



U.S. Food and Drug Administration

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Considerations for PET ANDAs

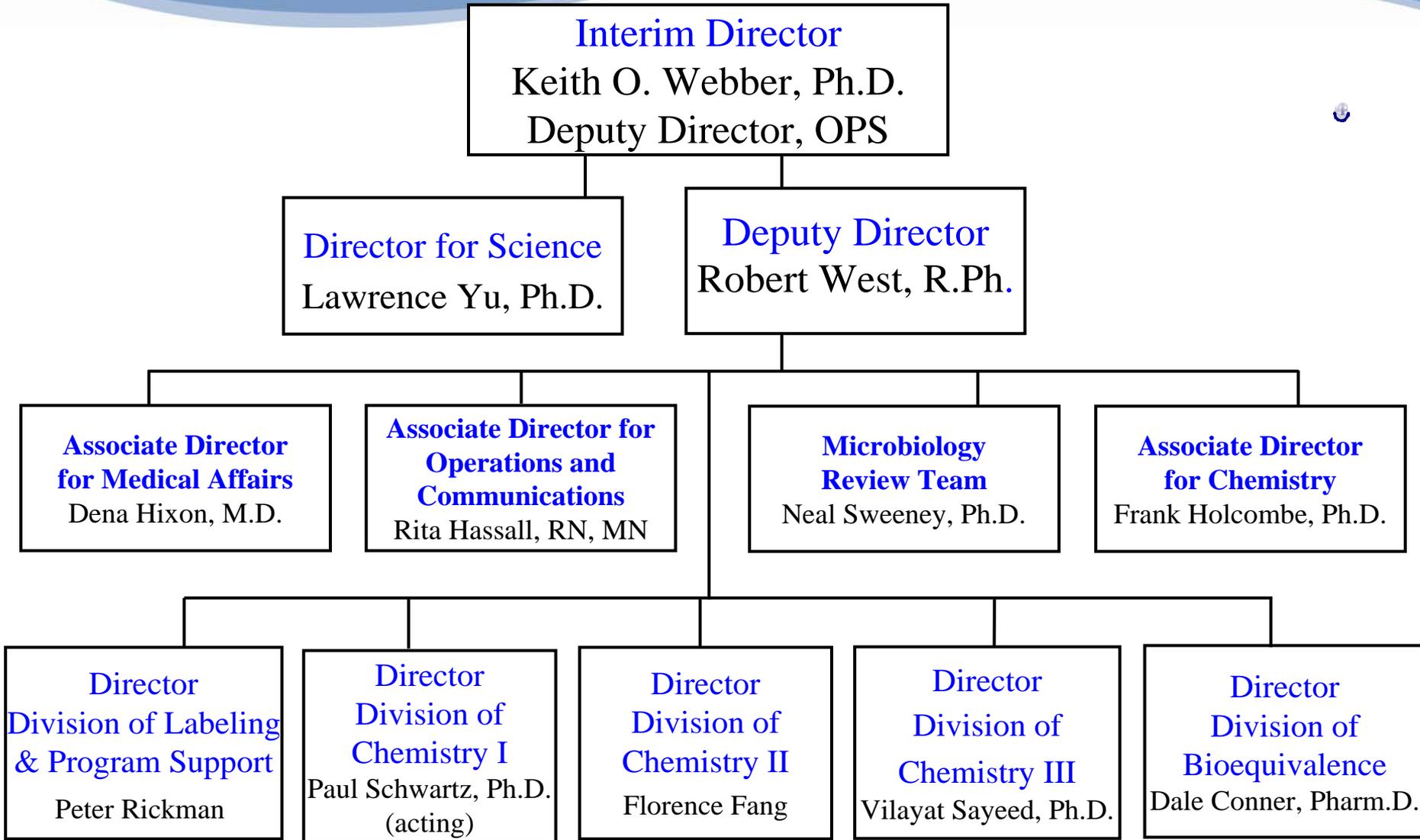
Capt. Martin Shimer
Office of Generic Drugs

March 2, 2011

Agenda

- Office of Generic Drugs (OGD):
background information
- Submission requirements for an ANDA
- Approval process and ANDA formatting
- Labeling requirements for ANDAs
- Resources

Office of Generic Drugs



OGD Facts

- OGD receives approximately 800 ANDAs each year.
- There are currently NO user fees assessed for the review of ANDAs.
- All CMC reviews for PET products are coordinated by Chemistry Team 41 within Chemistry Division IV.
- CMC reviews for PET original ANDAs are consulted to the Office of New Drug Quality Assessment (ONDQA)
- Branch V of the Division of Pre-marketing Assessment completes the CMC review, OGD completes BE, micro and labeling reviews.

