation/verification of analytical methods, refer to 211.160 through

167, and 211.194. Refer to 211.100, 211.192 and 211.198 for regulations relating to product deviations and investigations.

Related Guidance for APIs: For active pharmaceutical ingredients, refer to ICH Q7 Section 5.2, *Equipment Maintenance and Cleaning,* for equipment preventative maintenance, cleaning and sanitization. For the validation of analytical methods, refer to ICH Q7 Section 12.8, *Validation of Analytical Methods*. Refer to ICH Q7 Section 6.5, *Batch Production Records,* Section 6.7, *Batch Production Record Review*, Section 8.1, *Production Operations*, and Section 15, *Complaints and Recalls*, for guidance relating to product investigations.

Objective 1(b): A sound and appropriate program for sampling, testing, and evaluation of components (including APIs), in-process materials, finished products, containers and closures for purposes of releasing materials or products has been established.

Review sampling plans and procedures, including those described in batch records, to evaluate the establishment's intended approach to sampling components, in-process, and finished product. Sampling plans must assure that representative samples are collected and tested/examined as verification of product quality. The method of selecting samples, number of samples taken, the statistical criteria for the number of samples taken, the acceptable quality limit and the unacceptable quality limit should be scientifically-based and appropriate. The extent of experiences with the specific commercial process should be considered when determining adequacy of sampling plans. Also, areas of criticality or process vulnerability should receive special attention, as these points in a process generally require more extensive sampling. For example, a firm may consider the use of PAT (Process Analytical Technology).[22]

For finished dosage establishments purchasing multiple lots of components[23] from an external supplier, the supplier's variability and the specification criteria should be evaluated. For finished dosage and API establishments, the firm should establish statistical criteria for component, in-process, and finished product variability in comparison with the specification criteria. If the district believes that it is warranted, a for-cause sample of the component may be collected. The laboratory should be contacted for instructions prior to collection.[24]

Related Regulations for Finished Pharmaceuticals: 211.160 requires all sampling plans (and specifications) to be scientifically-based and appropriate; 211.165 requires sampling plans for finished product to be in writing and meet appropriate statistical quality control criteria, prior to batch release; 211.110, 211.134, and 211.166 address sampling in the context of in-process materials, labeling, and stability, respectively. 211.84 requires that all sampling of components, drug product containers, and closures be representative.

[22] Refer to Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, September 2004. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf).
[23] The term "component" includes APIs, excipients, and processing aids (21 CFR 210(b)(3)).
[24] Refer to CPGM 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection.

Related Guidance for APIs: For active pharmaceutical ingredients, refer to ICH Q7 Section 11.1, *Laboratory Controls-General Controls*, which requires all sampling plans to be scientifically sound and appropriate and sampling procedures to be in writing. This section also addresses sampling in the context of raw materials, intermediates, APIs and labels and packaging materials. ICH Q7 Section 7.3, *Sampling and Testing of Incoming Production Materials*, requires that samples should be representative of the batch of material from which they are taken. ICH Q7 Section 11.6, *Expiry and Retest Dating*, addresses sampling in the context of performing a retest.

Objective 1(c): The establishment has sufficient facility and equipment controls in place to prevent contamination of and by the application product (or API).

Coverage of this element is warranted for new construction or facility design, new uses of existing equipment that pose potential risks (e.g., addition of a highly potent product), or equipment operations unique to the application under review. Observe the firm's operations as you inspect the facility, and after reviewing blueprints, floor plans, or as-built diagrams of utility systems (such as the purified water system piping and air handling systems). It should be verified that the establishment has facility, equipment, and utility system controls in place (or planned) designed to prevent any contamination that could be deleterious to the specific application product, and to ensure that controls are in place to prevent cross-contamination of and by the application product.

Inspect new construction intended for the application product, as well as the installation of new equipment, and any other significant changes to the existing facility or practices relating to material/personnel flow. Evaluate the establishment's proposed compliance with related CGMP requirements. Special attention should be given to the new product or marketed products which are highly potent or potentially sensitizing in humans to ensure that the product is not liable to contaminate existing products in the facility.

Related Regulations for Finished Pharmaceuticals: 211.42 through 211.67 require facility and equipment controls to prevent contamination and to ensure well-organized operations.

Related Guidance for APIs: For active pharmaceutical ingredients, refer to ICH Q7 Sections 4.1 (*Buildings and Facilities - Design and Construction*) through 5.2 (*Process Equipment – Equipment Maintenance and Cleaning*), that require facility and equipment controls to prevent contamination and to ensure well-organized operations.

Objective 1(d): Adequate procedures exist for change control; investigating failures, deviations, complaints, and adverse events; conducting recalls; and for reporting this information to FDA.

Review the establishment's quality and change procedures and audit the establishment's compliance to their procedures for *already marketed product,* as appropriate (e.g., sampling of actual failure, deviation, and complaint investigations, or related adverse drug experience report handling, including submissions to FDA if required). Note that the regulations for ADE reporting only cover prescription and application products. If significant problems are found with the establishment's existing complaint

handling and reporting procedures, the district should consider recommending a directed inspection of the ADE reporting system under CP7353.001A.[25]

Related Regulations for Finished Pharmaceuticals: 211.192 and 211.198 address failure and complaint investigations; 211.100 addresses deviations from written manufacturing procedures; 314.81(b) (1) is the requirement for submitting a Field Alert Report to FDA. 314.80 addresses ADE reporting requirements for application products and 310.305 addresses ADE reporting requirements for marketed prescription drugs for human use without approved new drug applications.

Related Guidance for APIs: For active pharmaceutical ingredients, refer to ICH Q7 Section 6.5, *Batch Production Records*, Section 6.7, *Batch Production Record Review*, Section 8.1, *Production Operations*, and Section 15, *Complaints and Recalls*, for guidance relating to failure and complaint investigations and/or deviations from written manufacturing procedures.

Objective 1(e): The feasibility of the proposed commercial process and manufacturing batch record, including instructions, processing parameters and process control measures, are scientifically and objectively justified. This objective is linked to the firm's process validation program. [26]

An essential part of the inspection is evaluating the justification for the proposed commercial process and the manufacturing batch record. As part of the determination of process feasibility, evaluate development studies and knowledge gained about manufacturing operation vulnerabilities, including the influence of raw material variability. Determine the purpose of each study performed by the firm. For example, review studies conducted to establish process controls or process parameters directly related to the critical quality attributes of the drug product in the application. These may include studies of "worst case" or boundary conditions to establish "proven acceptable ranges" or more sophisticated studies involving design of experiment or multivariate analysis modeling. Assess the protocols, execution of the studies, and reliability of the data and conclusions. Investigators should include the inadequacy of data to support the filed processing approach, or the proposed Master Batch Record provided during inspection, on the FDA-483.

This evaluation includes a review of the firm's scale-up studies. Select and assess studies (e.g. the scale-up from the biobatch, or pivotal batches, to a larger (interim or full) scale batch). Note that the firm may need to change the submitted proposed commercial process as scale-up studies are completed and knowledge is gained. Such changes alone are not a violation and should not be cited as a deficiency.

Determine and report the firm's projected timeline for completion of any additional studies and the purpose of each study. Though not required at the time of the PAI, a firm may have completed all of the planned studies which demonstrate that the product can be reliably manufactured at commercial scale and meet all established limits and operational standards. If the firm states that all process validation activities necessary to distribute finished drug product, including commercial scale conformance

[25] Contact HFD-330, the CDER/OC division responsible for managing the ADE site inspection program for further guidance in conducting a specific inspection.

[26] Applications for aseptic processes, sterilization processes, and certain biotech processes include summaries of process validation studies. Review the studies and include deficiencies on the FDA-483.

batches, have been completed, fully audit and assess these studies and conclusions. These will include studies and experiments to scientifically establish appropriate processing parameters and other manufacturing instructions for significant processing steps. Additional studies will typically include commercial scale batches (conformance batches) which made at the site in accordance with the master batch and production control record using the qualified commercial scale equipment and utilities and trained production personnel. This study is typically conducted in accordance with a formal protocol and is intended as a confirmation of the process design before commercial launch. It also establishes a level of reproducibility and consistency at nominal processing conditions. One of the firm's conclusions from these process validation studies must be that a "high level of assurance" was achieved in that the commercial process is capable of consistently delivering quality product meeting its critical quality attributes. The manufacturer should also plan for sufficient on-going evaluation of the process once marketing approval has been granted by CDER.

