Generic Drug User Fee Act Program Performance Goals and Procedures

The performance efficiencies, metric goals and procedures to which FDA will agree upon commencement of a generic drug user fee act (GDUFA) program ("the program"), as jointly proposed by FDA and industry, are summarized below.

Overall Purpose of the Generic Drug User Fee Program:

To help FDA ensure that participants in the U.S. generic drug system comply with U.S. quality standards, and to increase the likelihood that American consumers get timely access to low cost, high quality generic drugs, FDA and industry have jointly agreed to a comprehensive user fee program, to be supplemental to traditional appropriated funding, that is focused on three key aims:

Safety – Ensure that industry participants, foreign or domestic, who participate in the U.S. generic drug system are held to consistent high quality standards and are inspected biennially, using a risk-based approach, with foreign and domestic parity.

Access – Expedite the availability of low cost, high quality generic drugs by bringing greater predictability to the review times for abbreviated new drug applications, amendments and supplements, increasing predictability and timeliness in the review process.

Transparency - Enhance FDA's ability to protect Americans in the complex global supply environment by requiring the identification of facilities involved in the manufacture of generic drugs and associated active pharmaceutical ingredients, and improving FDA's communications and feedback with industry in order to expedite product access.

Recognizing the critical role generic drugs play in providing more affordable, therapeutically equivalent medicine, the Generic Drug User Fee program is designed to keep individual fee amounts as low as possible to supplement appropriated funding to ensure that consumers continue to receive the significant benefits offered by generic drugs which provided more than $824 billion dollars in savings to the nation's health care system in the last decade alone.[1] The additional resources called for under the agreement, an inflation adjusted $299 million annually for each of the five years of the program, will provide FDA with the ability to perform critical program functions that could not otherwise occur. This program is not expected to add significantly to the cost of generic drugs: given that a reported 3.99 billion retail prescriptions per year were dispensed in the United States in 2010[2], and assuming that 78% of these prescriptions were filled

[1] Source: IMS Health Report – GPHA. Savings achieved through the use of generic pharmaceuticals: 2000-2009, July 2010.

[2] Source: "The Use of Medicines in the United States: Review of 2010", Report by the IMS Institute fore Healthcare Informatics, slide 8, available at http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMed_report.pdf.

by generic drugs,[3] it equates to less than a dime per prescription for the average cost of a prescription filled by a generic drug in the United States. Moreover, with the adoption of user fees and the associated savings in development time, the overall expense of bringing a product to market may decline and result in reduced costs.

In addition to the public health benefits outlined above, the program described in this letter is expected to provide significant value to small companies and first time entrants in the generic market who will benefit significantly from the certainty associated with performance review metrics that offer the potential to dramatically reduce the time needed to commercialize a generic drug when compared to pre-GDUFA review times.

In addition, the variety of funding sources for the program will assure that participants in the generic drug industry, whether finished dosage form (FDF) manufacturers or Active Pharmacuetical Ingredient (API) manufacturers appropriately share the financial expense and benefits of the program. Given that the total amount of annual user fee funding is expected to be derived from a broad funding source, including an estimated 2000 FDF and API facilities supporting Abbreviated New Drug Applications (ANDAs), as well as approximately 750 ANDAs, 750 prior approval supplements (PASs) and 350 Type II Active Pharmaceutical Drug Master Files (DMFs) annually, user fees are expected to provide a measurable return on investment related to predictability of inspection, and review timelines. The program's goals of ensuring FDA has necessary resources to conduct needed inspections as part of the complete review framework and achieve parity of Good Manufacturing Practice (GMP) inspections for foreign and domestic facilities by the 5th year of the user fee program will also provide significant value to industry participants given that outstanding inspections can result in delays of ANDA approvals.

Taken collectively, the user fee program and associated performance metrics and fees are expected to provide measurable public health benefits and are not expected to competitively disadvantage any company or business sector regardless of size or location.

1.) OVERVIEW

Overall Program Scope, Assumptions, and Aspirations

The goals to which FDA is committing for generic drugs are premised on the following assumptions:

I.) Funding for the program from user fees will be at agreed-upon levels of approximately $299 million annually adjusted for inflation and will supplement appropriated funding from Congress as described further below.