What are the requirements for a generic drug?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use

Compared to reference listed drug (RLD) - (previously approved product)

Key Point -

To submit an ANDA, there must be a reference listed drug (RLD).

Current RLDs for FDG in the Orange Book

Active section of Orange Book

-NDA 21870 Fludeoxyglucose F-18 20-200 mCi/mL Feinstein

-NDA 21768 Fludeoxyglucose F-18 10-100 mCi/mL Weill Medical

Discontinued section of Orange Book

-NDA 20306 Fludeoxyglucose F-18 4-40 mCi/mL Downstate Clinical

-NDA 20306 Fludeoxyglucose F-18 4-90 mCi/mL Downstate Clinical

****The Agency has already made a formal determination that the two different strengths of NDA 20306 were not discontinued for reasons of safety and/or efficacy. Therefore, these products may be cited as an RLD for an ANDA.

Current RLD for Ammonia N 13

Active Section of Orange Book

-NDA 22119 Ammonia N 13 30-300 mCi/8 mL Feinstein

Discontinued Section of Orange Book

-Not applicable



Ammonia N 13

Appl No	Prod No	ExclusivityCode	ExclusivityExpiration
<u>N022119</u>	001	<u>NCE</u>	Aug 23, 2012
<u>N022119</u>	001	<u>W</u>	Aug 23, 2012

NCE NEW CHEMICAL ENTITY

W EXCLUSIVITY ON THIS APPLICATION
EXPIRING ON THIS DATE HAS BEEN
WAIVED BY SPONSOR –

See Section 1.8 of the Orange Book Preface, Waved Exclusivity

Advice -

Carefully select your RLD. Once your ANDA is filed you **MAY NOT** amend your ANDA to reference a different RLD.

Suitability Petitions

- Differences in Strength when compared to the RLD:
 - May still be eligible for submission as an ANDA
 - 21 CFR 314.93, 10.20 and 10.30
 - SP must be approved before you may submit your ANDA
 - SP process is public
 - SP 97P-0432/CP1 has previously been approved for FDG. Copy available upon request.
 - Review of Suitability Petitions is coordinated by the OGD and takes anywhere between 60-120 days with most completed in the 90-100 day range.

Specific Requirements for Drug Products intended for Parenteral Use Submitted as ANDAs

- 314.94(a)(9)(iii)
 - Equivalence of inactive ingredients
 - Exception excipients

- Waiver requests
 - Request for waiver of the requirement to conduct in-vivo BE studies under 320.22(b)
 - (Applicant) requests that FDA waive the requirement for the submission of evidence demonstrating in vivo bioequivalence for (proposed drug product). The (proposed drug product) meets the provisions of 21 CFR 320.22(b)(1)(i) and (ii).

Patent Certifications

- All ANDAs must submit a patent certification per 21 CFR 314.94(a)(12)
 - PI through PIV
 - No relevant patents statement
 - In the opinion and to the best knowledge of [*insert applicant name*] there are no patents that claim the listed drug referred to in this application or that claims a use of the listed drug.
 - Exclusivity statements are required even if the NDA cited as the Reference Listed Drug is not protected by exclusivity. Example for NDA not protected by exclusivity:
 - According to the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) [*insert name of reference listed drug*] is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the act.