Results and data to the contrary should be fully examined in detail to determine if unresolved deficiencies exist. Some examples of situations requiring further follow-up include:

- Drug product or API does not meet its critical quality attributes and root cause has not been determined;
- Batch records, in-process data and/or process monitoring records reveal an unexpected highly variable process and the reason is unknown;
- Inconsistent execution of the batch record and manufacturing instructions and/or operator "work-arounds" (possible indication of poor process design or training);
- Control measures do not appear to align with the critical quality attributes or in-process parameters based on raw development data reviewed during the inspection (i.e., important parameters or material attributes are not being monitored or measured at the appropriate frequency);
- Sampling and monitoring plans are not justified and/or not sufficient during process qualification phase (conformance batch manufacturing) based on raw development data reviewed during the inspection, and sample results are therefore not considered representative of the entire lot; and
- Lack of objective scientific data justifying critical process parameters in that the impact on the material (in-process or final drug) is unknown.

Completed process validation studies for other drug products may be reviewed to evaluate the firm's capabilities and procedures. Interviewing key employees, such as the lead validation engineer, may be helpful in assessing a firm's capability to implement a sound process and control strategy.

Deficiencies in completed process validation studies should be listed on the FDA-483 and the firm should be advised that appropriate corrections must be completed prior to distribution of the first batch.

When the investigator is unable to provide sufficient process validation coverage, investigators are to report as such in the inspection report. Districts should cover these processes during the next surveillance or post-approval inspection.

Some information review may overlap between ORA and CDER review, as applicants are being encouraged to share more product and process development information with CDER in accordance with agency guidance. When such additional information is submitted to the agency prior to inspection, CDER should make this information available to the pre-approval manager. The field investigator

should incorporate CDER insights into the inspectional evaluation of the proposed commercial process. Inspection findings regarding the adequacy of the establishment's validation plans may be discussed with DMPQ/MAPCB. The investigator should discuss validation plan issues with the firm and document the discussion in the EIR for CDER review. When applicable, pertinent observations will be documented on an FDA-483.

Center reviewing offices will require that certain data be filed to demonstrate that aseptic filling, sterilization processes, and certain biotech processes are validated before approval is granted. CDER application reviewers may evaluate this information for some aseptic/sterilization process validation studies. Review of this summary information is complimented by FDA's on-site inspection of these operations. Evaluating the adequacy of process validation at a facility is critical to assure implementation of reproducible processes.

Related Regulations for Finished Pharmaceuticals: 211.100(a) and 211.110 require developing a well-designed and reproducible process and 211.22 covers the quality unit's responsibilities. Aseptic and sterilization processes are required to be validated by 211.113 and 211.42.

Related Guidance for APIs: For active pharmaceutical ingredients, refer to ICH Q7 Sections 12.1 (*Validation Policy*) through 12.5 (*Process Validation Program*) for guidance regarding process validation.

Objective 2: Conformance to Application

Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the biobatch (and other pivotal clinical batches, when applicable), the proposed commercial scale batch, and the API(s).

Directly observe the processing lines, directly observe the unit operations, both scale and type (including aseptic or sterilization processes), and laboratory methods and compare with the description and/or batch record submitted in the CMC section of the application (or Drug Master File). Audit the detailed manufacturing records and ensure their consistency with the more general descriptions of the processing method described in the application. Review the biobatch (and other pivotal clinical lots) and assess the comparability with the commercial scale process. Compare actual manufacturing records to the production method described in the application. Contact CDER product reviewers if the manufacturing of pivotal clinical lots indicates significant changes as this could undermine product equivalency.

Inspection coverage of analytical methods validation for tests described in the application should include methods for testing the components, in-process materials, and finished product. The methods filed should be compared with the methods in actual use in the facility. The validation data and reports for each method should be reviewed for significant variations from the filed method, including variations of the drug specifications. Whenever possible, inspect the actual performance of the methods during the PAI, including laboratory deviations trends and other indications of a lack of method reliability. Not all methods need to be covered during the PAI. Coverage should be given particularly

to those methods/examinations that are unique to the product application under inspection, that are technically complicated to perform, or that measure a critical quality attribute. Consultation with the CDER reviewer may be useful in identifying such methods.

When an inspected establishment also has sent samples to FDA for analysis (as described below and in **Part 4**), the PAI coverage of this objective should include an audit of the records. Report as soon as possible any finding that casts doubt on the authenticity of a biobatch or whether any samples from the biobatch provided to FDA may not actually be from the biobatch identified in the application (as filed in the CMC section). Records that are considered good candidates for audit when covering this objective for assessing biobatch integrity may include shipping records, equipment use logs, inventory records, analytical testing results, and related research/scale-up batch records.

Examine the records of testing the components used in the biobatch and finished product and records associated with the production of the biobatch for comparison with raw data not submitted in the application. Consultation with the CDER application reviewer in advance of the inspection is essential to learn which component attributes, finished product specifications, and processing methods are critical to establishing the comparability of the biobatch and proposed commercial process. Comparability of the biobatch and proposed commercial process is important to assure that batches placed on stability for expiration date determination will be representative of the marketed product.

Verify that the biobatch and stability batch sizes are as reported in the CMC section. For the biobatches (or pivotal clinical batches), FDA might not always visit the manufacturing establishment at which it was manufactured. However, it is important to make every effort to at least evaluate the records associated with the biobatch and understand its manufacturing context.

Coverage of this objective should also include inspection of laboratory methods, including auditing Research & Development notebooks. Review of inventory records or receiving records of APIs as well as other components is a way of verifying and evaluating the context and integrity of biobatch and stability batch information submitted in applications.

Verify the API manufacturer(s) is/are the same as reported in the CMC section and ensure that no other records indicate a different API manufacturer or quality from that described in the application. If the application submission is for an API manufacturer other than the primary supplier, the PAI should audit the data demonstrating the equivalence (e.g., impurity profiles, physical characteristics), including quality, of the new API manufacturer with the previous manufacturer.

Inspections and audits under this objective and Objective 3 are to verify factual and contextual integrity of the information filed in the application. Information that has factual integrity is information that is original and corresponds directly to that submitted to the agency (e.g., a chromatogram showing a peak area that directly calculates to an assay value submitted in a data summary sheet in the application). Information that has contextual integrity is information supported by additional information about the testing or manufacturing area and related products/processes that does not negate or significantly challenge the accuracy of the factual information (e.g., a chromatographic sequence that shows all the assayed samples and which does not reveal failing assay values). Missing records (batch or testing) and unexplained losses of inventory of components used in production may call into question the contextual integrity of the information filed in an application.

Related Regulations for Finished Pharmaceuticals: 314.50(d)(1)(ii)(b) addresses submission of biobatches and stability batch information and finished product testing results; see related CGMP regulations at 211.165, 211.166, and 211.188. Component quality is addressed at 211.80 and 211.84; production and process control records are to be created and handled in accordance with 211.188; records are required to be maintained as per 211.180, especially (a) and (b); methods are to be scientifically sound and validated as per 211.160 through 211.167.

Related Guidance for APIs: For active pharmaceutical ingredients, refer to ICH Q7 Sections 11.1, *Laboratory Controls-General Controls*, 11.2, *Testing of Intermediates and APIs*, 11.5, *Stability Monitoring of APIs*, and 6.5, *Batch Production Records*, that address results of testing, batch records and stability monitoring of APIs. Component quality is addressed in ICH Q7 Section 6.3, *Records of Raw Materials, Intermediates, API Labeling and Packaging Materials*; ICH Q7 Section 6.1, *Documentation System and Specifications*, addresses maintenance of records and ICH Q7 Section 12.8, *Validation of Analytical Methods*, and Section 11.1, *Laboratory Control-General Controls*, discuss the need for analytical methods to be scientifically sound and validated.

Objective 3: Data Integrity Audit

Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application and to verify that all relevant data were submitted in the CMC section such that CDER reviewers can rely on the submitted data as complete and accurate.

Audit the accuracy and completeness of data in the CMC section for the quality and specifications of components and finished product, and if submitted, data in the development report. Not every CMC data summary must be audited to accomplish this objective. The inspection strategy may select key data sets or randomly select data filed in the application. Generally, data on finished product stability, dissolution, content uniformity, and API impurity are good candidates for this audit.

The review should include data summary tables. Typically, applicants also submit additional testing for the finished product's performance and physicochemical attributes. During the inspection, compare raw data, hardcopy or electronic, such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the CMC section. Raw data files should support a conclusion that the data/information in the application is complete and enables an objective analysis by reflecting the full range of data/information about the component or finished product known to the establishment. Examples of a lack of contextual integrity include the failure by the applicant to scientifically justify non-submission of relevant data, such as aberrant test results or absences in a submitted chromatographic sequence, suggesting that the application does not fully or accurately represent the components, process, and finished product.