[3] Ibid, slide 22.

II.) It is estimated that FDA will receive the funding through approximately 750 abbreviated new drug applications (ANDAs) per year submitted electronically, approximately 750 prior approval supplements (PASs) approximately 350 newly referenced drug master files (DMFs) per year and through approximately 2000 facilities associated with ANDAs. While the total revenue collected can be defined in advance and is constant as the resourcing level must be constant, the individual fee will be determined each year based on the variability of the fee source.

III.) Over the five year course of the program, there will be no significant changes in the generic drug facility inventory, either in terms of general number of facilities, or the foreign and domestic facility split.

IV.) FDA will have streamlined hiring authority for all GDUFA-related positions prior to or concurrent with the implementation date of the program.

V.) FDA expects the program will be implemented starting on the first day of Fiscal Year 2013, October 1, 2012 and continue for five years, with the joint expectation that the program will be continued at the end of five years under terms to be negotiated before the end of FY 2017.

VI.) Industry and FDA will populate and maintain databases as necessary for facilities, fee assessments, efficiency and other enhancements as described further below and as needed to support the Generic Drug User Fee Act. Because certain databases to implement this program will need to be built, and existing systems need to be expanded or modified, industry will submit necessary information in electronic format to FDA using appropriate standards to be specified by the agency or as specified in statute.

VII.) FDA will aspire to the extent possible to maintain levels of productivity at least similar to pre-GDUFA levels, while hiring and training incremental staff necessary to achieve the program performance goals, building necessary systems and implementing outlined program changes in years 1 and 2 of the program (see goals for years 3-5 metrics).

VIII.) FDA will utilize a complete review standard (as defined below), will aspire to hold first cycle deficiency teleconferences with industry to discuss complete response questions at a level at least similar to pre-GDUFA levels in years 1 and 2 of the program (see goals for years 3-5 metrics) and will utilize an approach similar to the NDA review process whereby FDA uses telephone information requests to address easily correctable deficiencies during the review process before and after issuance of complete response letters.

IX.) FDA will aspire to complete reviews for applications with only minor administrative amendments pending prior to the expiration date of the controlling patent or applicable exclusivity date regardless of the amendment(s) goal date.

X.) FDA will work towards achieving performance goals to reach parity of GMP inspections of foreign and domestic establishments, will prioritize inspections using a risk-based

approach, and will prioritize inspections of establishments associated with ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection, as well as establishments associated with ANDAs that have not been inspected previously. In appropriate circumstances FDA can rely on a routine surveillance inspection in lieu of an application-specific inspection. Generally, among other considerations, FDA relies on a previous inspection of a finished product site occurring within 2 years of the current good manufacturing practice (CGMP) evaluation for a pending application, 3 years for an active pharmaceutical ingredient (API) site or a control testing laboratory, and 4 years for a packaging-only site. There are exceptions to this general practice, which are usually related to the nature of the drug being processed or the complexity of the associated processing operations. FDA intends to continue the practice of using a risk-based assessment in determining the length of time since the last inspection, guided by a 2-year cycle for finished dosage product sites and a 3-year cycle for API sites and consideration of the type of finished product or API in the application. Practically, this means that in making decisions about pending applications for which FDA does not have current inspection information within the time period indicated, FDA may use previous FDA inspection information and/or use inspection information from another regulatory authority as appropriate.

XI.) FDA will strive to review and act on all ANDAs that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted within 30 months of submission to avoid causing first applicants to inadvertently forfeit 180-day exclusivity eligibility under 21 U.S.C. § 355(j)(5)(D)(i)(IV).

XII.) Because the agreed generic drug user fee program is intended to be additive to budget appropriations, agreed upon legislative language will require that annual program appropriations from Congress must be equal to or exceed the FDA appropriation for FY 2009.

