Product Quality Assurance: Microbiological Regulatory Perspective

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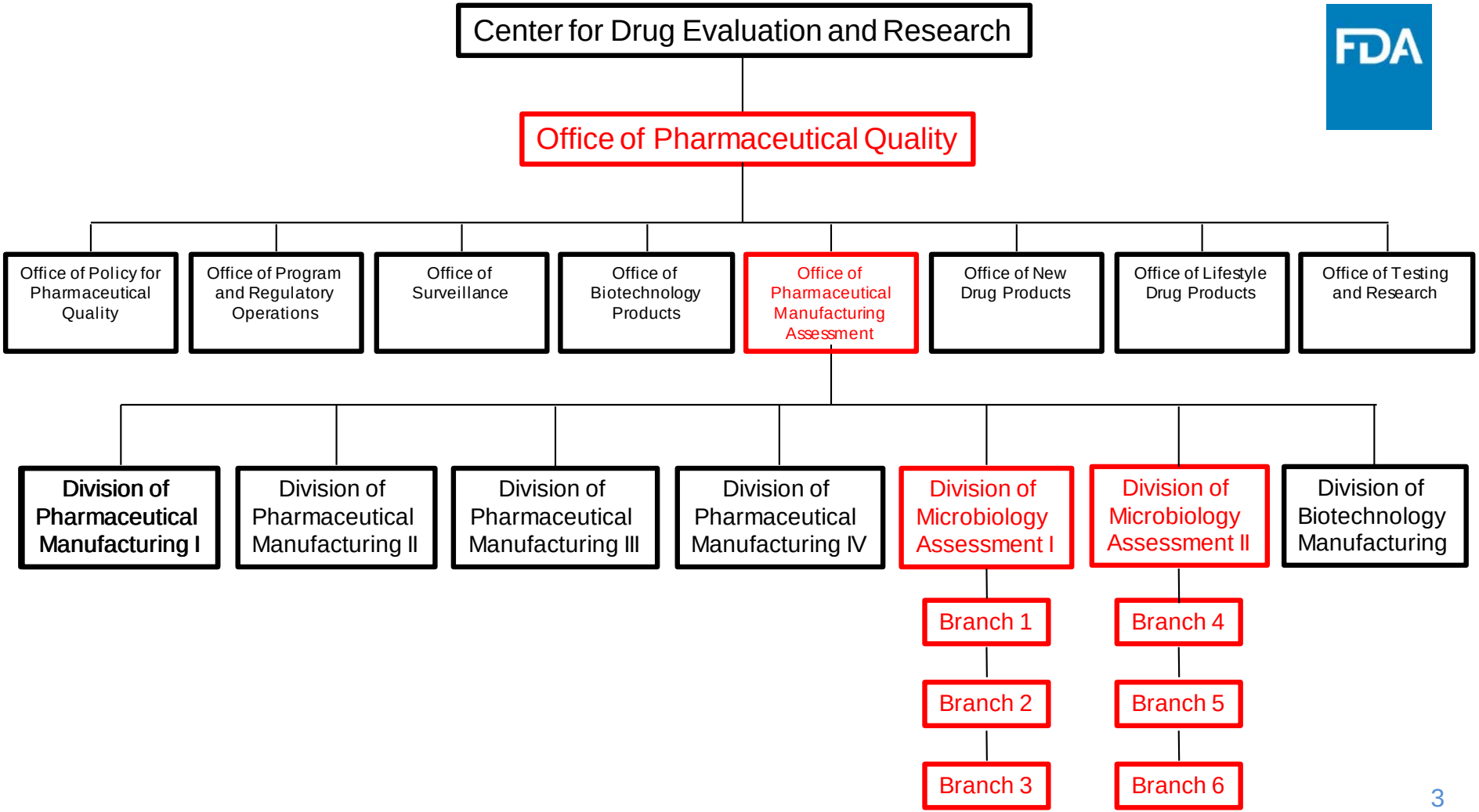
PET Drugs: A Workshop on Inspections Management and Regulatory Considerations
February 21st, 2020

Disclaimer

- The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA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Presentation Outline

- Aseptic operations during PET drug manufacture
  - Control of critical environments
  - Product vial assembly
  - Sterilizing filtration
- Operator Training
- Media fills
- Finished product microbiological testing
- Review Case Studies

Microbiological Considerations

- PET drug products have short half-lives and are administered before completion of all microbiology-related QC testing
- Aseptic operations and procedures are used to adequately ensure sterile PET drug products

Aseptic Operations During Manufacture

- Final product vial assembly
- Transfer of assembled product vial to hot cell
- All work activities downstream of sterilizing filtration
  - Withdrawal of QC samples, product dilution, transfer to multidose or single-dose vials or syringes for final packaging
  - Sterility testing
- Gowning/gloving procedures for personnel working in aseptic areas
- Environmental monitoring and cleaning/disinfection of aseptic/critical areas

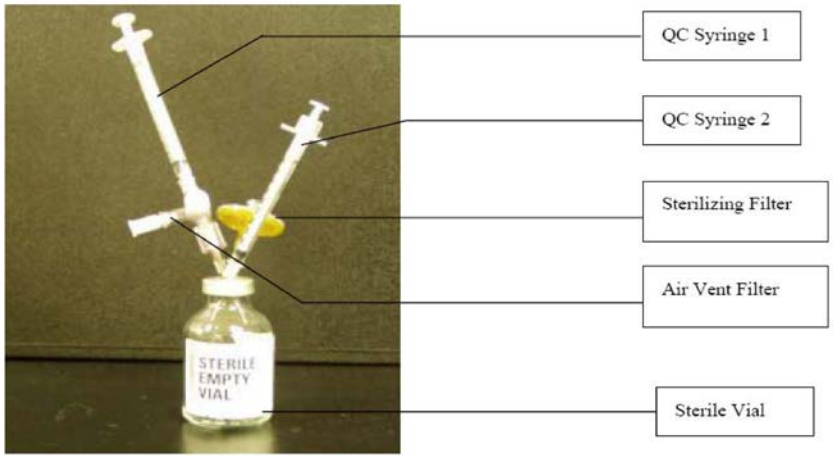
Control of Environment

- ISO Class 5 aseptic workstation/critical areas should be cleaned/disinfected prior to use
- Routine environmental monitoring program for ISO Class 5/critical areas
  - Type of monitoring, locations, frequency, alert/action levels, actions when levels exceeded
  - Performed routinely and during execution of aseptic operations (i.e., product vial assembly, sterility testing, media fills, etc.)

Product Vial Assembly

- Assembly of the product vial is performed in an ISO Class 5 aseptic workstation
- Storage conditions and maximum hold time for assembled vials

Figure 1: Completed vial assembly (30ml vial)



Product Vial Assembly

- Pre-sealed, pyrogen-free container/closure consisting of glass vial, rubber stopper and seal from commercial source
  - Provide supplier info: CoA or DMF#/LOA, if applicable

- If depyrogenating and sterilizing container closure system at PET manufacturing site
  - Provide validation information for depyrogenation and sterilization processes
  - 2004 FDA guidance *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, Section IX.C.*

Sterilizing Filtration

- Following synthesis, PET drugs are passed through a sterile 0.22 µm sterilizing filter
- Filtration should occur in a closed system
  - Chemical synthesis can occur in open or closed system
- The filtration system should be aseptically assembled from pre-sterilized, commercially available components
  - Provide CoA or DMF#/LOA, if applicable, for all sterile components including filter

Aseptic Operator Training

- Training for all aseptic manipulations and operations that occur during production
  - Assembly of sterile components, filtration and manipulations of the sterile drug product solution (i.e., QC sampling, product dilution/transfer to another container, etc.)
- Proper gowning and gloving techniques
  - Including clean lab coats, forearm sleeves, hair/beard covers, sterile/sanitized gloves that cover wrist
- Personnel involved in aseptic operations should perform media fill simulations

Media Fill Simulations

- Use microbial growth medium, in place of drug product solution, to assess the quality of aseptic operations
  - Evaluate aseptic assembly/operation of critical, sterile equipment
  - Qualify operators/assess technique
  - Demonstrate adequacy of environmental controls

- Include product vial assembly/transfer to hot cell and all aseptic manipulations downstream of product filtration step up to product release
  - Including packaging into finished product containers