When data integrity discrepancies are observed, the inspection should identify firm personnel responsible for application submissions and any decision to include or exclude data from the application. Determine what actions or inactions contributed to the data integrity problem and whether

any corrective actions were or are to be taken. The inspection should determine if data was not submitted to the application that should have been. For example:

- Was there any "passing" (i.e., within specification or otherwise favorable) data submitted to the application that was substituted in place of "failing" data (i.e., out of specification, or unfavorable) without a sufficient investigation and resolution of the discrepancy?
- Did the firm improperly invalidate OOS results, which were therefore not submitted in the application?

The following are possible indications of data integrity problems:

- Alteration of raw, original data and records (e.g., the use of correction fluid)
- References to failing bio-studies
- Discrepancies (e.g., color, shape, embossing) between biostudy samples and reserve samples
- Inconsistencies in manufacturing documentation (e.g., identification of actual equipment used) and other information in the submission

The following are some examples of data integrity problems that have been previously observed:

- Multiple analyses of assay with the same sample without adequate justification
- exclusion of specific lots from the stability program to avoid submitting failed results
- Reworking or process modifications not adequately justified and appropriately reported
- Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results
- Backdating stability test results to meet the required commitments
- Creating acceptable test results without performing the test
- Using test results from previous batches to substitute testing for another batch
- Determination that a site does not actually manufacture the drug as described in the drug application or the Drug Master Files (DMFs)[27] referenced therein

In the event that these situations are found, thoroughly document the unreliable data. The district should follow the agency's Application Integrity Policy (AIP) and consider submitting an AIP recommendation to CDER/DMPQ. Contact information and procedures can be found on the AIP website. [28]

Related Regulations for Finished Pharmaceuticals: 314.50(d) requires that the CMC section include "data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application." Several CGMP regulations require laboratory data to be collected and maintained, including 211.160 (General Requirements), 211.165 (Testing and Release for Distribution), 211.166 (Stability), and 211.167 (Special Testing Requirements).

Related Guidance for APIs: For active pharmaceutical ingredients, several ICH Q7 sections require laboratory data to be collected and maintained, including Sections 11.1 (*Laboratory Controls-General Controls*) through 11.5 (*Stability Monitoring of APIs*).

[27] Inspection team should determine if the operations appears beyond the capability of the firm and review various production records to determine if batches were truly produced at the site, or are being produced at a subcontracted "shadow factory" without FDA knowledge.

[28] http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy%20

3.4.2 Investigator Questions and Concerns during an Inspection

Following the principles of ICH guidelines Q8, Q9, and Q10,[29] the agency is implementing a more integrated approach towards preparing for and conducting inspections. CDER and ORA will collaborate in order to provide an efficient and effective use of inspectional resources. Questions that arise during an inspection should normally be directed to the DMPQ/MAPCB contact, who will coordinate a response within CDER, and the PAM. More specifically:

- Questions/concerns about CGMPs, such as facility control, process control, batch release, quality assurance, or manufacturing procedures should be addressed to DMPQ/MAPCB.
- Questions and concerns about submitted product development summaries, product attributes, or tests method should be directed to the CDER CMC reviewer. The DMPQ/MAPCB contact should normally be copied or notified. This notification is critical if the issue discussed may result in an FDA-483 citation.

The CDER application reviewer and the DMPQ/MAPCB contact are listed on the EER.

3.5 INSPECTION REPORTING

After the inspection is conducted, investigators communicate findings primarily through establishment inspection reports (EIRs). Telephone calls, emails, or EES are often used for timely update of CDER on problematic findings, to help resolve a specific issue, or ask a question before the EIR is written. When the inspection reveals a potentially violative CGMP finding, or data integrity issues, the district should enter a "Potential OAI Alert" into EES as soon as possible. For data integrity issues, the investigator's report should clearly indicate how the data/information observed on-site differs from the data/information filed in the application. It is essential that the district notify DMPQ/MAPCB of data integrity issues promptly in order to trigger an immediate evaluation of the authenticity of the application.

During an inspection of a manufacturing establishment, the investigator may find that the firm did not perform all of the process development and therefore does not have all of the development studies available for inspection. The investigator should collect information about each establishment involved in the process development, such as name, address, responsible person, and work performed. This information should be included in the EIR. If the district determines that a follow-up inspection is warranted, DMPQ/MAPCB should be notified.

Issuance of an FDA-483

Any reportable inspection observations will be issued to the establishment via an FDA-483 consistent with instructions in the Investigators Operations Manual (IOM). (If the inspection is a concurrent CGMP surveillance and PAI, the FDA-483 should be organized by CPGM 7356.002, Drug Process Inspections, and the IOM.)[30] If these types of findings are observed, they should appear on the FDA-483:

[29] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm

[30] The investigator should indicate in the EIR which of the three objectives in **Part 2.2.2** of this program pertain to each observation.

- Differences from the filed CMC description of the process for the biobatch, stability; or the lack of an adequate or sufficiently specific proposed commercial batch record to provide for a reproducible manufacturing operation
    - Differences in formulations, processing principles, equipment use logs, or discrepancies in raw material lot reconciliation (inconsistencies in firm's records for receipt, inventory, or use in production)
- Missing data related to the data filed in the CMC section
    - Data or information that was submitted to the application that was potentially unreliable or misleading and the relevance of this data or information
    - Unexplained or inappropriate gaps in a chromatographic or analytical sequence
    - Any instance of an inappropriately disregarded test result, e.g., the result was not clearly or thoroughly presented within the application
    - A pattern of inappropriately disregarded test results when such data was of a type not required to be filed to the application and which reflects on the quality of biobatch, stability batch, or other drug quality
    - Data or information not submitted to an application for which the applicant failed to have adequate justification for the non-submission
- Insufficiency, discrepancy, or failing of an analytical method validation program
- Lack of suitability of the facility or equipment or manufacturing operations intended for making the commercial API or finished product to the CGMP regulations
- Other specific non-conformance (e.g., conditions, practices, procedures) to the CGMP regulations

Completion of the Establishment Inspection Report

The investigation team will prepare a narrative establishment inspection report (EIR) per instructions in the IOM (Chapter 5) in addition to the following: a description of the objectives and specific data and areas covered, inspection strategy, and citations and discussion with management organized by objective (described in **Part 2** of this program). If the inspection is a concurrent CGMP surveillance and PAI, the EIR should be organized by CPGM 7356.002, Drug Process Inspections. Any further instructions for report content or information organization should be addressed by the report. These further instructions are in specific objectives of this program or in a focused assignment memorandum.

A streamlined EIR may be submitted only for pre-approval inspections where the district recommends approval. If the district elects the streamlined option, then the EIR may consist of the following headings:

- SUMMARY
  This section should be consistent with the IOM SUMMARY.
- MANUFACTURING DESIGN/OPERATIONS
  This section should include a **brief** description of the responsibilities of the inspected firm in relation to the NDA, ANDA, or BLA application. Additionally, a description of the manufacturing operation and concise summary of coverage provided during the inspection should be included in this section.
- OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE
  This section should be consistent with the IOM OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE. It should include the observation and sufficient information

so that other agency staff can readily understand the relevance and significance of the observation to the product application.

- ADDITIONAL INFORMATION
  This section should include any additional information necessary for review by other agency staff. The investigator may include a subheading, "REQUIRING FURTHER CDER EVALUATION." Examples include:
  - Concerns not cited on the FDA-483 but still needing further evaluation by CDER compliance and review staff. An investigator should report any information that is potentially important for CDER to know regarding the application. For questions regarding which findings are appropriate to include on the FDA-483, contact a CDER DMPQ Subject Contact and the PAM.
  - A minor discrepancy regarding stated commitments, data, or information in the Chemistry, Manufacturing, and Controls (CMC) section of an application. Such information might also compliment or augment an FDA-483 citation.
  - Any inability to cover the objectives required for the PAI. For example, the district should report any instance when it is unable to thoroughly inspect due to a change in establishment or original records maintained at another location need to be inspected. In such cases, include sufficient information about the additional location and responsible personnel to facilitate an inspection request (and notify DMPQ/MAPCB by phone).
  - Any inability to inspect the biobatch facility or equipment (e.g., the investigator finds that batches were made at other establishments or the facility or equipment no longer exists).
  - Inappropriate handling of any samples sent to the designated FDA laboratory by the establishment.