XIII.) In order to generate the agreed upon levels of user fee funding to achieve the enclosed performance goals, metrics and efficicienies, legislative language will require that approximately 70% of GDUFA fees shall be derived from facility fees (for facilities producing or pending review to produce active pharmaceutical ingredients or finished dosage forms for a generic drug application), approximately 30% of GDUFA fees shall be derived from application fees (DMF Fees and ANDA and PAS (Prior Approval Supplement) Fees). As discussed and agreed by the various industry business segments, overall fees will be divided 80 percent to 20 percent between the finished dosage form (FDF) and API and manufacturers, respectively in industry. In the first year of the program, $50 million of the total GDUFA user fee funding shall be generated by a one time backlog fee for ANDAs pending (except for ANDAs that are pending but have received tentative approval) on October 1, 2012.

XIV.) For appeals of decisions concerning procedural or scientific matter involving review of pending ANDAs, ANDA amendments and ANDA supplements FDA will aspire that the

response to appeals of decisions will occur within 30 calendar days of OGD receipt of the written appeal when possible, though no reportable performance goals are required.

Note: If these assumptions differ significantly from actuality, FDA may not be able to achieve the goals and efficiency enhancements outlined in this goals letter, despite the supplemental funding provided by the program.

Summary of Major Program Goals including Five Year Goals

Major Program (including 5 year) goals can be summarized as follows[1]:

Application metrics *– For Abbreviated New Drug Applications (ANDAs) in the year 5 cohort, FDA will review and act on 90 percent of complete electronic ANDAs within 10 months after the date of submission. Certain amended applications may have differing metrics as discussed below.*

Backlog metrics *– FDA will review and act on 90 percent of all ANDAs, ANDA amendments and ANDA prior approval supplements regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012 by the end of FY 2017.*

CGMP Inspection metrics *– FDA will conduct risk-adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.*

Efficiency Enhancements *– FDA will implement various efficiency enhancements discussed below on October 1, 2012 or upon enactment of the program, whichever is later.*

Regulatory Science *– FDA will continue, and for some topics begin undertaking various regulatory science initiatives discussed below on October 1, 2012 or upon enactment of the program, whichever is later, focusing first on the initiatives discussed below and with additional initiatives to be identified with input from an industry working group.*

Details follow.

[1] Note that FDA agrees to additional 5 year goals, as set forth later in this goals letter, such as goals on amendments, controlled correspondence, and prior approval supplements, as well as goals for years prior to year 5 of the program. The goals summarized in this section are a subset of the complete year 5 goals, and are intended simply to illustrate the scope of the program.

2.) EFFICIENCY ENHANCEMENTS TO BE UNDERTAKEN ON OCTOBER 1, 2012, OR UPON ENACTMENT OF THE PROGRAM, WHICHEVER IS LATER.

A.) ANDA Review Efficiency Enhancements

- Starting on October 1, 2012 or upon enactment of the program, whichever is later, FDA will issue complete response letters, rather than discipline specific letters, for all ANDAs, including those pending on October 1, 2012.

- Complete response letters will reflect full division-level review of deficiencies from all relevant review disciplines, including inspections, and address other matters relating to the ANDA and associated DMFs as well as consults with other agency components (these will be subsumed into the application metrics).

- FDA reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in the ANDA and will utilize an approach similar to the NDA review process whereby FDA uses telephone information requests to address easily correctable deficiencies during the review process before and after issuance of complete response letters.

- When requested by the ANDA sponsor within 10 business days of FDA issuing a first cycle complete response letter, as provided by the sponsor in a written request that outlines specific written questions the applicant would like to discuss (limited to the content of the letter), FDA will schedule a 30 minute teleconference to clarify issues and answer questions. Priority for such teleconferences will be given to expedited and first major amendment applications. Although FDA will begin to develop procedures and tracking systems for such teleconferences coincident with the start of the program, there will be no teleconference goals for the first two years of the program although FDA will aspire to conduct such teleconferences as requested when reportable performance goals are not otherwise required. In the first two years, FY 2013 and FY 2014, FDA would aspire to hold teleconferences with industry to address complete response questions at a level similar to pre-GDUFA levels. Subsequently, the goals for number of reportable teleconferences (although FDA may conduct more such teleconferences) will be:

    - Closing out the teleconference request for 200 meetings in FY 2015;
    - Closing out the teleconference request for 250 meetings in FY 2016;
    - Closing out the teleconference request for 300 meetings in FY 2017.