Considerations for Media Fills

- Represent worst-case conditions for aseptic operations
- Performed using same rooms/critical equipment used during commercial production
- Include positive control
- Performed in triplicate for new operator qualification; annual requalification for each operator
- Performed when procedures/equipment are changed significantly

Incubation Conditions and Conclusions

- After the simulation, the media filled vial(s) should be incubated for 14 days and assessed for growth
  - Examine every 2-3 days for growth
  - No growth = pass; growth = fail
- Failed media fills should result in operator re-training and repeat media fill(s)
- 2012 FDA guidance *Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs*

Microbiological Tests for PET Drug Products

- Microbiological tests included in release specification
  - Filter integrity
  - Bacterial endotoxins
  - Sterility

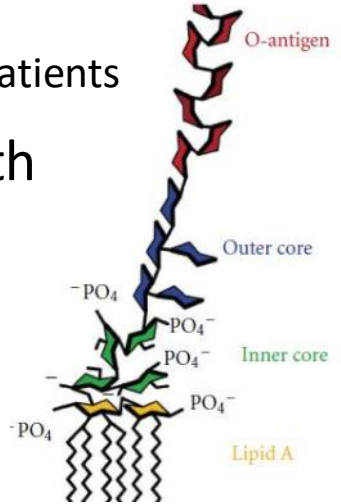
- No microbiological testing required for stability
  - Microbiological testing may be necessary for products with longer shelf-life

Filter Integrity

- Performed after completion of filtration but prior to release of the PET drug product
  - Ensures integrity of filter not compromised during or before use
  - Per manufacturer's recommended test (i.e., bubble point test)
- CoA from filter manufacturer should be provided
- Test method, wetting agent and acceptance criteria included in release specification
  - Results and filtration conditions included in batch records

Bacterial Endotoxins

- Testing should be performed in accordance with USP <85> recommendations
  - Initiated promptly after product manufacture is complete but prior to product release
  - Endotoxins specification for PET drug products: 175 EU/V (14 EU/V for intrathecal administration)
    - Consideration of low body weight for administration to pediatric patients
- Can be performed on QC-sub batches for radionuclides with very short half-lives (i.e., ^{15}O, ^{62}Cu, ^{13}N)
- Test method and acceptance criteria should be included in release specification
  - Results included in batch records



Sterility

- Testing should be performed in accordance with USP <71> recommendations
  - Inoculation of drug product sample into two types of media (TSB/SCDM and FTM)
  - Incubate for 14 days at 20-25°C (TSB or SCDM) and 30-35°C (FTM)
- Initiated within 30 hours of the completion of manufacture
  - If initiated after 30 hours, must demonstrate equivalence of results
- Should be performed in ISO Class 5 workstation to prevent false positives
- Test method and acceptance criteria should be included in release specification
  - Results included in batch records

For A/NDA Applications

- Provide method suitability studies/results for proposed bacterial endotoxins and sterility test methods
- Actions following test failures should be discussed

Review Case Study 1
Environmental Monitoring

- The applicant provided a summary of the personnel monitoring program that indicated that fingertip monitoring is not performed during routine production for all operators who perform tasks in the ISO Class 5 workstation. It is only performed for new operators until they have been working for 6 successive months and have NMT 3 CFU/touch plate. All operators perform fingertip monitoring during annual media fill requalification.

- **FDA Response:** Inadequate. Fingertip monitoring should be performed for all operators performing tasks in the ISO Class 5 workstation. Media fills should simulate all aseptic operations and the environmental monitoring program that will be performed during routine commercial production.

Review Case Study 2
Media Fills

- Application indicated that commercial production of the subject PET drug product includes the addition of sterile saline to the sterile drug product solution (for tonicity adjustment). However, the addition of the sterile saline was not simulated during the media fill.

- **FDA Response:** Inadequate. All aseptic operations downstream of the sterile filtration step, including dilution or repackaging of the sterile drug product solution should be included in the media fill simulation.

Review Case Study 3
Method Suitability Testing

- Application included method suitability testing (inhibition/enhancement) for the bacterial endotoxins test method that did not use the subject drug product.

- **FDA Response:** Inadequate. All method suitability testing, including bacterial endotoxins and sterility, must be performed with the subject drug product to ensure that the results are reliable and consistent during routine testing of the drug product using the proposed procedure.

U.S. FOOD & DRUG ADMINISTRATION

Thank you!!!

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Microbiological Safety of Positron Emission Tomography Drugs

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PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

FDA White Oak Conference Center
Silver Spring, MD USA

February 21, 2020

PET Drugs are Different

- Prepared in small batches (typically 1 vial, about 15 to 40 mL/vial)
- Prepared in pre-sterilized closed systems using aseptic processes
  - Require radiation protection measures
  - Require aseptic controls during preparation
- Have short shelf lives
- Are administered within hours of preparation
- Are administered to patients in small doses (less than 1 mL)

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FDA Studied PET Drug Manufacture to Establish a Regulatory Framework

- PET production site visits beginning in 1991
- Collaborative development of USP <823>
- Collaborative development of draft FDA guidance
- Collaborative development of product vial
- Publication (Federal Register) of proposed rule for CGMPs (February 1995)
- Public Workshop on regulatory strategy (March 1995)
  - Concluded that 21 CFR 211 was too stringent
  - FDAMA 1997, Sec 121 (d) withdrew the proposed rule

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FDAMA 1997 Amended the FD&C Act, Sec 121

Section 121(c) of Pub. L. 105–115 provided that:

‘‘(1) PROCEDURES AND REQUIREMENTS.—

‘‘(A) IN GENERAL.—In order to take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs, not later than 2 years after the date of enactment of this Act [Nov. 21, 1997], the Secretary of Health and Human Services shall establish—

‘‘(i) appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); and

‘‘(ii) appropriate current good manufacturing practice requirements for such drugs.

21 CFR 212 was developed, and Guidance for Applications were published

Microbiological Risk

- Microorganisms (e.g., bacteria and fungi) are ubiquitous in the environment
  - … but undesirable in aseptic areas
- Patients and everyone are exposed constantly
  - Human defense from infection is primarily skin
  - Immune defenses deal with microbes that penetrate barriers
    - Microorganisms (small numbers) enter through skin with every injection
    - Great numbers of microorganism enter the blood stream with dental cleaning
- Infections result when defenses are overwhelmed
  - Invasive microorganisms
  - Too many microorganisms

Pharmaceutical Microbiology and Sterile Products

- Sterile is an "absolute" condition (complete absence of viable organisms)
  - It cannot be measured by a test (statistically and microbiologically)
    - Francis Bowman (FDA 1969) published microbiological culture-based deficiencies
    - CDC (1973), EPA (1985), Halvorson and Ziegler (1933) and other laboratories have shown culture methods only detect a fraction (<10%) of the viable organisms
  - Sampling can only select contaminated units when about 10% or more of a larger batch is contaminated (Pflug, 1972, and Sutton, 2012)
  - A 'clean' sterility test does not indicate sterility – It indicates the absence of evidence of contamination
- Generally, process control measures will better indicate product sterility

Statistics of the Sterility Test

from - Pflug, in Industrial Sterilization, Proceedings of the International Symposium, 1972 (Duke University Press, 1973)

Table 8 Probability of finding at least one unit nonsterile in samples of size *N*

Percentage of non-sterile units in lot	*Number of units in random sample*						
	10	20	50	100	500	1000	10,000
0.001	0.000100	0.000200	0.000500	0.001000	0.004988	0.009950	0.095164
0.002	0.000200	0.000400	0.001000	0.001998	0.009950	0.019802	0.181271
0.005	0.000500	0.001000	0.002497	0.004988	0.024691	0.048772	0.393477
0.01	0.001000	0.001998	0.004988	0.009951	0.048773	0.095167	0.632139
0.02	0.001998	0.003992	0.009951	0.019803	0.095172	0.181286	0.864692
0.05	0.004989	0.009953	0.024696	0.048782	0.221248	0.393545	0.993270
0.1	0.009955	0.019811	0.048794	0.095208	0.393621	0.632305	0.999955
0.2	0.019821	0.039249	0.095253	0.181433	0.632489	0.864935	1.00 000
0.5	0.048890	0.095390	0.221687	0.394230	0.918428	0.993346	1.000000
1.0	0.095618	0.182093	0.394994	0.633968	0.993430	0.999957	1.000000
2.0	0.182927	0.332392	0.635830	0.867380	0.999959	1.000000	1.000000
5.0	0.401263	0.641514	0.923055	0.994079	1.000000	1.000000	1.000000
10.0	0.651322	0.878423	0.994846	0.999973	1.000000	1.000000	1.000000