For data integrity issues, the EIR should identify who was responsible for the submission (including omitted data) and how the responsible personnel handled the questionable data. The EIR should also describe the establishment's actions and/or inactions surrounding the data integrity problem and document the establishment's actions or inactions to resolve the questionable data results. Any promised corrective actions provided during the inspection should be included in the EIR so that they may be considered in the decision about the application.

All completed EIRs should be submitted to DMPQ/MAPCB within 30 business days after the close of the inspection (even in instances when no FDA-483 was issued) to ensure further evaluation before a decision is made on the application. If the 30 business day time frame occurs after the district goal date, the district must notify DMPQ/MAPCB as soon as possible. Refer to **FIELD REPORTING REQUIREMENTS (Inspectional)**. An accelerated review by DMPQ/MAPCB will then be performed and all other available information will be considered, such as discussions with the investigator/PAM or comments on the firm's FDA-483 response.

Note that profile class codes are only comprehensively updated after a CGMP surveillance inspection. For an inspection that *only* covered pre-approval issues where the firm is distributing product, only the profile class code covered during the pre-approval inspection should be updated.

3.6 SAMPLE COLLECTION OR SAMPLE SUBMISSION REQUESTS[31]

Investigators should not routinely collect samples during the pre-approval inspection. The following types of samples are associated with the drug application review process:

- Method Validation/Verification Samples, which are used to evaluate new drug application methods in FDA laboratories.
- Profile – Innovator and Applicant Drug Samples (not collected at the Biotest Laboratory), which are used to establish the profile of the ANDA product and ensure the integrity of the demonstration of bioequivalence.
- Biobatch Facility Samples, which are used to verify that the products used for the ANDA bioequivalence testing are representative of the authentic innovator and applicant products.

If an official sample is collected at an establishment, use PAC 46832B/46832C (NDAs) or 52832B/52843C (ANDAs) to report sample collection time.

3.6.1 Method validation/verification samples are now requested directly from the establishment at the request of the agency's Method Validation/Verification coordinators and sent to the agency laboratory. There are two coordinators for Method Validation Samples. For NDAs, CDER is the lead coordinator of samples. Please contact DMPQ/MAPCB for the contact information of the current NDA Method Validations Coordinator. For ANDAs, ORA is the lead coordinator. Please contact ORA's Division of Field Science for the contact information of the ANDA Methods Validation Coordinator.

Investigators may collect for-cause method validation/verification samples only after approval from their PAM or supervisor and concurrence by DMPQ, who will check with the other program coordinators to verify that samples have not already been collected and can be analyzed.

3.6.2 Profile Samples are used to support the integrity of the bioequivalence study, demonstrating equivalency of a generic product with the innovator product and providing a reference for post-marketing surveillance samples. These were formerly called "forensic" or "fingerprinting" samples. This sample involves the collection and comparison of the innovator drug and the generic drug biobatch batch samples. Each solid oral dosage application is a potential candidate for profile sample collection and analysis.

Profile samples are collected on a for-cause basis only. A determination to collect a profile sample for-cause may be initiated by DMPQ/MAPCB, an FDA laboratory, or the district. If DMPQ/MAPCB determines that a profile sample should be collected, MAPCB will issue a for-cause assignment to the district. If districts and FDA laboratories determine that a for-cause sample should be collected, they should contact DMPQ/MAPCB for issuance of the assignment. After a for-cause sample is requested, ORA/Division of Field Sciences (or the servicing laboratory[32]) will coordinate the analysis. Any collection of a profile sample should be documented in the EIR.

[31] For permit information regarding sampled derived from animal sourced material, refer to the Investigations Operations Manual (IOM) Chapter 3.2.1.6. For the collection of narcotic and controlled prescription drugs, refer to the IOM Chapter 4.2.5.3.

[32] Refer to **Attachment B**.

For profile samples at API facilities, investigators should only collect samples upon specific request for collection from the Forensic Chemistry Center (FCC). Such requests will be made through DFI. This process is described in CPGM 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection, Part IV.

Profile samples from non-US locations: A request for collection of profile samples located from non-US locations is to be sent to DFI for coordination with inspection scheduling. Sample collection of APIs from non-US locations is described at CPGM 7356.002F, Part IV. Samples shipped to the US are to be accompanied by the US Customs Letter (see **ATTACHMENT B-3**).

3.6.3 Biotest facility samples are analyzed to verify that the products used for the ANDA bioequivalence testing are representative of the authentic innovator and applicant products. These are samples of the innovator and applicant products used by and collected from the biotest facility to determine bioequivalence. These products are compared with the profile sample collected from the applicant and the innovator sample collected from the innovator or marketplace. Refer to Attachment B for instructions and CPGM 7348.001, In Vivo Bioequivalence.

The collection of the biotest sample is initiated when the profile laboratory makes a request to the home district where the biotest facility is located. A list of products from A/NDAs and biotest facilities is compiled by the profile laboratory and submitted to the district in the first week of each quarter. The districts are requested to collect the samples within thirty business days of receipt of the assignment. Additionally, CDER/Office of Compliance/Division of Scientific Investigations may request the collection of a biotest profile sample via assignment.

Requests for collection of biotest samples located in foreign countries will be sent to the Division of Field Investigations (DFI) for coordination with foreign inspection scheduling.

For questions during collection or submission, contact the Forensic Chemistry Center (Central, Southwest, and Pacific Regions) or the Northeast Laboratory (Northeast and Southwest Regions) (refer to **Part 6 – References**).

PART IV - ANALYTICAL

The sampling assignment will provide instructions to the laboratory regarding the type of analyses, the reporting codes, and the storage of any remaining portion of the sample. Refer to **Attachment B** for typical instructions.

Completed analytical worksheets will be maintained by the analyzing laboratory. The analyzing laboratory will notify CDER/Division of Manufacturing and Product Quality (DMPQ), the review division and the home district via e-mail of class 3 (adverse) findings. Report adverse findings by sending a copy of the worksheet to the following three recipients:

- The home district of the applicant;
- CDER Office of Compliance, Division of Manufacturing & Product Quality (HFD-320); and
- CDER Review Division to which the application is assigned for review.

If warranted, district offices will recommend an appropriate regulatory action to CDER Office of Compliance (HFD-300).

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Districts are asked to either perform an inspection for a specific establishment named in a specific application or to provide a recommendation of site acceptability. At the conclusion of a pre-approval inspection, the district needs to make a recommendation to approve or withhold approval based on outcome of the establishment inspection.

District directors or their designee should enter a **Recommend Approval** in EES when none of the criteria for withholding apply. District directors or their designee should enter a **Recommend Withholding Approval** in EES when there are significant findings[33] or when there is any other information that, in the district's judgment, warrants further evaluation by CDER before recommending approval of the application.

Findings and deficiencies that should result in a district recommendation to withhold approval include:

1. Significant data integrity problems including misrepresented data or other conditions related to the submission batch
2. Serious CGMP concerns with the manufacture of a biobatch or demonstration batch, such as a changes to formulation or processing that may cause FDA to question the integrity of the bioequivalence study
3. Significant differences between the process used for pivotal clinical batches and the NDA submission batch
4. Lack of complete manufacturing and control instructions in the master production record or lack of data to support those instructions
5. Lack of capacity to manufacture the drug product or the API (if the firm is not ready for an inspection, the district should request a letter from the establishment)
6. Failure to meet application commitments
7. Full scale process validation studies were attempted prior to the PAI, demonstrate that the process is not under control and establishment is not making appropriate changes
8. For products for which full scale summary information is provided in the application,[34] establishment has not demonstrated that the product can be reliably manufactured at commercial scale and meet its critical quality attributes
9. Incomplete or unsuccessful method validation or verification
10. Records for pivotal clinical or submission batches do not clearly identify equipment or processing parameters used
11. Significant failures related to the stability study that raise questions about the stability of the product or API
12. Failure to report adverse findings or failing test data without appropriate justification

Depending on district policy, the district PAM or compliance officer is encouraged to discuss any findings that are material to the district's recommendation with the firm's management to ensure that the final district recommendation is based on accurate information and understood in its proper context.

[33] This includes instances where the district is recommending a Warning Letter due to overall CGMP non-compliance that significantly impacts marketed products.

[34] Products may include aseptic processes, sterilization processes, and certain biotech processes.

If the district recommends withholding approval due to findings that apply to commercially marketed product, districts should investigate further and consider recommending enforcement action. A systems-based CGMP surveillance inspection pursuant to CPGM 7356.002 will be added if due by work plan or if findings from the PAI raise concerns that indicate the need for coverage of marketed products, as determined by district management.