- FDA will develop enhanced refusal to receive standards for ANDAs and other related submissions by the end of year 1 of the program and will publish such standards in advance of implementation.

- For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted. Expedited review will be implemented consistent with existing

procedure for expediting applications as set forth in CDER's MAPP 5240.3, and will also include those applications that become eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.

- Review metric goals (described below) only apply to submissions made electronically, following the eCTD format in effect at the date of submission.

- Backlog review metric goals (described below) apply to all ANDA applications, amendments, and supplements regardless of current review status in the queue as of October 1, 2012, regardless of whether they were submitted in paper, electronic, or hybrid format.

B.) Drug Master File (DMF) Review Efficiency Enhancements

- After the program's implementation date, upon payment of the DMF fee by DMF holders anticipating reference by a generic drug manufacturer, FDA will conduct a completeness assessment of Type II API DMFs. Following a satisfactory completeness assessment, FDA will deem the DMF available for reference, placing the DMF number in a publicly available list of Type II API DMFs available for reference.

- Review metric goals (described below) will only apply to Type II API DMFs submitted after the program's implementation date, if they are submitted electronically. Electronic DMFs will follow the eCTD format in effect at date of submission.

- FDA will issue a letter detailing all identified deficiencies, rather than discipline specific letters, for all DMFs including those under review at the time of enactment of the implementing legislation.

- The DMF deficiency letters will reflect full division-level deficiency review of deficiencies from all relevant review disciplines, including inspections, and address other matters relating to the DMF review such as consults with other agency components (these will be subsumed into the DMF metrics).

- FDA reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in the DMF and will continue to utilize an approach similar to the NDA review process whereby FDA uses telephone information requests to address easily correctable deficiencies during the review process before and after issuance of complete response letters.

- When requested by a DMF holder within 10 business days of FDA issuing a first cycle DMF deficiency letter, as provided by the DMF holder in a written request that outlines specific written questions the DMF holder would like to discuss (limited to the content of the letter), FDA will schedule a 30 minute teleconference with a limit of one teleconference per DMF holder per month, with the total number of teleconferences not to exceed the number of teleconferences for ANDAs, a teleconference to clarify issues and answer questions. Priority

- Once a DMF has undergone a complete review and the ANDA referencing same is either approved or tentatively approved – at such time there being no further outstanding deficiencies to the DMF – FDA will issue the DMF holder a letter to indicate that the DMF does not have any further open matters as part of the review associated with the referencing ANDA.

C.) Inspection Efficiency Enhancements

- To maximize the number of applications that can be reviewed within the metric goals and to assist in securing the pharmaceutical supply chain, FDA will employ a risk-adjusted biennial CGMP surveillance inspection model for inspection of generic API and FDF manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic establishments in FY 2017 and will prioritize inspections of establishments associated with ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection, as well as establishments that have not been inspected previously.

- FDA will make inspection classification results and date of the last facility inspection available to the public and industry on FDA's website on timely basis.

- During the five years of the program, FDA will undertake a study of foreign government regulator inspections (CGMP and bioequivalence), report findings publicly, and develop a program to utilize foreign inspection classifications when and where appropriate.

D.) Other Efficiency Enhancements

- FDA will develop new and/or enhance existing facility databases (API and FDF manufacturing and clinical/ bioequivalence site) to be populated by industry. These databases will, at a minimum, contain information for generics-related firms, including addresses and Data Universal Numbering System (DUNS) numbers, and will link facilities to DMFs and ANDAs and will contain other information as necessary.

- FDA will develop a current chemistry manufacturing and controls (CMC) records database to aid in the efficiency of review and inspection.

- FDA will develop and issue electronic data submission standards.

- Because certain databases to implement this program will need to be built, and existing systems need to be expanded or modified, industry will submit necessary information in electronic format to FDA using appropriate standards to be specified by the agency or as specified in statute.

3.) REGULATORY SCIENCE INITIATIVES

A.) Working Group

- FDA will convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER Director.