GDEA Certifications and Statements

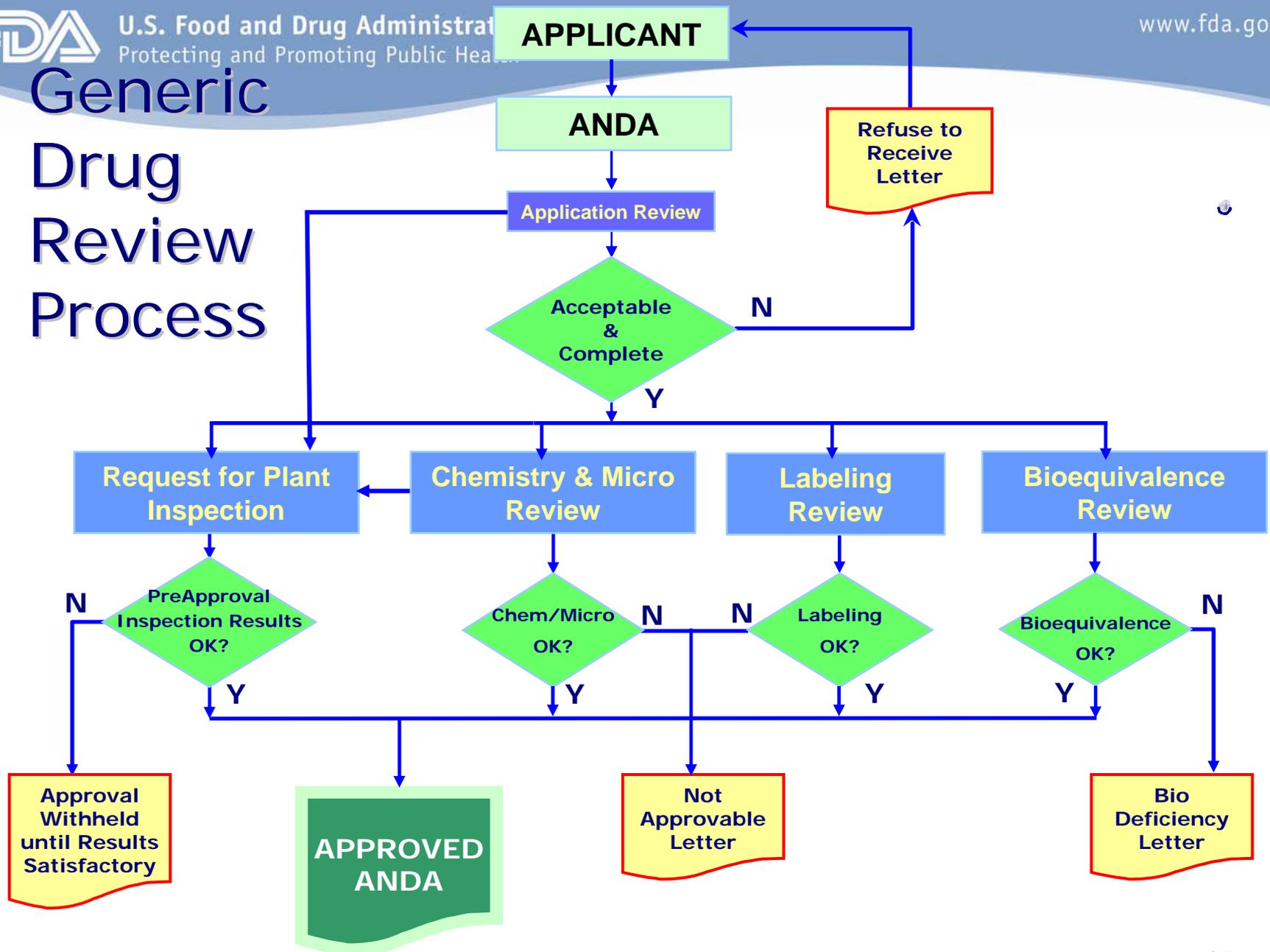
Generic Drug Enforcement Act of 1992

- **Debarment Certification:**
 - [Name of applicant] certifies that [the applicant] did not and will not use in any capacity the services of any person debarred under section 306 of the act in connection with this application

- **Convictions Statement:**
 - If neither the firm nor its affiliated persons have convictions to list the applicant may state that neither the applicant nor its affiliated persons responsible for the development or submission of the application has been convicted of a relevant offence within the last 5 years.

 - Alternatively, the applicant must list the names of all individuals convicted within the last 5 years as described in sections 306(a) and (b)

Generic Drug Review Process



Consults

- Currently, the CMC review for all PET drug products are consulted to ONDQA for review.
 - Consult of CMC information is sent immediately upon the filing of your ANDA
 - Consult is tracked by the project manager in OGD and OGD's Consult Coordinator.
- In the future, OGD will have a dedicated subject matter expert for the review of CMC.

Submission Types in Order of Preference (Highest to Lowest)

- eCTD format (gold standard), preferred method for submission
 - Standard XML backbone provides hierarchy for documents and enables ease of review with FDA review tools
 - Easy-to-navigate
 - Automated validation by FDA's Automated Submission Receipt (ASR) program
 - Can be sent either via the Gateway or on physical media
 - Primary standard for all electronic submissions after January 1, 2008
 - Required to obtain a pre-assigned ANDA number for Gateway submissions
- Other electronic submissions-hybrids
 - Scanned electronic copy organized in CTD format submitted via the Gateway or on physical media
 - Required to obtain a pre-assigned ANDA number
 - Unable to validate automatically using the ASR. Validation completed manually.
 - Sponsor must obtain electronic waiver from the Esub group to submit in this manner
 - PDF files on CD or DVD
 - Use of Hyperlinks required to enhance document navigation
- Paper submissions
 - Must be organized in CTD format
 - Multiple copies required
 - Difficult to archive and send on consult
 - Labeling still required to be submitted electronically

*****All submissions that are sent on physical media should be accompanied by a paper copy of the cover letter and FDA form 356h in case the physical media is unreadable.