The district director or designee will send a District Notification Letter to the inspected establishment with the recommendation to approve or withhold approval. The district will submit the report (EIR, FACTS endorsement, attachments, and exhibits) to DMPQ/MAPCB within the time frame based on the **FIELD REPORTING REQUIREMENTS (Inspectional)** section. For cases that are not sent concurrently to the Domestic Case Management Branch with a regulatory enforcement recommendation, DMPQ/MAPCB will review and enter a recommendation into EES within 20 business days of receiving the report. This will be followed by a memorandum to the review division with a copy sent to the district. This recommendation will include an overall decision and a conclusion regarding each deficiency contributing to the withhold recommendation. If a firm's response and district evaluation is submitted after the MAPCB review has been entered in EES, MAPCB and the district may then update the recommendation in EES. A subsequent recommendation to approve the application is contingent upon satisfactory correction of the findings that led to the initial withhold recommendation. The district has the discretion of confirming such correction by an on-site visit.

Process Validation

Districts will not recommend withholding approval of applications based on lack of complete commercial scale process validation (see also CPG 7132c.08, *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*.).[35] While sufficient process validation studies may not have been completed at the time of the pre-approval inspection in order to release product, the firm must achieve a high degree of assurance that the manufacturing process consistently produces product which meets all of its quality attributes prior to distribution. A warning letter, seizure or injunction should be recommended on finding that the firm distributed product prior to demonstrating that the manufacturing process was in a state of control.

Warning Letter

If the firm does not market FDA regulated products, Warning Letters are not appropriate as regulatory action to a pre-approval inspection.

If the firm markets other FDA regulated product and the pre-approval deficiencies apply to marketed drug product, a Warning Letter may be recommended by the district for the pre-approval inspection. These letters should include the following statement: "Due to the deficiencies listed on the attached FDA-483 and with the support of CDER Office of Compliance, we are recommending that ANDA […] not be approved."

[35] Refer to the Draft Guidance for Industry: Process Validation: General Principles and Practices (*draft dated November 2008*). Note that this statement does not apply to applications that include completed process validation studies, such as aseptic, sterile, and biotech areas.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

6.1 REFERENCES

6.1.1 Code of Federal Regulations, Title 21
- Part 210 and 211: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs and Current Good Manufacturing Practice for Finished Pharmaceuticals
- Part 310: New Drugs
- Part 314: New Drug Applications

6.1.2 Code of Federal Regulations, Title 29
- Part 1910: OSHA Hazard Communications Standards

6.1.3 Compliance Program Guidance Manuals
- CPGM 7356.002: Drug Manufacturing Inspections
- CPGM 7356.002F: Active Pharmaceutical Ingredients
- CPGM 7356.002M: Inspections of Licensed Biological Therapeutic Drug Products
- CPGM 7348.001: In-Vivo Bioequivalence Inspections

6.1.4 United States Pharmacopeia

6.1.5 Guidance and Guidelines
- Guideline on Preparation of Investigational New Drug Products, March 1991
- CPG Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients subject to Pre-Market Approval, March 2004
- Guideline on General Principles of Process Validation, May 1987
- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004
- Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (Q7 – ICH), September 2001
- Pharmaceutical Development and Annex (Q8(R2) -- ICH), August 2009
- Quality Risk Management (Q9 -- ICH), November 2005
- Pharmaceutical Quality System (Q10 -- ICH), June 2008
- Format and Content of the Chemistry, Manufacturing and Controls Section of an Application, February 1987
- Submitting Documentation for the Manufacturing of and Controls for Drug Products, February 1987
- Submitting Documentation for the Stability of Human Drugs and Biologics, February 1987
- Guidance for Industry: Bioanalytical Method Validation, May 2001
- Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, October 2006
- Guidance for Industry: Analytical Procedure and Methods Validation

- Chemistry, Manufacturing, and Controls Documentation (DRAFT), August 2000
- Reviewer Guidance: Validation of Chromatographic Methods, November 1994
- Guidance for Industry: Process Validation: General Principles and Practices (DRAFT), November 2008

6.1.6 Agency Inspection Procedures and References

- Guide to Inspection of Pharmaceutical Quality Control Laboratories, July 1993
- Guide to Inspection of Microbiological Pharmaceutical Quality Control Laboratories, July 1993
- Guide to Inspection of Validation of Cleaning Processes, July 1993
- Guide to Inspection of Lyophilization of Parenterals, July 1993
- Guide to Inspection of High Purity Water Systems, July 1993
- Guide to Inspection of Foreign Pharmaceutical Manufacturing Plants, September 1993
- GWQAP Manual, Profile System, Chapter 15
- Regulatory Procedures Manual, Chapters 7 and 8
- Staff Manual Guide 4831.3, Validation of NDA Analytical Methods
- MAPP 5310.2, Drafting, Circulating, and Signing Chemistry, Manufacturing, and Controls Letters, 10/27/1998
- MAPP 5310.6, Procedures for Assessing Chemistry, Manufacturing, and Controls Data in NDA Annual Reports, 10/10/2002
- Investigations Operations Manual
  - Chapter 3.2.1.6, Federal Agency Interaction (Animal Plant Health Inspection Service/USDA (APHIS))
  - Chapter 4.2.5.3, Dealer Relations (Narcotic and Controlled Rx Drugs)

6.1.7 Prescription Drug User Fee Act (PDUFA)

6.2 ATTACHMENTS

- Attachment A – Roles of Investigator and CDER Product Reviewers by *Specific Area* of CMC Review and Assessment
- Attachment B – Profile Sampling Instructions
- Attachment C – Recommended Scope of Coverage for a Priority Pre-Approval Inspection

6.3 CONTACTS

6.3.1 Center for Drug Evaluation and Research

CGMP program and related enforcement/compliance issues
Office of Compliance, Division of Manufacturing and Product Quality

Subject Contacts (including program contact names and phone numbers):
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm

Laboratories:
Division of Pharmaceutical Analysis (HFD-920)
1114 Market St., Room 1002
St. Louis, MO 63101
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm136991.htm

New Drug Applications:
Contact Offices for NDAs (General):
- Application Receipt and Filing Questions:
  - Business Information Staff (HFD-141)
- Application File Management Questions:
  - The Division of Records Management (HFD-143)
- Office of Generic Drugs (HFD-600)
- Questions about NDA and ANDA content: Refer to contacts in EES listed in Contact folder of the application in question

Bioequivalence Study Issues
Office of Compliance, Division of Scientific Investigations (HFD-48)
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm

Biological Licensing Applications
Refer to CPGM 7356.002M for contact information
http://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograMManual/default.htm

6.3.2 Office of Regulatory Affairs/Office of Regional Operations
- Division of Field Investigations (HFC-130)
  - Domestic Operations Branch
  - International Operations Branch
- Division of Field Science (HFC-140)
- Northeast Regional Laboratories
- Forensic Chemistry Center
- ORA Program Coordinators
  - See IOM for updated references
  - http://www.fda.gov/ICECI/Inspections/IOM/ucm124008.htm

6.4 ACRONYMS

ADE: Adverse Drug Experience
ANDA: Abbreviated New Drug Application
API: Active Pharmaceutical Ingredient
BLA: Biologic Licensing Application
BMT: Biotechnology Manufacturing Team (CDER/OC/DMPQ/MAPCB/BMT)
CMC: Chemistry, Manufacturing, and Controls
DMPQ: Division of Manufacturing and Product Quality (CDER/OC/DMPQ)
EER: Establishment Evaluation Request
EES: Establishment Evaluation System
EIR: Establishment Inspection Report
FEI: Firm Establishment Inventory Number
IB: Investigational Branch
ICH: International Conference on Harmonization
ICB: International Compliance Branch (CDER/OC/DMPQ/MAPCB/ICB)
IND: Investigational New Drug
MAPCB: Manufacturing Assessment and Pre-Approval Compliance Branch (CDER/OC/DMPQ/MAPCB)
NDA: New Drug Application
NDMS: New Drug Microbiology Staff (CDER/OPS/NDMS)
NGDMT: New and Generic Drug Manufacturing Team (CDER/OC/DMPQ/MAPCB/NGDMT)
OBP: Office of Biotechnology Products (CDER/OPS/OBP)
OGD: Office of Generic Drugs (CDER/OPS/OGD)
ONDQA: Office of New Drug and Quality Assessment (CDER/OPS/ONDQA)
OPS: Office of Pharmaceutical Science (CDER/OPS)
OTR: Office of Testing and Research (CDER/OPS/OTR)
PAI: Pre-Approval Inspection
PAM: Pre-Approval Program Manager

PART VII - CENTER RESPONSIBILITIES

FDA launched a major initiative, "Pharmaceutical CGMP for the 21st Century – A Risk-Based Approach," in August 2002. One of the specific goals of the initiative was to ensure that "the product review program and the inspection program operate in a coordinated and synergistic manner." Based on this goal, CDER organizational components have had several meetings to determine how best to implement a strategy which can ensure this goal is accomplished in CDER.