B.) FY 2013 Plan

- The FY 2013 plan is appended.

4.) METRIC GOALS/MEASUREMENTS

A.) Human Resources Metrics

- FDA will hire and train at least 25 percent of incremental staff in FY 2013, 50 percent in FY 2014 and will strive to complete GDUFA-funded human resources hiring goals in FY 2015 as necessary to achieve the program's performance metrics and goals.

B.) ANDA, ANDA Amendment, and ANDA Prior Approval Supplement Review Metrics and DMF Reviews as Subsumed in Each

- ANDAs will be categorized according to cohort year.

- Once an ANDA is in a given year's cohort, dates of submission of a subsequent amendment will not change the cohort year. Regardless of the year in which an amendment is submitted, any additional time periods to be added to the base review period will be calculated using the time periods corresponding to the original cohort year.

- Original (complete) ANDA Review (Certain amended applications may have differing metrics as discussed below.)
    - FDA will review and act on 60 percent of original ANDA submissions within 15 months from the date of submission for the year 3 cohort.
    - FDA will review and act on 75 percent of original ANDA submissions within 15 months from the date of submission for the year 4 cohort.
    - FDA will review and act on 90 percent of original ANDA submissions within 10 months from the date of submission for the year 5 cohort.

- For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.

- Amendment Review
  - All amendment metric goals are incremental, and the time periods specified are calculated from the date of submission. They will be added to the original review goal, but in no case shall they shorten the original goal date. (In other words, an amendment with a 6 month metric which was submitted 4 months prior to original goal date would add 2 months to the review clock).
    - An amendment pre Complete Response Letter adjusts the goal date for the original application.
      - Subsequent amendments pre Complete Response Letter also adjust the goal date for the application and are additive.
    - An amendment post Complete Response Letter sets a new goal date for the application.
      - Subsequent amendments post Complete Response Letter also adjust the goal date for the application and are additive.
  - Delaying amendments or amendments containing information that FDA would otherwise ask for as a result of post ANDA submission reference listed drug changes do not add to the count of amendments.
  - If any amendment contains multiple elements, the longest goal date shall apply.
  - Amendments shall be grouped as Tier 1, Tier 2 or Tier 3. FDA agrees that unsolicited amendments that are submitted to a pending ANDA that are neither Tier 1, Tier 2 or Tier 3 amendments, but rather are routine or administrative in nature and do not require scientific review (e.g., requests for final ANDA approval, patent amendments, general correspondence, and USP monograph updates), will not lengthen or impact the original review goal date.

    - Tier 1 amendments include:
      - All solicited first major and the first five minor amendments
      - All unsolicited amendments indicated by sponsor and agreed by FDA to be a result of either delaying actions as determined by FDA's Office of Generic Drugs taking into account the facts and information supplied by the ANDA applicant or that otherwise would eventually be solicited.

    - Tier 2 amendments include:
      - All unsolicited amendments not arising from delaying actions as determined by FDA's Office of Generic Drugs taking into account the facts and information supplied by the ANDA applicant excepting those amendments which only remove information for review.

    - Tier 3 amendments include:

- Any solicited major amendment subsequent to the first major amendment
- Any solicited minor amendment subsequent to the fifth minor amendment

- Tier 1 amendment goals:
  - First major amendment
    - FDA will review and act on 60 percent of first major amendment submissions within 10 months from the date of submission for the year 3 cohort.
    - FDA will review and act on 75 percent of first major amendment submissions within 10 months from the date of submission for the year 4 cohort.
    - FDA will review and act on 90 percent of first major amendment submissions within 10 months from the date of submission for the year 5 cohort.
  - Minor amendments (first – third)
    - FDA will review and act on 60 percent of first through third minor amendment submissions within 3 months from the date of submission for the year 3 cohort.
    - FDA will review and act on 75 percent of first through third minor amendment submissions within 3 months from the date of submission for year 4 cohort.
    - FDA will review and act on 90 percent of first through third minor amendment submissions within 3 months from the date of submission for the year 5 cohort.
  - Minor amendments (fourth - fifth)
    - FDA will review and act on 60 percent of fourth through fifth minor amendment submissions within 6 months from the date of submission for the year 3 cohort.
    - FDA will review and act on 75 percent of fourth through fifth minor amendment submissions within 6 months from the date of submission for year 4 cohort.
    - FDA will review and act on 90 percent of fourth through fifth minor amendment submissions within 6 months from the date of submission for the year 5 cohort.
  - Except that if any Tier 1 amendment requires an inspection, the goal shall be 10 months.