Sterility Tests

- There many approaches to testing product sterility
  - Culture a sample (takes days or weeks)
  - Other tests for presence of viable things (metabolic activity (gas production, ATP production), viable stains (cytometry))
- All tests have a statistical likelihood of a false-negative
- All tests have potential for a false-positive
- With most PET drug processes, 100% of the units are tested

Process Controls for PET Production

- PET drugs are prepared using aseptic procedures in classified environments
  - The drug is collected in a sterile finished product vial (FPV) that was assembled aseptically in a Laminar Air Flow Hood (LAFH) or BioSafety Cabinet (BSC) - Both maintain ISO Class 5 environments
  - The drug is synthesized in a closed and automated module that delivers the bulk through disposable transfer tubing, then into the FPV through a sterilizing grade filter
    - Filter integrity testing (process control) must 'pass' before product release
  - The drug is often synthesized with microbial lethal reagents.
  - Drug is tested for its release criteria (except sterility) before dispensing
    - The test for endotoxins is completed before release
    - The culture for sterility testing requires at least 14-days incubation

Aseptic Manipulations and Risk: ISO Class Monitoring

- Controls for ISO classified environments maintain clean air at work areas where aseptic processes are performed
  - ISO 14698-1 "Biocontamination Control" definitions
  - 3.1 action level - microbiological level set by the user in the context of controlled environments, which, when exceeded, requires immediate intervention, including investigation of cause, and corrective action
  - 3.2 alert level - microbiological level set by the user for controlled environments, giving early warning of a potential drift from normal conditions
  - 3.11 risk - combination of the probability of the occurrence of harm and the severity of that harm

Microbiological Monitoring of Processing - Air

- In the 1995 proposed rule, the proposed microbiology EM procedures from the 1987 aseptic processing guidance were determined by FDA as too intrusive for PET facilities
  - Quantitative measurements during production created opportunities for process failures in small spaces
  - Passive measures (settle plates) were adequate for detecting loss of process control (Whyte, 1981) without process interference or excess resource (personnel) demands
  - Periodic requalification of classified areas were deemed sufficient assurances of environmental control
- EM for closed system processing of products used before microbial growth could occur (a risk factor) was a process control indicator

Microbiological Monitoring of Processing – Surfaces and Personnel

- Touch contamination (operator gloves) has been considered a potential contamination risk in aseptic processing
  - Operator qualification and monitoring remains a point of emphasis
- Surfaces are an indicator of process control
  - Contact plates are used to monitor microbial contamination in classified areas
  - An appropriate frequency was recommended for these processes
- For PET production, components remain closed minimizing risks of adventitious contamination

Aseptic Manipulations and Risk: The FPV

- Vial Assembly –
  - A qualified gowned operator inserts:
    - a capped sterilizing grade filter on a sterile needle into the septum of a sterile injection vial
    - a sterile vent filter on a sterile needle into the septum of a sterile injection vial
    - a sterile sampling syringe on a sterile needle into the septum of a sterile injection vial
  - The FPV is placed into a sterile bag for storage until use
- All components are dry – in the absence of moisture, no microbial growth is possible, and vegetative contaminants would begin to die

Aseptic Manipulations and Risk: The Solution Transfer

- The drug solution is provided through a clean and disinfected transfer set to the Hot Cell (radiation containment chamber)
- The transfer set is connected to the sterilizing grade filter, and the drug enters the FPV
- The bulk product is in a saline solution
  - The drug is dispensed (practice of pharmacy) and administered (clinical practice) within hours
    - The drug will not support microbial growth in the time before administration, preventing adventitious contamination from becoming a risk
    - This closed system prevents adventitious contamination with more than one or very few microorganisms (like when you get a flu shot)

Observed Safety of PET Drugs

- Silberstein (2014) reported a survey of 15 institutions' adverse event Reports (AERs) for radiopharmaceutical procedures from 2007 through 2011 (over 1 million administrations)
  - AERs included allergic, noxious, or unintended outcomes, signs, symptoms, and laboratory abnormalities
  - PET drug procedures became a greater proportion (17% to 26%) of radiopharmaceutical procedures during this period
  - The incidence of AERs remained stable at 2.1 $\pm$ 0.6 per 100,000 during this period and trended downward

Recently Observed Safety of PET Drugs

- From “Survey of PET Drug Manufacturers, February 4-10, 2020”
  - 13 academic respondents and 5 commercial respondents (18 total)
  - Covered years 2013 through 2019
  - No AERs reported due to infections
  - 0.013% frequency of OOS sterility results
  - OOS nearly always conclude “lab error”

	Batches		Sterility OOS
2013	51603		4
2014	50771		2
2015	50658		9
2016	52925		12
2017	51973		5
2018	54195		10
2019	58225		6
Sum	370350	Sum	48

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Moving Forward

- Consider incorporating PET into CDER's 2004 initiative "PHARMACEUTICAL CGMPS FOR THE 21ST CENTURY — A RISK-BASED APPROACH"
  - It's guiding principles:
    - Risk-based orientation
    - Science-based policies and standards
    - Integrated quality systems orientation
    - International cooperation
    - Strong public health protection

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Closing Thoughts

- PET drugs are prepared in a closed system using aseptic procedures in controlled and classified environments. Filter integrity and endotoxin testing are completed before PET drug release. A very low percentage of PET drugs fail the 14 day sterility test.
- There is no evidence of public health risks due to sterility failures in PET drug manufacturing.
- Environmental monitoring for closed system processing of products that are used before microbial growth could occur is less critical.
- Standards should be established for all PET Drug manufacturing facilities so that compliance may be uniform among all sites.

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Session III
Chemistry and Product Quality Assurance

Christopher Ignace, PharmD, PhD

PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

FDA White Oak Conference Center
Silver Spring, MD USA

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Chemistry and Product Quality Assurance (#1)

PET sites and PET networks produce many batches and generate vast amount of data.

→ Management Review Process Requirements: 21.CFR.212 vs. 211.180 (e)(f)

The Management Review system shall include: 1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities […] (2) Periodic quality reviews […], (3) any follow-up actions from previous management reviews .
"Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management"

- **Applicability of ICH Q10 to PET?**
- **Inspectors request an Annual Product Review, which is not specified in 21.CFR.212.**
- **Some inspectors request site specific APRs in addition to network.**
- **FDA view on alternate approaches to APR?**

- **Help identify compliance requirements and discuss acceptable documentation for sites and networks.**

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Chemistry and Product Quality Assurance (#2)

FDA presents new expectations and standards at symposias and conferences ("Podium Policies")

→ Formalization and dissemination of Compliance information to PET field (academia and Industry)

- **2/3rd of respondents received citations for new interpretation of regulations.**
- **Very rapid FDA compliance enforcement (days)**

- **Help define "change control" regarding interpretation and implementation of regulations**
- **Define reasonable grace period for Agency field implementation**

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Chemistry and Product Quality Assurance (#3)

FDA inspections typically include daily debriefing with discussion of issues uncovered with sponsor.

→ ***Inspectors allow sponsor the ability to understand the issue(s) and offer context and rationale for procedures and practices.***

- **Some inspectors will only communicate with local Quality Assurance staff**
- **Some inspectors have been unwilling to describe the area of findings and/or rationale for determining potential non-compliance prior to issuing a 483.**

- **Considerations about network corporate QA role(s)**
- **Guidance on how to maintain line of communication (non-confrontational/argumentative) and follow the Office of Compliance request to be contacted prior to 483 issuance.**

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Chemistry and Product Quality Assurance (#4)

Personnel qualification

→ ***Providing adequate experience, expertise and training or appropriate combination thereof.***

- ***Recent experience with inspector requested staff be trained by degreed microbiologist and did not accept training delivered by experienced non-degreed trainer.***

- **Guidance on implementing compliant training programs and expectations for training by degreed SMEs such as Microbiologists versus trainers qualified via OJT programs.**

Chemistry and Product Quality Assurance (#5)

Environmental monitoring

- → ***Action vs. alert limits***
- → ***EM during Process qualification***
- → ***Incubation temperatures***
- → ***<USP 825> EM applicability***

Sponsors seek clarity on impact of micro findings on both qualification and routine operations

- **Clarify how to best handle EM finding (growth) during/within process qualification.**
- **Can FDA comment on dual incubation temperature expectation of EM samples?**
- **Can FDA confirm enforcement of USP <825> EM standards onto pharmacy dispensing only?**

- **Agency discuss/clarify EM expectations (updated guidance if appropriate)**

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Chemistry and Product Quality Assurance (#6)

Sterility testing

- → *14-day incubation failures*
- → *Sterility test errors implications*
- → *FAR implication of the above*

Sponsors seek clarification about the appropriateness of a FAR under the following circumstances:

- **FAR appropriateness when 14-day incubation was not completed (e.g. deviation)?**
- **FAR appropriateness when sterility testing could not be completed (e.g. dropped sample)?**

- **Clarify expectations around FARs for PET manufacturing.**

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Chemistry and Product Quality Assurance (#7)

Conditions of approval

Established based on:
→ CDER Review
→ PAI inspection (MAPPs)

Conditions of approval define FDA's expectations and sponsors obligation:.
"Reciprocal obligations" or "contract" between Regulatory Body/Sponsor.