In implementing this strategy, CDER focused on the main principles of the initiative which included comprehensive modern quality systems and risk management approaches for regulating pharmaceutical quality. The new framework established under the initiative is currently being applied to the review, compliance, and inspectional components of FDA regulation and is intended to encourage the adoption of modern and innovative manufacturing technologies. The overarching philosophy articulated in both the CGMP initiative and in a robust modern quality systems is: *Quality should be built into the product, and testing alone cannot be relied on to ensure product quality*.

This strategy will encompass a more synergistic approach to the assessment and the pre-approval inspection programs. The manufacturer has the primary responsibility for quality control and quality assurance. Hence, it is critical that a robust quality system incorporate a scientific and risk based approach to change control to allow the manufacturer to manage appropriate post-approval changes without the need for regulatory submission. Accordingly, FDA will be reviewing regulations and drafting guidance to ensure that the agency empowers manufacturers to continually improve manufacturing processes without unnecessary regulatory oversight.

The CGMP initiative not only modernized the agency's regulatory approaches to pharmaceutical CGMPs, it also served as the catalyst for establishing a modern product assessment system. The final report of the initiative issued in September 2004 outlined the establishment of a new risk-based pharmaceutical quality assessment system (PQAS) to replace the CMC review process. This new system (1) allows FDA to adopt a scientific risk-based approach to setting product specifications, (2) facilitates innovation and continual improvement throughout the product lifecycle, and (3) enables FDA to provide regulatory flexibility to post-approval changes based on scientific knowledge and understanding of the product and manufacturing process.

Accordingly, FDA pre-approval scrutiny will reflect a manufacturer's demonstration of a meaningful understanding of the product and its manufacturing process. FDA will also implement steps to reduce post-approval filing burden for manufacturing changes for all drug products. FDA's revisions to regulations governing post-approval submissions will be modified to ensure that the agency facilitates continual improvements without undue regulatory scrutiny for both newly approved product and legacy products. FDA's objective is to shift responsibility to a manufacturer's quality system to evaluate changes to the manufacturing operation through internal formal change control systems.

Integrated Review-Inspection System

In order to ensure a scientific and risk-based approach to regulatory decision-making, it is essential for there to be a continuum in the regulatory process from review through inspection. An important part of this continuum is communication. It is imperative that the Center product reviewers and the field investigators work together as a team and communicate directly. CDER Office of Compliance will

facilitate the interaction between product reviewers and field Investigators to promote direct communication between product reviewers and field investigators. In addition, CDER compliance officers will participate, as needed, as members of the review inspection team. The reviewer will assess the firm's identification of critical product quality attributes and critical product performance parameters proposed by the applicant and the findings will be shared with the investigator prior to the PAI to facilitate a scientific risk-based inspection. Product attributes and performance parameters should be limited to those that are surrogates for clinical performance.

In order to facilitate review of proposed product specifications, the Center reviewers may participate on the pre-approval inspection team. The Center product reviewers may also be called on to provide information about a product prior to or during a PAI and CGMP inspections in coordination with the CDER Office of Compliance. When application review raises manufacturing issues that need to be addressed at the firm, that information will be highlighted in the inspection request (e.g., via the Knowledge Transfer Program; in the inspection assignment for BLAs). Following the PAI, all findings will be evaluated by the Office of Compliance for a decision on site acceptance. This integrated review-inspection system will facilitate a true scientific risk-based regulatory oversight, enhance Center-Field communication, ensure product quality, expedite the approval process, and provide an atmosphere of collaboration and trust.

ATTACHMENT A - NEW DRUG APPLICATIONS AND ABBREVIATED NEW DRUG APPLICATIONS

Responsibilities of on-site inspection and CDER review by Specific Area of CMC Review and Assessment:

AREA		SITE INSPECTION RESPONSIBILITIES	CDER REVIEW RESPONSIBILITIES
1.	All sites -- Raw data review	Audits integrity of data submitted in application and related data not submitted in the application. **This responsibility applies to all sections in this table.**	Reviews descriptions and submitted data.
	For all sites that include Biobatch and/or Stability Lot Manufacture	Evaluates establishment's compliance with CGMP. Audits biobatch and stability batch data for authenticity. Specifically, reviews raw data and records from batches used for pivotal clinical, bioavailability, bioequivalence, and stability studies.	Reviews data submitted in the application with respect to components, batch composition and general manufacturing/ control instructions, approves product specifications.
2.	API Manufacturing (including micronization)	Evaluates CGMP compliance of the manufacturer. Refer to ICH Q7, "CGMP Guidance for Active Pharmaceutical Ingredients," and CPGM 7356.002F.	Reviews API manufacturing process descriptions and data submitted in the application or a properly referenced Type II Drug Master File.
3.	Novel excipient manufacturing (e.g., novel manufacturing, non-compendial excipients used in specialized dosage forms & special delivery systems)	Novel excipient manufacturers are not routinely inspected, unless requested by CDER or District Office (DO) For-Cause assignment. If inspected, evaluates if manufacturing and laboratory capabilities are in compliance with CGMP. For finished dosage form manufacturers: evaluates adequacy of component vendor qualification, ongoing QC testing regimen, and storage/handling practices and procedures.	Reviews manufacturing process descriptions and data associated with novel excipients, including starting materials, key intermediates, reagents and solvents, and approves excipient specifications.
4.	Intermediates	Establishments manufacturing only intermediates are not routinely inspected unless requested by CDER or DO assignment. If inspected, refer to ICH Q7 for guidance.	Reviews intermediate specifications as part of API review.
5.	Manufacturing Facility Controls	Evaluates establishment's compliance with CGMP (e.g., environmental monitoring, equipment, facilities and processes, and operating procedures and practices).	--

AREA		SITE INSPECTION RESPONSIBILITIES	CDER REVIEW RESPONSIBILITIES
6.	Control of Components (raw materials)	When inspecting finished dosage form manufacturer: evaluates adequacy of finished dosage form manufacturer's component vendor qualification and ongoing QC testing regimen. For raw material vendors: assesses manufacturing and laboratory capabilities in accordance with CGMP. Also, assesses storage/handling and sampling procedures at dosage, API, and excipient manufacturers.	Reviews the raw material test methods and approves specifications (acceptance criteria) for adequacy and appropriateness.
7.	Manufacturing and Controls of Finished Product	Evaluates establishment's compliance with CGMP. Determines if facility can meet commitments made in the application. Assesses equipment and facilities, as well as details of the manufacturing process and control (batch records).	Reviews and approves drug product formulation (components and composition), test method selection, and specifications.
8.	Container/Closure System(s)	Evaluates that container closure systems are consistent with what is submitted in the application. This responsibility includes ensuring an ongoing QC program for incoming containers/closures, and evaluating investigations of any adverse data on container-closure system.	Reviews submitted information and approves the container/closure system for both the API and drug product.
9.	Packaging and Labeling Processes and Controls	Evaluates that establishment's packaging and labeling operations comply with CGMP.	Reviews adequacy of packaging and labeling materials, test method selection, and acceptance criteria.
10.	Finished Product Test Methods and Acceptance Criteria	Evaluates integrity of data submitted in application and reports questionable data to CDER/OC. Assesses whether laboratory method has been verified to operate under the specific laboratory's conditions of use. See **Part 3 – Objective 2**. Inspection also assesses whether proper laboratory controls exist.	Reviews and approves product test method selection and acceptance criteria submitted in applications.
11.	Stability, Finished Product	Evaluates establishment's compliance with CGMPs and determines whether or not stability test procedures, method validation, and stability data are consistent with what is stated in the application.	Reviews stability protocol and data submitted in support of drug product expiration dating period and API retest or expiration dating period. Approves specifications.