- Tier 2 amendment goals:
    - FDA will review and act on 60 percent of amendment submissions within 12 months from the date of submission for the year 3 cohort.

- FDA will review and act on 75 percent of amendment submissions within 12 months from the date of submission for year 4 cohort.
- FDA will review and act on 90 percent of amendment submissions within 12 months from the date of submission for the year 5 cohort.

- Tier 3 amendment goals:
  - There will be no GDUFA metrics for tier 3 amendments.

- Review of Complete Prior Approval Supplements (PASs) (Certain amended PASs may have differing metrics as discussed above in the Amendment Review section).
  - FDA will review and act on 60 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2015; FDA will review and act on 60 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2015.
  - FDA will review and act on 75 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2016; FDA will review and act on 75 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2016.
  - FDA will review and act on 90 percent of PASs not requiring inspection within 6 months from the date of submission for receipts in FY 2017; FDA will review and act on 90 percent of PASs requiring inspection within 10 months from the date of submission for receipts in FY 2017.

C.) Controlled Correspondence Metrics

- Controlled Correspondence
  - FDA will respond to 70 percent of controlled correspondence in 4 months from date of submission in FY 2015.
  - FDA will respond to 70 percent of controlled correspondence in 2 months from date of submission in FY 2016.
  - FDA will respond 90 percent of controlled correspondence in 2 months from date of submission in FY 2017.
  - If the controlled correspondence requires input from the clinical division, one additional month will be added to the goals outlined above.

- In the case of controlled correspondence which raises an issue or question that is the same as or related to the issue or question that is the subject of one or more pending citizen petitions, or petitions for stay or reconsideration, the above goals will apply from the date FDA issues responses to the pending petitions.

D.) CGMP Inspection metrics

- FDA will conduct risk-adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

E.) Backlog metrics

- FDA will review and act on 90 percent of all ANDAs, ANDA amendments, and ANDA prior approval supplements regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012 by the end of FY 2017**.**

Definitions

For the purposes of this goals letter:

Act on an application - means FDA will either issue a complete response letter, an approval letter, a tentative approval letter for an ANDA, or a refuse to receive action.

Active pharmaceutical ingredient -- means
(A) a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended to be used as a component of a drug and intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or
(B) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become the final active pharmaceutical ingredient as defined in paragraph (A).

Backlog – refers to the queue of pending ANDAs, ANDA amendments and ANDA supplements pending as of October 1, 2012.

Delaying amendments – refers to amendments to an ANDA from the ANDA sponsor to address actions by a third party that would cause delay or impede application review or approval timing and that were not or may not have been initially recognized by FDA as necessary when the application was first submitted. FDA's Office of Generic Drugs shall have broad discretion to determine what constitutes a delaying event caused by actions generally outside of the applicants control taking into account facts and information supplied by the ANDA sponsor.

Closing out a request for a first cycle review teleconference - means: 1) holding the teleconference; or 2) responding to questions in the sponsor's teleconference request in writing in lieu of holding the teleconference.

Cohort – The program is structured based on 5 cohorts of submission dates (original ANDAs, PASs and DMFs), corresponding to the five fiscal years to be covered by the program. The year 1 cohort refers to the dates of submissions made electronically in FY 2013 (October 1, 2012 to September 30, 2013). The year 2 cohort refers to the dates of submissions made electronically in FY 2014 (October 1, 2013 to September 30, 2014). The year 3 cohort refers to the dates of submissions made electronically in FY 2015 (October 1, 2014 to September 30, 2015). The year 4 cohort refers to submissions made electronically in FY 2016 (October 1, 2015 to September 30, 2016). The year 5 cohort refers to submissions made electronically in FY 2017 (October 1, 2016 to September 30, 2017).