- **Sponsors are cited during routine inspections by inspectors challenging science, although remaining within the conditions of approval.**
- **Sponsors need clear/recognized definition of commitments in the applications.**
- **Sponsors wanting to avoid "renegotiating" conditions of approval post approval.**

- **FDA to expand on specifics of PAI versus routine compliance inspections.**
- **FDA further training to applicability of respective FDA Inspection Guidance documents.**

Thank you!


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Discussion Items – Microbial EM recovery “standards”

- Confusion exists regarding identification of all microbial growth. Some inspectors require identification of all microbial growth in ISO Class 5 areas and others don’t
- Confusion exists with some FDA inspectors who have expectations of no microbial growth in ISO Class 5 areas
  - ISO Class 5 is not a sterile environment
  - Risk comes from catastrophic loss of control (e.g. filter integrity loss)
- New PET drugs may present different challenges, but for now the processes are very low risk

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Discussion Items – Microbial EM recovery “standards”

- Given that all manufacturers are producing the PET Drug under similar conditions it seems reasonable to expect that all facilities would be held to the same standards. Those standards would be defined based on the safety and risk associated with PET Drug manufacturing.

Discussion Items: Sterility assurance for A/NDA vs IND Applications

Confusion exists regarding the sterility assurance information that should be submitted in A/NDA applications. IND applications are much shorter, and do not require, in most cases, facility information, process validation studies, description of EM or Media Fills, method suitability testing or stability. The following list includes the information that is commonly left out of A/NDA applications for PET drug products:

- Facility or equipment descriptions
- Description of EM program
- CoAs for all sterile filtration/filling components
- Filter integrity testing in the release specification
- When sterility testing is initiated, or not providing justification/equivalence testing when initiated after 30 hours

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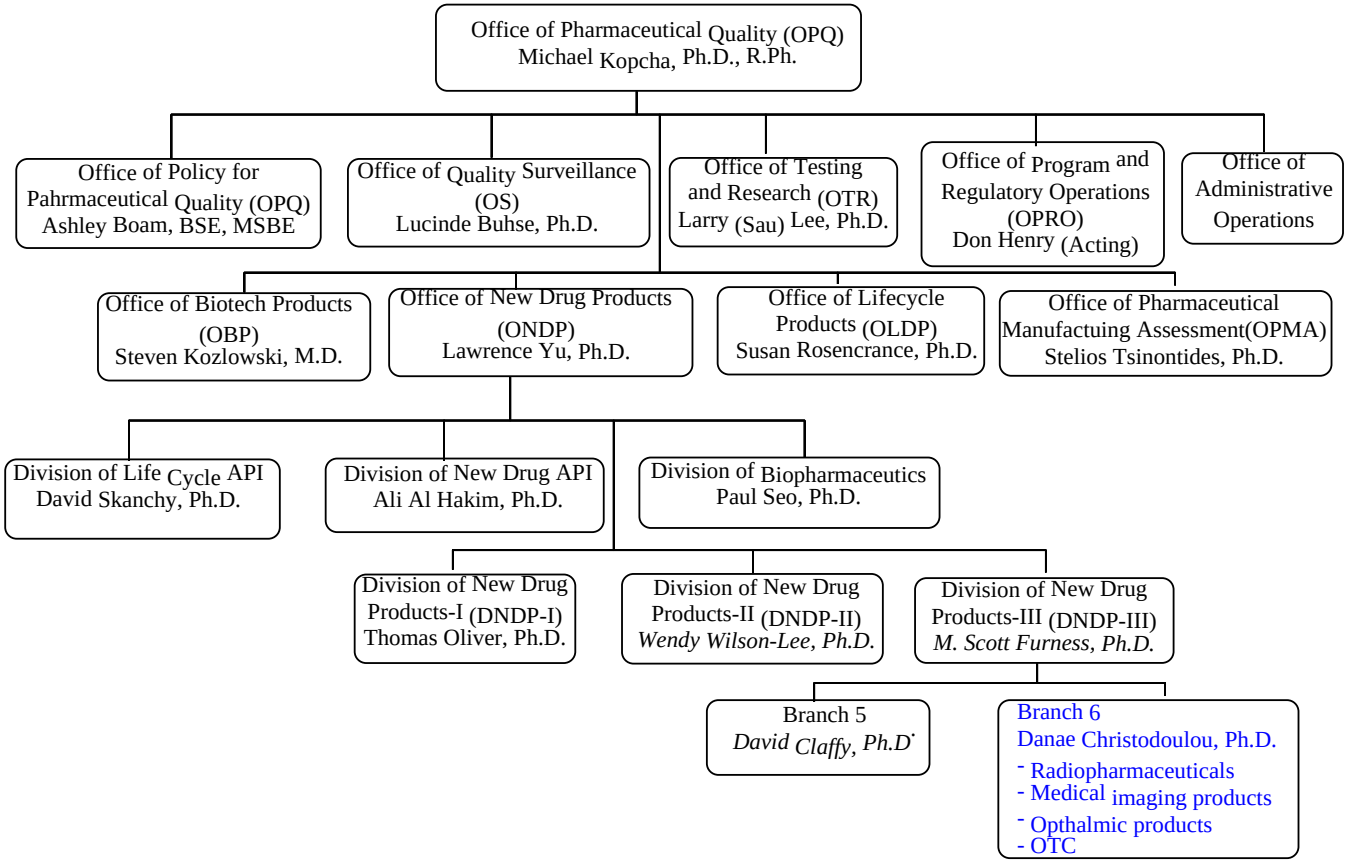
Discussion Items –Sterility Testing and FAR?

During Inspection, FDA has asked that particulates and other non-viable growths in TSB/FTM media incubated per USP <71> which do not cause turbidity in the media should trigger a Field Alert Report and seems to have treated the incident as a potential sterility positive. This appears to be in conflict with interpretation of USP <71> Chapter, where for a positive result, turbidity must be observed. What is the FDA's position on what constitutes a positive result on a sterility assay?

Changing Landscape of PET Drugs

Ravindra K. Kasliwal, Ph.D.
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
CDER / FDA

OPQ ORGANIZATIONAL STRUCTURE



Outline

- Historical
- Changes in nature of PET drugs since 2009
  - New technologies
- Biotech PET drugs
- Regulatory – NDA; BLA

PET Drugs – Historical

- Pre FDAMA (1997) – approved PET drugs
  - Sodium fluoride F 18 injection
  - Rubidium Rb 82 generator
  - Fludeoxyglucose F 18 injection

  } Manufactured under 21 CFR 211 at approval
- 21 CFR 212 regulations were Published in 2009
- 2009 USP Chapter <823> → ^{18}F, ^{11}C, ^{13}N, ^{15}O
- 21 CFR 212 and USP <823> (2009) largely considered manufacturing of PET drugs based on the above 4 isotopes

Some Unique Aspects of PET Drugs

(considered at the time of formulation of regulations)

- Short Half-Life
  - Sub batch approach for PET drugs with isotopes < 20.0 min half life
- Entire batch produced in a multiple dose vial – 100% testing
- Limited number of doses in a batch

New PET Drugs (NDAs) Approved Since 2009

- Fluorodopa F 18 injection
- Fluciclovine F 18 injection
- Florbetapir F 18 injection
- Florbetaben F 18 injection
- Flutemetamol F 18 injection
- Choline C 11 injection
- Ammonia N 13 injection
- Sodium Fluoride F 18 injection
- Fludeoxyglucose F 18 injection
- Kit for the preparation of gallium Ga 68 dotatate injection
- Ga 68 DOTATOC injection

Critical Drug Product Differences

E.g.: Fludeoxyglucose F 18 Injection

- Manufactured as a multiple dose vial as a ready to use solution
- 100 % tested
- Dispensed in unit doses by nuclear pharmacy

E.g.: Kit for the preparation of gallium Ga 68 dotatate injection

- Kit (marketed product) contains :
  - Vial 1 (reaction vial with lyophilized powder) contains: 40 mcg dotatate, 5 mcg 1,10 phenanthroline; 6 mcg gentisic acid; 20 mg mannitol.
  - Vial 2 (buffer vial) contains: 60 mg formic acid; 56.5 mg sodium hydroxide and water for injection.