ANDA Format

- Common Technical Document (CTD)
 - Module 1: Administrative or regional
 - Forms, certifications, labeling, BE waiver request, etc.
 - Module 2: Summaries
 - Quality Overall Summary, drug substance and drug product information, clinical BE summary
 - Module 3: Quality-CMC information
 - Broken down into drug substance (3.2.S), drug product (3.2.P) and regional (3.2.R) subsections
 - Module 4: Not applicable to ANDA submissions
 - Module 5: Clinical Study Reports
 - PET ANDAs will need to submit section 5.3.1, which is related to formulation

- OGD's ANDA Checklist-contains detailed information about where documents are to be placed.

ANDA Labeling

FD&C Act defines labeling as follows:

The term "labeling" means all labels and other written, printed, or graphic matter

- (1) upon any article or any of its containers or wrappers, or
- (2) accompanying such article

ANDA Labeling

- ANDA labeling is required to be “the same as” the last approved labeling for the reference listed drug (RLD) except for differences allowed by the regulations
 - Section 505(j)(2)(A)(v) of the Act
 - 21 CFR 314.94(a)(8)

- Ensures that health care practitioners are provided sufficient information to use the product safely

ANDA Labeling

21 CFR 314.94(a)(8)

- Generic labeling must be the **same as** the RLD except for differences because of
 - Approved changes under a suitability petition
 - Different manufacturers
 - Expiration date
 - Formulation
 - Bioavailability
 - Pharmacokinetics
 - FDA labeling guidelines
 - Omission of an indication or other aspect of labeling protected by patent or exclusivity

Electronic Submission of Labeling

- 21 CFR 314.50(l)(i)
 - The package insert or professional labeling must be submitted to FDA in electronic format
 - In the original ANDA submission, OGD expects a text-based PDF file (do not submit image based PDF) and a copy submitted in Microsoft Word
 - OGD will accept a commitment to provide Structured Product Labeling (SPL) upon approval of the ANDA. ANDA approval letters instruct that the applicant has 14 days in which to provide SPL.

Electronic Submission of Labeling

- Labeling required at time of ANDA filing
 - A copy of the currently approved RLD labeling
 - A copy of your proposed labeling
 - An annotated side-by-side comparison of your proposed labeling to the RLD with all differences annotated and explained

Electronic Submission of Labeling

- Labeling required at time of ANDA approval
 - OGD will approve draft labeling for PET submissions
 - OGD prefers to approve FPL (final printed labeling) prior to ANDA approval but will accept it post approval.
 - OGD highly recommends submission of SPL prior to approval, but will accept SPL after approval

What is SPL?

- SPL is the content of labeling in a standardized electronic file format with tagged blocks of text and data elements in extensible markup language (XML).
- SPL is the electronic form that FDA has adopted to process, review, and archive insert labeling

Benefits of SPL

- Allows approved labeling to be transmitted to the National Libraries of Medicine (NLM), which provides SPL via an electronic repository called the *DailyMed*. Patients, health care practitioners and health systems use the information from *DailyMed*
- Can be used by decision support systems to improve patient care and reduce medical errors
- Human-readable labeling content compatible across systems

Recommendations

- Use the ANDA filing checklist as a template for compiling your ANDA
- Have OGD review your proposed formulation prior to submission of your ANDA.
 - Controlled correspondence
- Contact either me or Dat Doan (Project Manager for PET drug products) with questions regarding the submission and/or approval process

Where to Submit

- Address for ANDA submissions
 - Currently

FDA/Office of Generic Drugs/CDER/FDA
Attn: Keith O. Webber, Ph.D
Metro Park North VI
7620 Standish Place
Rockville, MD 20855

***Check OGD website for address updates

Submission Resources

- eCTD website: <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>
- eCTD Table of Contents:
<http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>
- OGD Filing Checklist:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM151259.pdf>
- OGD website
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm119100.htm>

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Resources for You

- [Drugs@FDA](#)
- [Inactive Ingredient Search for Approved Drug Products](#)
- [Abbreviated New Drug Application \(ANDA\): Generics](#)
- [Orange Book Query](#)
- [Generic Drugs: Information for Industry](#)
- [Understanding Generic Drugs](#)

Office of Generic Drugs

Welcome from the Director, Office of Generic Drugs

Note: We highly recommend that firms consider submitting documents in electronic format. The OGD document room has limited space and resources to maintain paper documents.

Organization and Contact Information

- [Office of Generic Drugs: Chemistry and Bioequivalence Review Teams](#)
- [Office of Generic Drugs: Phone Directory](#)

Contact Us

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- Dat Doan: Project Manager, Division of Chemistry 1, Team 1, FDA, Office of Generic Drugs
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- Identify in subject line that the e-mail is related to a PET drug product
- Phone numbers are on the OGD webpage and subject to change