Complete response letter - refers to a written communication to an applicant or DMF holder from FDA usually describing all of the deficiencies that the agency has identified in an abbreviated application (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. Complete response letters will reflect a complete review and will require a complete response from industry to restart the clock. Refer to **21 CFR 314.110** and

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm for additional details. When a citizen petition may impact the approvability of the ANDA, FDA will strive to address, where possible, valid issues raised in a relevant citizen petition in the complete response letter. If a citizen petition raises an issue that would delay only part of a complete response, a response that addresses all other issues will be considered a complete response.

Complete review – refers to a full division-level review from all relevant review disciplines, including inspections, and includes other matters relating to the ANDA and associated DMFs as well as consults with other agency components.).

Controlled correspondence - FDA'S Office of Generic Drugs provides assistance to pharmaceutical firms and related industry regarding a variety of questions posed as "controlled documents." See http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm120610.htm Controlled correspondence does not include citizen petitions, petitions for reconsideration or requests for stay.

DMF or **Type II Active Pharmaceutical Ingredient Drug Master File** -- means a submission of information to the Secretary by a person that intends to authorize the Food and Drug Administration to reference the information to support approval of a generic drug submission without the submitter having to disclose the information to the generic drug submission applicant.

Electronic– refers to submissions in an all electronic eCTD format in effect at the date of submission.

Expedited review of application – While generally, review of original ANDAs, ANDA amendments and ANDA supplements are reviewed in the order received, (first-in, first-reviewed), certain applications may be identified at the date of submission for expedited review, as described in CDER's MAPP 5240.3. (See http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf) which includes expedited review of the orginial submission and amendment(s) associated with the expedited review qualifying application. Products to respond to current and anticipated public health emergencies, products under special review programs, such as the President's Emergency Plan for AIDS Relief (PEPFAR), products for which a nationwide shortage has been identified, and first generic products for which there are no blocking patents or exclusivities on the reference listed drug currently may qualify for expedited review. For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.

Facility -- means business or other entity under one management either direct or indirect and at one geographic location or address engaged in manufacturing or processing an active pharmaceutical ingredient or a finished dosage form, but does not include a business or other entity whose only manufacturing or processing activities are one or more of the following: repackaging, relabeling, or testing. For purposes of this definition, separate buildings within close proximity are

considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and are capable of being inspected by the Food and Drug Administration during a single inspection.

Finished Dosage Form – means
(A) a drug product in the form in which it will be administered to a patient, such as a tablet, capsule, solution, or topical application;
(B) a drug product in a form in which reconstitution is necessary prior to administration to a patient, such as oral suspensions or lyophilized powders; or
(C) any combination of an active pharmaceutical ingredient, as defined in paragraph (m)(2), with another component of a drug product for purposes of production of such a drug product.

First major deficiency application - means an ANDA which has been issued its first complete response letter classified as having major deficiency(ies).

Generic Drug Program – refers to all agency activities related to the determination of approvability of an ANDA.

Major and minor amendments – All references to "major" and "minor" amendments in this goals letter are intended to refer to the distinctions that FDA described in its Guidance for Industry: Major, Minor, Telephone Amendments to Abbreviated New Drug Applications. See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072888.pdf

Parity – in reference to inspections, as between foreign and domestic facilities, means inspection at an equal frequency plus or minus 20 percent with comparable depth and rigor of inspection.

Refuse to receive – means refusal to file an application. See 21 CFR 314.101 and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080561.pdf 1993

Solicited amendment -- an amendment submitted in response to a Complete Response letter.

Submission date – is the date an ANDA, ANDA amendment, ANDA supplement, or Type II active pharmaceutical drug master file arrives in the appropriate electronic portal of the FDA.

Prior Approval Supplements - A prior approval supplement is a submission to allow a company to make a change in a product that already has an approved ANDA. CDER must approve all important ANDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are still met.
(Source: http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#S)

Unsolicited amendment – an amendment with information not requested by the FDA except for those unsolicited amendments considered routine or administrative in nature and that do not require scientific review (e.g., requests for final ANDA approval, patent amendments, general

correspondence, and USP monograph updates).