Kit for the preparation of gallium Ga 68 dotatate injection

- Radiolabeling in Nuclear Pharmacy (directions provided in insert)
  - Gallium Ga 68 chloride is obtained from a $^{68}Ge/^{68}Ga$-generator
  - Gallium Ga 68 chloride reacted with vial 1 contents (containing vial 2 buffer)
  - QC – visual, pH, ITLC (radiochemical purity)
  - Preparation passing QC can be administered to patients

Changing Landscape

- Kit for the preparation of gallium Ga 68 dotatate injection → Similar to many technetium Tc 99m kits
  - Manufacturing of lyophilized vial containing API
  - Manufacturing of associated components, if any
  - Radiolabeling and dispensing at nuclear pharmacy

Changing Landscape

Original Isotopes

Radioisotope	Half Life	Positron decay (%)
Fluorine -18 (^{18}F)	109.8 min	96.9
Carbon-11 (^{11}C)	20.4 min	99.8
Nitrogen-13 (^{13}N)	9.97 min	100
Oxygen-15 (^{15}O)	2.03 min	99.9
Rubidium-(^{82}Rb)	1.25 min	96

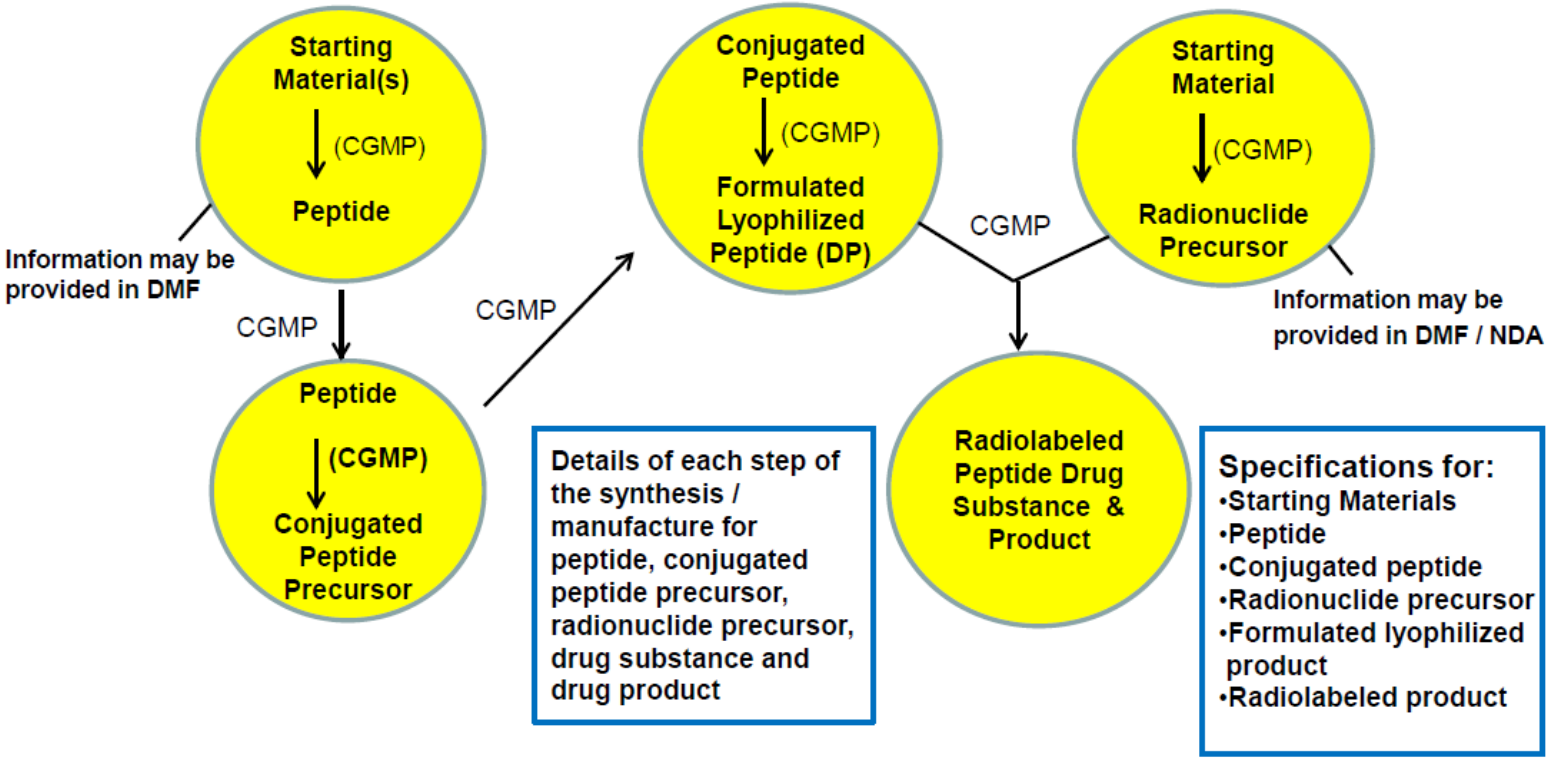
Newer Isotopes

Radioisotope	Half Life	Positron Decay (%)
Gallium-68 (^{68}Ga)	68.1 min	90
Copper-64 (^{64}Cu)	12.7 hours	19.3
Iodine-124 (^{124}I)	4.2 days	25
Zirconium-89 (^{89}Zr)	3.3 days	23
Copper-62 (^{62}Cu)	9.7 min	97.8