AREA	SITE INSPECTION RESPONSIBILITIES	CDER REVIEW RESPONSIBILITIES
12. Comparison of Pilot-Scale Batches and Proposed Commercial Scale Batches	Compares manufacturing processes for pilot (small scale) batches with the proposed commercial size batches. Reports significant manufacturing process changes and differences in equipment operating principles.	Determines if differences between pilot scale and commercial batch processes affect the safety and effectiveness of the product.
13. Sterility Assurance (if the finished product purports to be sterile)	Evaluates the state of control of the process as well as the manufacturing procedures, practices, and controls employed to assure sterility of the product.	Performs an initial review of a description of the sterility assurance program to support the sterilization validation, e.g., filtration efficacy validation. Reviews the adequacy of critical process parameters for the sterilization cycle. Approves specifications, test method selection, and sterilization method.
14. Parametric Release for Moist Heat Terminal Sterilization	Evaluates establishment's CGMP compliance. Emphasizes state of control and past performance of the terminal sterilization process. Ensures adequate preventative maintenance program, facility, equipment and quality system (investigations and batch release). See CPG 460.800.	Reviews current and proposed terminal sterilization cycle and acceptance criteria, and approves specification changes that allows for measured critical process parameters to act as a surrogate for sterility testing.

ATTACHMENT B - PRE-APPROVAL SAMPLING

B-1: Description of Pre-Approval Sampling Assignments and Laboratory Analysis
B-2: Example of Sample Collection Instructions for Solid Oral Dosage Finished Product Manufacturers
B-3: Example of Sample Collection Instructions for Independent Biotest Laboratories for Solid Oral Dosage Products
B-4: U.S. Customs Letter
B-5: Example of memorandum soliciting innovator sample

ATTACHMENT B-1 - DESCRIPTION OF PRE-APPROVAL SAMPLING ASSIGNMENTS AND LABORATORY ANALYSIS

B-1.1 Profile Samples

Profile samples are used to support the integrity of the bioequivalence study, demonstrating equivalency of a generic product with the innovator product and providing a reference for post-marketing surveillance samples. These were formerly called "forensic" or "fingerprinting" samples. This sample involves the collection and comparison of the innovator drug and the generic drug biobatch batch samples. Each solid oral dosage application is a potential candidate for profile sample collection and analysis.

The following types of samples of drug products may be collected for profile analysis under this program:

- Innovator product
- Generic biobatch, collected from the generic drug applicant and/or the independent biotest laboratory
- API samples collected from the source(s) intended for use in the dosage form pending approval

Each of these types of samples has a different method of collection and submission to the FDA analyzing laboratory, as described in this Attachment.

B-1.2 Instructions if a Profile Sample is Requested from the Manufacturing Establishment

If a for-cause assignment is issued to collect a profile sample at a finished dosage manufacturer, the investigator will either collect the sample or provide instructions to the manufacturer to collect and submit the sample to the FDA laboratory.

If the manufacturer is collecting the sample, the profile sample should be submitted to the servicing FDA laboratory prior to the end of the inspection, so as to permit the investigator to verify that the sample was submitted. The investigator will state in the EIR how the sample was prepared and submitted to FDA. For example, the EIR statement might read, "Profile sample submission instructions were provided to [insert name of firm official] on [insert date instructions were provided]. I verified via [method of verification, e.g., affirmation by firm official or documented receipt from shipped package] that a profile sample for A/NDA [12-345] was submitted to [insert name of receiving laboratory] on [insert date of submission]."

For questions about the profile sample submission, contact the Forensic Chemistry Center (Central, Southwest, and Pacific Regions) or Northeast Regional Laboratory (Northeast and Southeast Regions) (refer to **Part 6 – Program Contacts**).

For innovator samples, the designated analyzing laboratory will typically request the sample directly from the manufacturer. However, CDER or the field laboratory may request that an investigator collect an official innovator sample from the innovator or marketplace. Sample sizes and instructions will be provided by the designated analyzing laboratory. Refer to **Attachment B-5** for an example of memorandum soliciting innovator samples.

If an official sample is collected at an establishment, use PAC 46832B (NDAs) or 52832B (ANDAs) to report sample collection time.

B-1.3 Profile Sample Analysis

FDA's profile sample analysis is used to benchmark the formulation of the drug product biobatch as the authentic formulation reported in the application. These benchmark analytical results are electronically stored for future reference to resolve questions of authenticity, either by a future drug product marketed by the applicant or other entity. This type of profile sample analysis is only performed on solid oral dosage forms.

One method of ensuring authenticity of the applicant's formulation is to determine if substitution occurred during bioequivalence or bioavailability studies. To rule out substitution or other possible unscrupulous manipulations, the FDA laboratory compares analytical results of the profile samples collected under this program against analytical results of the biotest samples collected under CPGM 7348.001.

B-1.3.1 Instructions to FDA Laboratories performing Profile Analysis

FDA's analyzing laboratory coordinates the comparison of the analytical results of the innovator and generic samples, collected from the biotest laboratory, with the results of the innovator and generic profile samples collected under this program. In particular, FDA's laboratory compares the biobatch sample collected from the applicant against the biobatch sample collected from the biotest facility and compares the innovator sample collected from the innovator or marketplace against the innovator sample collected from the biotest lab. The two biobatch samples should match, as should the two innovator samples. The biobatch and innovator samples should be unique and distinctive and capable of being differentiated based on composition, fingerprint, or physical appearance.

B-1.3.2 Analytical Testing Instructions

Sample profiles, or "fingerprints," are analyzed at the Forensic Chemistry Center (Central, Southwest, and Pacific Regions), Northeast Regional Laboratory (Northeast and Southeast Regions), and DPA. The type of analysis should be determined prior to the collection of the sample. It may include the following types of analysis:

- An analytical technique capable of assessing the overall makeup of the submission batch and detecting later changes by comparison with analytical results of future samples of the applicant's product or a suspected counterfeit.
- Pantone color identifications to determine any discrepancies of solid oral dosage forms. This analysis includes photographs of the top, bottom, side and end views of the capsule or tablet, including any distinctive markings or fragmentation or picking of tablet or capsule shells. In order to document standard photographic conditions, the Pantone color guide that matches the outer surface of the tablet or capsule should be included in all photographs. These photographs will be filed for later use in comparisons with innovator product or with later batches of the applicant product.

Note that innovator and applicant profile and biotest samples are analyzed using the same analytical method.

B-1.3.3 Profile Sample Analysis Reporting

Report time for sample analysis in FACTS under PAC 46832B for NDA Profile Sample Collection/Analysis and under PAC 52832B for ANDA Profile Sample Collection/Analysis.

B-1.3.4 Storage of the Profile Sample

The laboratory will maintain any remaining portion of the sample in reserve for at least five years for future comparisons. Additionally, the laboratory will manage computer storage of the profile and biotest sample results for the following purposes:

- Comparison with samples collected after marketing approval, including samples collected under the CDER drug surveillance sampling program (CPGM 7356.008) in order to detect unreported changes
- Comparisons of future questionable drug products, either marketed by another manufacturer or in pending applications by the applicant

ATTACHMENT B-2 - EXAMPLE OF SAMPLE COLLECTION INSTRUCTIONS FOR SOLID ORAL DOSAGE FINISHED PRODUCT MANUFACTURERS

The following checklist is for the collection and submission of samples to the FDA laboratory.

1. Assemble the following:
   a. Finished product – 20 units
   b. Active pharmaceutical ingredients – 2-5 grams
   c. Excipients – 2 grams (e.g., lactose, starch, microcrystalline cellulose)
   d. Manufacturing instructions for the lot collected (biobatch batch record)
   e. Certificates of analysis for active and excipients

      i. Use of plastic spatulas is recommended. Submit an unused plastic spatula with the sample.

      ii. Use necessary precautions to protect the samples from contamination by human hands, dust, etc. Only opaque, non-reactive, small plastic or glass containers are appropriate as sample containers. Plastic bags are not recommended due to leakage. Precaution and care should be taken when shipping amber glass bottles to ensure breakage will not occur.

      iii. Each container should be labeled with the name of the ingredient, the expiry date, the lot number, the complete name of your establishment, and the application number and name of product.

      iv. For an international establishment shipping the sample through US Customs, a US Customs Letter should accompany the sample. Refer to Attachment B-4 for a sample letter.

2. A Material Safety Data sheet for each ingredient, especially for hazardous substances.

3. A copy of the biobatch batch record and a flowchart and brief description of the manufacturing process. Also, include the impurity test methods and impurity limits for each API. Per FDA requirements, this information will be kept completely confidential.

4. The complete firm/company name, contact information (telephone number, fax number, email), and contact person at the manufacturing establishment.

Please indicate on the shipping documents that the sample is intended for laboratory testing and has no commercial value.