FY 2013 Regulatory Science Plan

Topic 1: Bioequivalence of local acting orally inhaled drug products
Impact: Continue to develop new and improved PD endpoints and study designs or establishment of alternative approaches to ensure equivalent local delivery of orally inhaled drug product to the lung would lead to more efficient development of generic products in a sector that lacks any generic competition

Topic 2: Bioequivalence of local acting topical dermatological drug products
Impact: Continue developing new bioequivalence methods in order to reduce the need for relatively insensitive clinical endpoint bioequivalence studies. Development of in vitro release tests or other product characterization to ensure consistent drug release or product performance

Topic 3: Bioequivalence of local acting gastro-intestinal drug products
Impact: Developing new bioequivalence methods for direct measurement of drug concentrations in the GI tract and establishing better correlations between pharmacokinetic measurements and GI concentration would allow more efficient demonstration of bioequivalence than by clinical endpoint studies.

Topic 4: Quality by design of generic drug products
Impact: Continue developing science-based recommendations for product development, raw material, APIs and process controls, and life-cycle management of complex dosage forms (e.g. orally inhaled drug products and modified-release dosage forms)

Topic 5: Modeling and simulation
Impact: Modeling and simulation (including in-vitro and in-vivo correlations) is essential to efficient implementation of quality by design and can help to identify and eliminate unneeded in-vitro and/or in-vivo studies. Models (PK/PD, exposure-response, clinical use simulation) support generic drug evaluation policies especially for NTI drugs and complex products.

Topic 6: Pharmacokinetic studies and evaluation of anti-epileptic drugs
Impact: Improving public confidence in bioequivalent generic epilepsy drugs.

Topic 7: Excipient effects on permeability and absorption of BCS Class 3 Drugs
Impact: Extension of biowaivers to BCS Class 3 Drugs and eliminating the need for unnecessary in vivo bioequivalence studies

Topic 8: Product- and patient-related factors affecting switchability of drug-device combination products (e.g., orally inhaled and nasal drug products and injection drug products)
Impact: Establishing a systematic, science- and risk-based approach to ensure device switchability, and improving the patient's compliance and acceptability of generic devices

Topic 9: Postmarketing surveillance of generic drug usage patterns and adverse events.

Impact: Improved data collection about usage patterns (which strengths are used in which populations, extent of switchability, back switches to RLD products, medication errors) will be fed back into regulatory policy development including those for excipients and impurities. Baseline data collection on adverse event reports on switching to an authorized generic would improve the ability to investigate reports.

Topic 10: Evaluation of drug product physical attributes on patient acceptability
Impact: Laboratory and human studies on physical attributes such as tablet size, shape, coating, odor perception (residual solvents), score configuration, taste masking or color on the ability of patient to use (for example swallow) or perceive quality (for example smell) will allow OGD to provide better guidance to applicants on how these physical attributes should be controlled and compared to the RLD.

Topic 11: Postmarking assessment of generic drugs and their brand-name counterparts
Impact: Stronger public confidence in generic drugs because of pro-active responses to product concerns. An integrated response to product concerns involving laboratory investigations and post-marketing data collection.

Topic 12: Physicochemical characterization of complex drug substances
Impact: Developing analytical methods for demonstrating pharmaceutical equivalence for complex drug substances (non-small molecules) characterized by natural source origin, polydisperse mixture, and/or supramolecular structure, and therefore expanding the boundary of the generic drug program for these complex drug products

Topic 13: Develop a risk-based understanding of potential adverse impacts to drug product quality resulting from changes in API manufacturing and controls.
Impact: The ability to predict the potential impacts of manufacturing changes on product quality will allow manufacturers to target assessments and controls on high-risk areas for regulators to focus their reviews on these areas too.

FY 2014 Regulatory Science Preliminary Topics for Consideration

In addition to those topics to be identified by the Working Group described in section 3.A of this letter, topics will include recommendations for draft guidances to clarify FDA recommendations with regard to complex product development and to help limit deficiencies in applications.