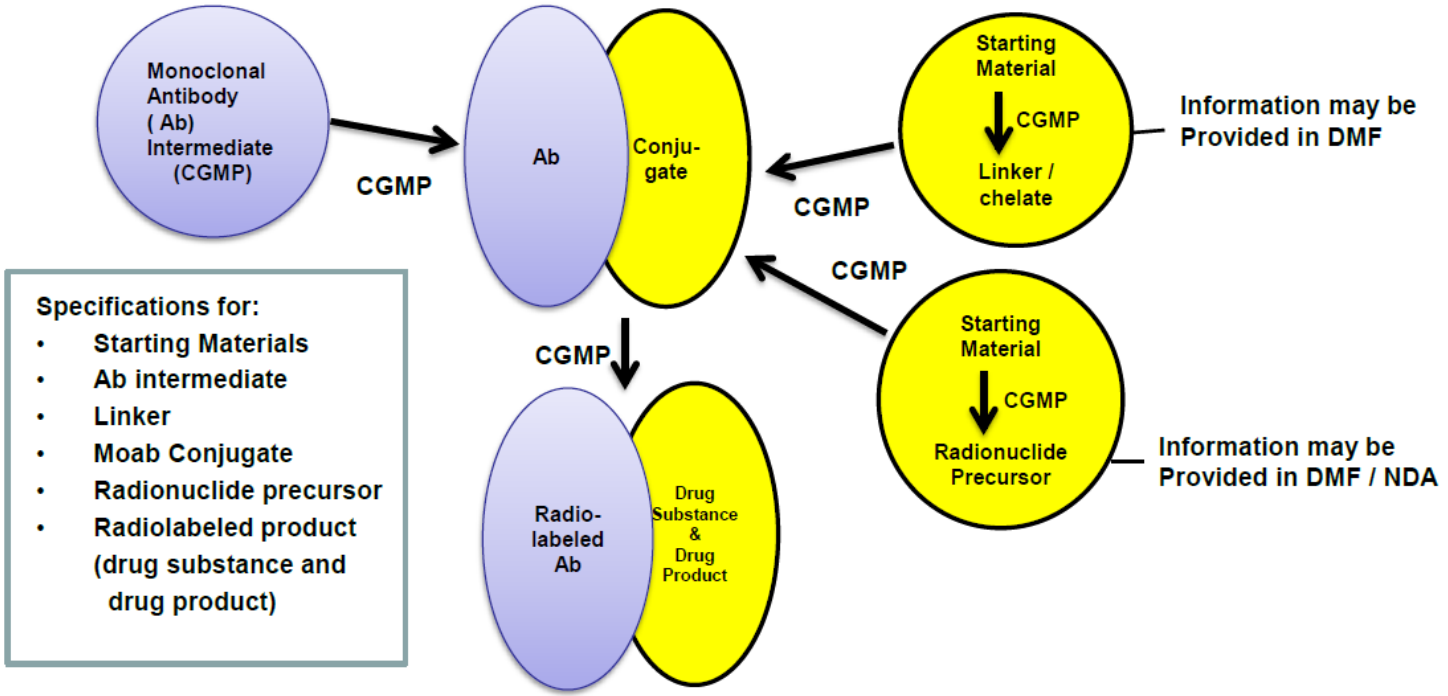
Changing Landscape

- Kit form of PET drug products:
  - Small molecules, peptides, modified peptide, conjugates
  - Protein conjugates
    - -Monoclonal antibodies, including various modifications
- Radionuclide generators
  - $^{68}Ge/^{68}Ga$ generator – long shelf-life
- Manufacturing considerably more complex then e.g., ^{18}F FDG
  - Antibody manufacture
  - Antibody / peptide conjugate manufacture
  - Kit manufacture – lyophilization, terminal sterilization (?)

Manufacturing of Kit form of PET Drugs



Manufacturing of Antibody Based PET Drug



Radionuclide Generators (PET)

Generator	Half life		β^+ branch (%)	$E_{\beta+}$/MeV
	Parent	Daughter		
$^{68}Ge/^{68}Ga$	270.8 d	1.14 h	89.0	0.74
$^{82}Sr/^{82}Rb$	25.6 d	1.27 min	95.0	1.41
$^{44}Ti/^{44}Sc$	60.3 y	3.927 h	94.0	0.597
$^{62}Zn/^{62}Cu$	9.26 h	9.74 min	97.0	1.28
$^{110}Sn/^{110m}In$	4.1 h	1.15 h	62.0	0.623
$^{72}Se/^{72}As$	8.4 d	1.083 d	88.0	1.02
$^{140}Nd/^{140}Pr$	3.37 d	3.39 min	51.0	0.544
$^{118}Te/^{118}Sb$	6.00 d	3.6 min	74.0	0.882
$^{122}Xe/^{122}I$	20.1 h	3.6 min	77.0	1.09
$^{128}Ba/^{128}Cs$	2.43 d	3.62 min	69.0	0.869
$^{134}Ce/^{134}La$	3.16 d	6.4 min	63.0	0.756
$^{52}Fe/^{52m}Mn$	8.28 d	21.1 min	97.0	1.13

Am J Nucl. Med Mol Imaging 2019;9(1):30-66

Newer Isotopes - Issues

- Long lived impurities
  - ^{68}Ge ($t_{1/2}$= 270 days) in ^{68}Ga ($t_{1/2}$= 1.14 hr.)
  - ^{125}I ($t_{1/2}$= 42 days) in ^{l24}I ($t_{1/2}$= 4.2 days)
- Multiple production methods, multiple suppliers
  - Equivalency of isotopic preparation
- Need for coordination with NRC on new isotopes and long lived radionuclidic impurities

Long Shelf Life Generators - Issues

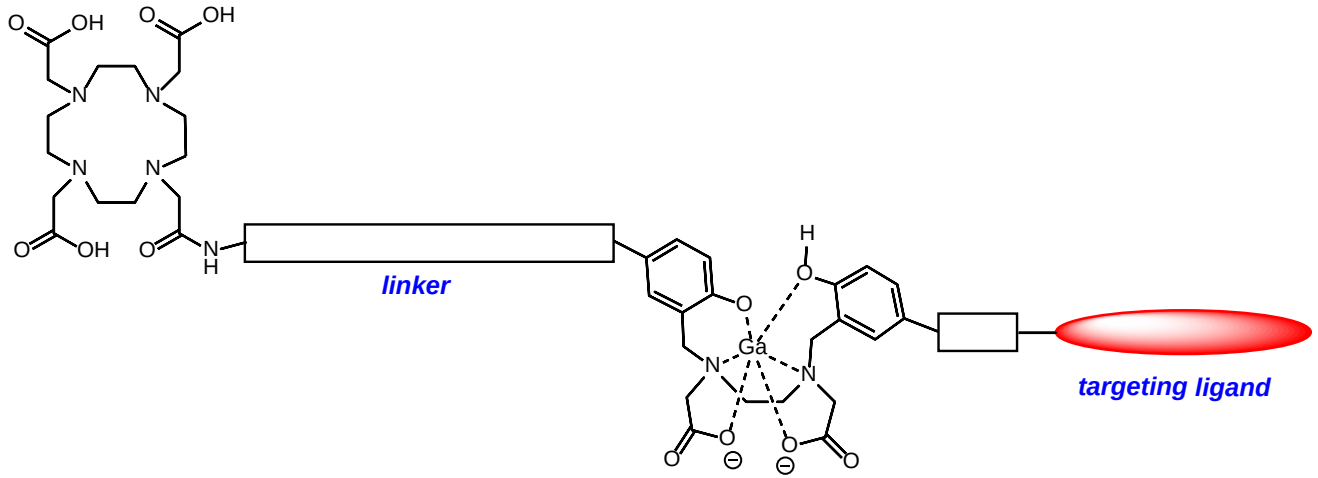
- Microbiological control over the shelf-life
- Stability
- Leachables

Complex Drugs - Issues

- Characterization of radioactive drug substance (radiometal complexes)
- Non-radioactive drug substance reference standards
  - Preparation, structure characterization
- In some cases mixture of isomers
  - Either purify or have control over the isomer ratio
    - Should be same as studied for safety and efficacy
- Need for advanced analytical methods for purification and analysis
  - Cartridge purification approach may be of limited use in some cases

Structure Characterization

- Multiple chelation sites



From Chris Galliford, Ph.D. presentation at SNMMI 2019

CMC Considerations

- The structure of a radiometal chelate should be adequately supported (at least two orthogonal methods) by a fully characterized non-radioactive reference standard.
- In early development, if the drug exists as a mixture of isomers, the ratio of isomers should be identified and controlled so that the same drug is administered to patients from batch to batch and at each study site. It is generally not necessary to identify or qualify each isomer at this stage.
- A robust analytical method (e.g., HPLC, and *u*HPLC) should be used to separate and characterize mixtures of closely related structures.
- In general, with a robust analytical method in hand, an appropriate i-TLC method may still be used to release a drug product, provided it has been adequately validated by an appropriate HPLC-based method.
  - The product release at the manufacturer's site should use a more robust analytical methods.
- The goal is that the same drug, as determined to be safe and effective, is administered to patients from batch to batch.

Regulatory Pathways for Radiopharmaceuticals

- **Peptide** - any polymer composed of **40 or fewer alpha amino acids** – regulated under FD&C Act
- **Protein** -any alpha amino acid polymer with a specific, defined sequence that is **greater than 40 amino acids** in size – considered a biological product
- Biological product application must be submitted under section 351 of the PHS Act

Regulatory Framework for Drug and Biologic Radiopharmaceuticals

Drugs

- Investigational Use – IND
- Pre-Market Approval
  - § 505(b)(1) NDA
  - § 505(b)(2) NDA
  - § 505(j) ANDA

Biologics

- Investigational Use – IND
- Pre-Market License
  - § 351(a) BLA (PHSA)
  - § 351(k)(2)(A) Biosimilar
  - § 351(k)(2)(B) Interchangeable Biosimilar

Product Reviews-Biologics

CDER

- Proteins
  - Cytokines, enzymes;
- **Monoclonal antibodies, including various modifications**
- Immunomodulators
- Growth factors

CBER

- Vaccines
- Blood Products
  - **Albumin based radiopharmaceuticals**
- Tissues
- Gene Therapy Products
- Antitoxins, antivenins, venoms
- Allergenic extracts

Products for Cell Labeling

- Currently no approved PET drug
- Example: Indium In 111 oxyquinoline
  - Approved product is small molecule
  - Use is radiolabeling of autologous leukocytes
  - Small molecule products are regulated under FD&C Act
    - NDA and ANDA

Drug Master Files

- When referencing a DMF, you must include a letter of authorization (LOA) obtained from DMF holder in your application
- Identify what the DMF is being referenced for
  - Type II - Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
    - Examples - Radionuclide (including radionuclide generator), Precursor, Synthesizer cassettes, etc.
- Type III - Packaging materials
- Type IV - Excipient, colorant, flavor, essence, or materials used in their preparation
- Type V - FDA accepted reference information (You must get permission to submit type V DMF)

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

Conclusion

- Organizational structure and multidisciplinary review of applications
- New types of PET drugs
  - New manufacturing technologies
  - Complex CMC
- Regulatory aspects – Drugs and Biologics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ADMINISTRATION

EXTRA SLIDES

BLAs

Biosimilar

- "Highly similar to the reference product notwithstanding minor differences in clinically inactive components" and "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency."
- Not "generics" because the active ingredients are not the same, but merely similar.