ATTACHMENT B-3 - EXAMPLE OF SAMPLE COLLECTION INSTRUCTIONS FOR INDEPENDENT BIOTEST LABORATORIES FOR SOLID ORAL DOSAGE PRODUCTS

The following checklist is for the collection and submission of samples to the FDA laboratory.

1. Assemble the following:
   a. Applicant biotest product – no fewer than 6 tablets/capsules

   b. Innovator product used during bioequivalence testing – no fewer than 6 tablets/capsules

      i. Use of plastic spatulas is recommended. Submit an unused plastic spatula with the sample.

      ii. Use necessary precautions to protect the samples from contamination by human hands, dust, etc. Only opaque, non-reactive, small plastic or glass containers are appropriate as sample containers. Plastic bags are not recommended due to leakage. Precaution and care should be taken when shipping amber glass bottles to ensure breakage will not occur.

      iii. Each container should be labeled with the application number and name, manufacturer's batch number, date of receipt by the biotest laboratory, and any number assigned by the biotest facility.

      iv. For an international establishment shipping the sample through US Customs, a US Customs Letter should accompany the sample. Refer to Attachment B-4 for a sample letter.

2. A copy of the biobatch batch record and a flowchart and brief description of the manufacturing process. Also, include the impurity test methods and impurity limits for each API. Per FDA requirements, this information will be kept completely confidential.

3. The complete firm/company name, contact information (telephone number, fax number, email), and contact person at the manufacturing facility.

Please indicate on the shipping documents that the sample is intended for laboratory testing and has no commercial value.

ATTACHMENT B-4 - U.S. CUSTOMS LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Division of Field Science
Rockville, MD 20857
Telephone:
Fax:

Date:

U.S. Customs Inspector:

The U.S. Food and Drug Administration (FDA) has requested samples of (PRODUCT) from (Company Name) for the analysis by (Designated Laboratory). We are testing the product in connection with a (n Abbreviated) New Drug Application that has been filed with the Food and Drug Administration.

For this reason we are requesting that the U.S. Customs Inspector refrain from opening the immediate container. If for some reason the immediate container must be opened, please contact my office so that the sample can be opened in the presence of an FDA representative.

If there are any questions regarding this request, please contact me by telephone at (Telephone) or by fax (Fax Number).

Sincerely,

District Director/DFI Drugs Coordinator/DFS

ATTACHMENT B-5 - EXAMPLE OF MEMORANDUM SOLICITING INNOVATOR SAMPLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Laboratory Name
Laboratory address
Telephone:
Fax:

Date:

Firm's Name & Address

Dear Sir/Madam:

The U.S. Food and Drug Administration (FDA) will be performing profile studies on (Product Name and Strength) in connection with an Abbreviated New Drug Application that has been filed. These tests will enable the FDA to determine that bioequivalence testing was performed appropriately. In order to rule out substitution or other manipulations, we would like a sample of your product, which was used for comparison in this testing.

In order to perform the necessary studies, we ask that you provide us with a sample of not less than 20 units each, along with the batch formulas for the lots being sent.

Please forward these materials within ten days of receipt of this letter via express or overnight mail to:

Laboratory Name and Address
Attn: Contact Name

Thank you in advance for your cooperation. Please do not hesitate to call or fax if you have any questions. You may contact me directly by telephone at (Telephone) or by fax (Fax Number).

Sincerely,

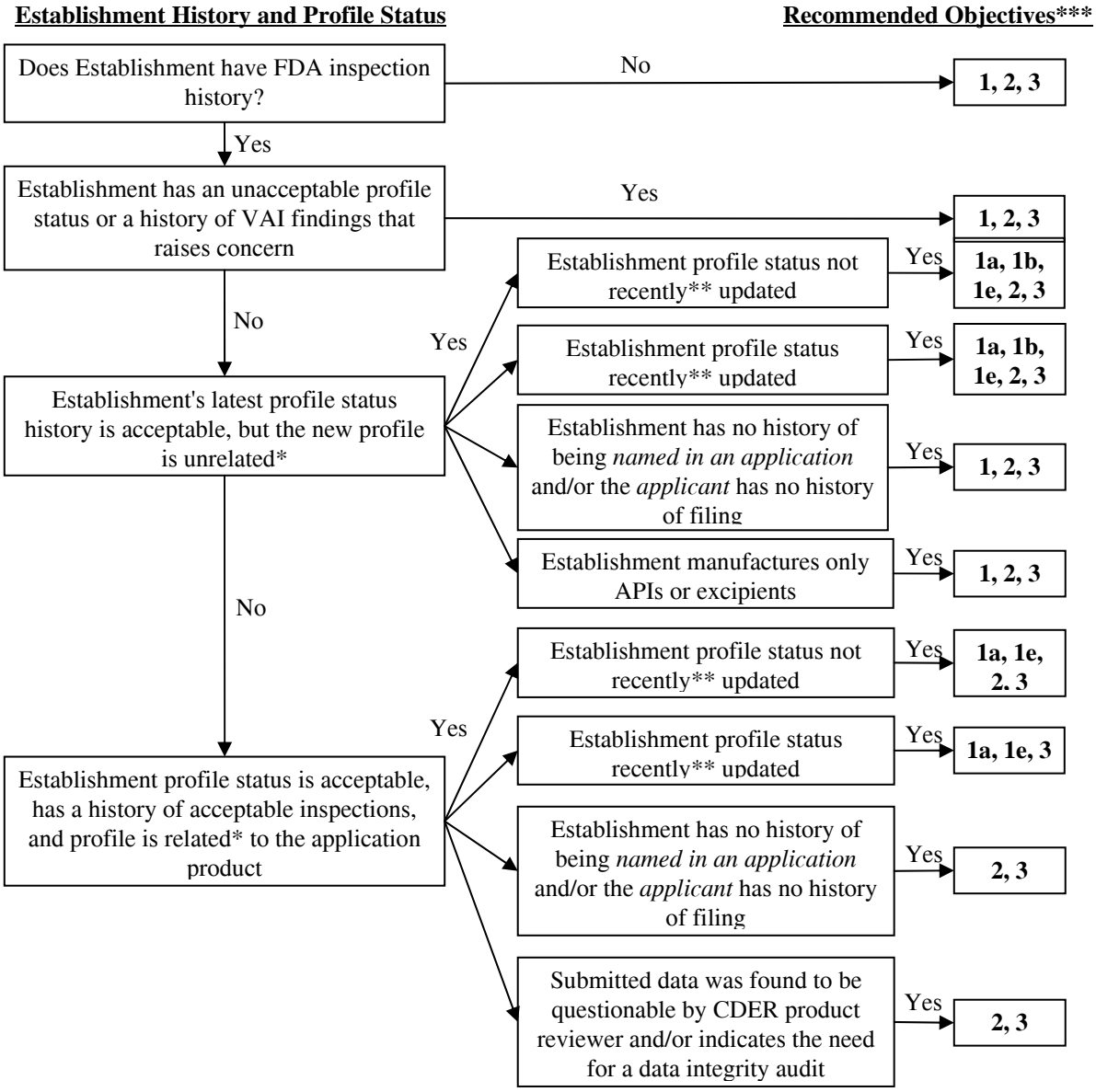
Laboratory Contact/Coordinator/Director

ATTACHMENT C - RECOMMENDED SCOPE OF COVERAGE FOR A PRIORITY PRE-APPROVAL INSPECTION

If one or more Priority Pre-Approval Inspection Criteria is met and the district recommends that a PAI should be performed, at least one objective must be addressed during the PAI. Based on the specific responsibilities of the establishment to be inspected and the difference between profile classes, the district determines the degree of coverage. The district should use this Attachment as a guide and apply additional coverage if there are overlaps.

For example, if an establishment has a recently updated and acceptable profile status related to the application product yet has a history that lends concern from VAI findings, the district should cover Objectives 1, 2, and 3. As a second example, if an establishment only meets the Priority criteria because the application product is a new molecular entity and the profile status is related and recently updated, coverage of Objectives 1 and 3 is recommended. Finally, in the event that the API is derived from animal tissues, this high risk situation merits coverage of all three objectives.

Figure 1: Recommended Scope of Coverage for a Priority Pre-Approval Inspection



*Refer to the *Related Profiles* section in **Part 3.3, Inspection/Audit Strategy**.
**The term "recently" is used consistently with Priority Pre-Approval Criteria #9, in that the profile has been updated within the past 2 years (or 3 years for control laboratories and 4 years for packaging and labeling).
***When Objective 1 is listed, all subparts should be included.