Interchangeable Biosimilar

- Meets the standards in subsection 351(k)(4) and biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. (351(i)(3))
- 351(k)(4) requirements
  - Biosimilarity, and
  - Can be expected to produce the same clinical results as the reference product in any given patient, and
  - No additional risk of switching between reference and interchangeable product

FDA U.S. FOOD & DRUG ADMINISTRATION

Drug Labeling

Michele Fedowitz, MD

February 21, 2020

Agenda

- Labeling Terminology
- Prescribing Information (PI)
- Information contained in various sections of the PI
- Abbreviated New Drug Application (ANDA) requirements for Pregnancy and Lactation Labeling Rule (PLLR) updates

Terminology

Label

Any display of written, printed, or graphic matter ***on the immediate container*** of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity

21CFR1.3 (b) / FD&C Act section 201(k)

Labeling

All labels, as well as other written, printed, or graphic matter ***accompanying the product***.

21CFR1.3 (a) /FD&C Act section 201(m)

“Labeling”

- Carton and Container Labels
- Prescribing Information (PI) “Package Insert”
- Patient Labeling
  - Patient Instructions for Use, Patient Information, Medication Guide
- Operator Guide (User Manual)

“Labeling”

- Carton and Container Labels
- **Prescribing Information (PI) “Package Insert”**
- Patient Labeling
  - Patient Information, Patient Instructions for Use, Medication Guide
- Operator Guide or User Manual

Prescribing Information Basics

- PI is written for the Prescriber - not the Patient
- PI is a summary of the essential scientific information needed for safe and effective use of drugs and biological products
- The entire drug development process contributes to the data to support the NDA
- The label is supported by data in the NDA

Prescribing Information Basics

- Physician Labeling Rule (PLR) Format took effect in 2006

- Contents of the Prescribing Information (PI)
  - **Highlights**
  - **Table of Contents**
  - Full Prescribing Information

21 CFR 201.56 and 201.57

Physician's Labeling Rule Requirements for Prescribing Information

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

BOXED WARNING

BOXED WARNING

Dosage and Administration (2)

- DOSE
- ADMINISTRATION
- IMAGING INSTRUCTIONS
- PREPARATION
- DOSIMETRY
- SPECIAL INSTRUCTIONS

Dosage and Administration

DOSE

- Recommended Dose
- Dose Range / Maximal Dose

ADMINISTRATION

- Duration
- Medication Withdrawal (Drug Interactions)
- Fasting / Activity (Exercise Abstinence)

Dosage and Administration

IMAGING INSTRUCTIONS

- Image Acquisition Guidelines
  - Timing and Duration
  - Location (head, body)
  - Patient Instructions (voiding)
  - Device Parameters (e.g. 2D or 3D PET, software reconstruction)
- Image Display
  - Orientation
  - Coloring Display
- Image Interpretation
  - “Positive” vs. “Negative”

Dosage and Administration

(no) PREPARATION

- **Ready Made Product**

- Ga 68 DOTATOC Injection
- Fludeoxyglucose F 18 Injection
- Florbetapir F 18 Injection
- Flutemetamol F 18 Injection
- Florbetaben F 18 Injection

Dosage and Administration

PREPARATION

Kits – kit for the preparation of:

- Ga 68 Dotatate Injection
- Tc 99m Exametazime Injection
- Tc 99m Pentetate Injection
- Tc 99m Sestabamibi Injection
- Tc 99m Tetrofosmin Injection
- Tc 99m Sulfur Colloid Injection

Generators (to elute):

- Technetium Tc 99m
- Rubidium Rb 82
- Gallium Ga 68

Dosage and Administration

PREPARATION (kits/generators)

- Radiopharmacy Instructions
  - Procedures to reconstitute (radiolabel) the kit components to produce the end product
  - Procedures to elute the generator
  - Quality Control / Acceptance Criteria
    - Radiochemical Purity (labeling efficiency)
    - pH
    - Appearance

Dosage and Administration

PREPARATION

- Shelf life of the product
- Storage and disposal of radioactive product

Dosage and Administration

DOSIMETRY

- Estimated radiation absorbed dose to the patient by organ and total effective dose
- Established early (Phase 1/safety)
- International Commission on Radiological Protection (ICRP)

Dosage and Administration

SPECIAL INSTRUCTIONS

- Reduction of radiation exposure for patients
- Reduction of radiation exposure for workers
- Proper disposal of unused product

Use in Specific Populations (8)

- **PLLR** Pregnancy and Lactation Labeling Rule
- December 2014 final rule ***revised the content and format of pregnancy (8.1), lactation (8.2), and females and males of reproductive potential (8.3)*** information in labeling
- Rule is effective June 30, 2015
- Labeling approved following June 30, 2001 is required to come into compliance

PLLR

- Label ***format change*** to reflect an integrated assessment of known risks relevant to pregnancy, lactation and infertility based on available information/data

Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf

Pregnancy and Lactation Labeling Final Rule

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

Use in Specific Populations (8)

PREGNANCY (8.1)

- Risk Statement
  - Animal data
  - Human data
  - Pharmacologic data
- What is the risk to the fetus from the drug?
- Does it cross the placenta?
- Most diagnostic radiopharmaceuticals are NOT contraindicated in pregnancy

Use in Specific Populations

LACTATION (8.2)

- Risk Statement
  - Animal data
  - Human data
  - Pharmacologic data
- Is it excreted in breast milk?
- Is it ingested by the baby?
- What is the duration of breastfeeding interruption to limit exposure?

Description (11)

- Contains important chemical and physical information

- Radioactive Characteristics
  - Radioactive decay scheme (types of radiation emitted)
  - Decay properties (half-life)

Storage and Handling (16)

- Typically for the pharmacist or the person receiving shipment
- NDC Code
- Radiopharmaceuticals safe and effective use require a radioactive materials (RAM) license

Patient Counseling Information (17)

- Information from a healthcare provider to a patient **after** administration or a decision to administer drug is made.
  - Measures to reduce radiation exposure
  - Breast feeding interruption
  - NOT contraindications
  - NOT patient instructions for use

Abbreviated New Drug Applications (ANDAs) and the Pregnancy and Lactation Labeling Rule (PLLR)

ANDA Labeling

- ANDA proposed labeling must be the same as the as reference listed drug except for
  - Changes required because of differences approved under a petition (21 CFR 314.93)
  - Different manufacturer/distributor
  - Indications or other aspect of labeling protected by patent or exclusivity
  - Occasional exceptions or carveouts

21 CFR 314.94(a)(8)(iv)

Updating ANDA Labeling

- ANDA holder is responsible for updating their label to comply with the Reference Listed Drug Labeling
- Updates within a reasonable timeframe
- CBE (0)

In Conclusion

- PET products are NDAs governed by the drug labeling regulations *(21 CFR 201.56 and 201.57)*
- New updates and formatting to the PI are geared to make information easier to access, read, and use
- ANDA label should match the RLD and is the responsibility of the ANDA holder

REQUIREMENTS FOR ELECTRONIC SUBMISSION OF REGULATORY APPLICATIONS

PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

February 21, 2020

CDR Mathilda Fienkeng, PharmD, MS, RAC
Director, Division of Medical Policy Development
Office of Medical Policy Initiatives
Office of Medical Policy
Center for Drug Evaluation and Research

Focus of Presentation

- Regulatory Background
- Electronic Common Technical Document (eCTD) Guidance Revision 7 Updates
- Regulatory Submission Requirements for Positron Emission Tomography (PET) drugs and Type II Drug Master Files (DMFs):
  - For PET drugs that qualify for a waiver (including process for requesting a waiver)
  - For PET drugs that do not qualify for a waiver

Regulatory Submission - Background

- Section 745A(a) of the FD&C Act:
  - **Authorization for FDA to implement** the statutory electronic submission requirements in guidance
  - Required that FDA "shall" issue such guidance
- Section 745A(a)(2) of the FD&C Act:
  - **Allows FDA to establish exemptions** from the electronic submission requirements
- FDA issued the eCTD guidance which describes how sponsors and applicants **must organize the content** that they submit to the Agency electronically **for all submission types** under section 745A(a) of the FD&C Act

Implementation Timeline

- May 5, 2017: New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs), must be submitted using eCTD format
- May 5, 2018: Commercial Investigational New Drug Applications (INDs) and Master Files must be submitted using eCTD format
- July 27, 2018: FDA implemented validation check for fillable form
- As of May 2020, eCTD Guidance (revision 7) will be in effect

eCTD Guidance (Revision 7) Overview

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Guidance for Industry) describes **how sponsors and applicants must organize the content** that is submitted to the Agency electronically

Why was Revision 7 Necessary?

FDA identified certain submission types **that warrant an exemption, or a long-term waiver,** from the requirement to submit to the Agency in eCTD format

Updates in Revision 7

- Section I. Introduction
- Section III.C. Types of Submissions That are Exempted
- **Section III.D. Types of Submissions That May Qualify for a Long-Term Waiver***
- Section III.E. Types of Submissions That May Qualify for a Short-Term Waiver

*Applicable to PET Drugs

PET Drug-Related Considerations

- PET Drugs
  - **Unique production methods**
  - Many are **characterized by their short half-lives** requiring facilities close in proximity to the patients to whom the drugs are administered
- Certain Type II DMFs
  - Submitted in **support of an application for a PET drug** (i.e., IND, NDA, ANDA, or BLA) and
  - Contain information regarding **radiolabeled drug products** or **production of PET radionuclides**, and
  - The Type II DMF holder is an **academic institution**, **government** (state or federal) **entity**, or a **non-profit research organization**

Waivers from eCTD Requirements

- Section 745A(a)(2) authorizes FDA to **establish criteria for waivers** from its electronic submission requirements
- FDA **may grant a long-term waiver** from the eCTD requirements under section 745A(a)(2) in ~~the~~ certain circumstances
- Certain PET Drugs and Type II DMF Submissions **may qualify for a waiver** from the eCTD requirement

Criteria for eCTD Waivers

PET Drugs and Certain Type II DMFs

- PET drugs are the **only FDA-regulated drug products** (other than noncommercial drug or biologic products) **manufactured or produced by the sponsor or applicant**

- The sponsor or applicant explains that, because it

- Submitted in **support of an application for a PET drug** (i.e., IND, NDA, ANDA, or BLA) and

- Contain information regarding **radiolabeled drug products** or **production of PET radionuclides**, and

- The Type II DMF holder is an **academic institution, government** (state or

FDA may grant a waiver

Requesting a Long-Term Waiver

- A waiver request should be sent to FDA **before submitting the document(s)** for which the corresponding waiver is being requested
  - Explanation **why compliance cannot be achieved**
  - Description of **proposed alternative submission format** to be used during the waiver period (e.g. PDF files following CTD structure)

Where to Submit Waiver Requests

- CDER: Email to esub@fda.hhs.gov
- CBER: Email to ESUBPREP@cber.fda.gov
- Waiver Request should reference all products that are to be covered by the waiver
- Waiver request should be clearly titled "**LONG-TERM WAIVER REQUEST — eCTD REQUIREMENTS**" in bold capital letters at the top of the first page of the submission

FDA Response to Waiver Requests

- Requests are considered on a **case-by-case basis**
- FDA responds in writing (generally):
  - Noting whether the waiver is granted or denied, and whether the proposed alternative submission format is acceptable
- Process for Subsequent Requests (after initial request is granted):
  - The requestor should include a statement in the cover letter of each subsequent submission(s) indicating that an eCTD submission waiver has been granted previously by FDA, including the dates for the waiver

Granted Long-Term Waivers

- **Valid for five (5) years** from the date the waiver is granted
- **Apply only to the requestor**, and is not transferrable to another sponsor or applicant
- Sponsor/applicant **may reapply to recertify their eligibility for this waiver up to 6 months before the waiver expiration date**, using the same process
- If the criteria are no longer met at the time of recertification, the waiver will not be granted

Requirements for Submissions that Do Not Qualify for a Waiver

- Sponsors and applicants **must** organize the content that they submit to the Agency **electronically** for all submission types under section 745A(a) of the FD&C Act

- For additional information on how FDA interprets and intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, please see the guidance for industry ***Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act*** (December 2014)

- For the most recent version of a guidance, check the FDA eCTD web page at **https://www.fda.gov/ectd**

Requirements to Submit Electronically

- eCTD Specifications
  - Sponsor must submit electronic submissions using the version of eCTD **currently supported by FDA**
- Pre-Submission Considerations
  - Before making the first electronic submission to an application, you must obtain a **pre-assigned application number** by contacting the appropriate Center
- Submission Structure
  - Document granularity, or the level for which the submission content is broken out into separate files, **must be consistent** with the *Granularity Document* found in the ICH guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* (October 2017)
- File Formats and Versions
  - Files within an eCTD submission **must adhere** to the formats and versions specified in the associated FDA technical specification *Specifications for File Format Types Using eCTD Specifications*

Requirements to Submit Electronically

- Document Life Cycle
  - If a document **replaces a document previously submitted** with an eCTD backbone file within the same application, you **must use the eCTD replace operation** to indicate this
- Summary of Clinical Efficacy and Summary of Clinical Safety
  - The location of these documents within the eCTD **must adhere** to the FDA guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (April 2009)
- Datasets and Study Information
  - Datasets **must only be provided in modules 3, 4, or 5**
- Transmitting Electronic Submissions
  - For submissions that are **10 GB or smaller**, you **must use the FDA ESG***
- FDA Forms
  - Electronic submissions **must include only FDA fillable forms** (e.g., Form FDA 1571 or Form FDA 356h) and **electronic signatures**

*Electronic Submissions Gateway

Restrictions on Submission of Paper Copies

- When submitting in eCTD format, **paper copies** of the application, including review copies and desk copies in paper, **must not be submitted**
- The **only exception** to this is the **submission of paper copies of meeting briefing materials**, **when requested**, as described in the FDA guidances for industry on formal meetings between the FDA and sponsors or applicants

Receipt Date

- The **receipt date** for an electronic submission **will be determined only after the submission has passed a technical validation check** to ensure that it can be opened, processed, and archived
- The **submitter is responsible for monitoring their receipt pathway** to determine whether a submission has been rejected

Submission of Promotional Materials

- Submissions of promotional materials to the Office of Prescription Drug Promotion in CDER and the Advertising and Promotional Labeling Branch in CBER include:
  - **Postmarketing submissions** of promotional materials using Form FDA 2253
  - Promotional materials for **accelerated approval products** and other products where such submissions are required for approval
- The guidance *Providing Regulatory Submissions in Electronic and Non-Electronic Format — Promotional Labeling and Advertising Materials for Human Prescription Drugs* explains certain aspects of electronic submission of promotional materials in module 1 of the electronic common technical document (eCTD), using version 3.3 or higher of the *us-regional-backbone* file.
- For more information on submissions of promotional materials for human prescription drugs:

  https://www.fda.gov/media/128163/download

See eCTD Website for Further Information

- For current versions and updates of the eCTD guidance, important dates, notices, and a complete listing of the current technical supportive files:

  https://www.fda.gov/ectd

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- Paris A. Watson
- Dorothy West

Questions


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Back-up Slides

eCTD Specifications

- Sponsor must submit electronic submissions using the version of eCTD currently supported by FDA
- The version of eCTD currently supported is specified in the Data Standards Catalog (available at https://www.fda.gov/media/85137/download) and is further described in the following technical specification documents:
  - International Council for Harmonisation (ICH) *Electronic Common Technical Document Specification*
  - ICH *eCTD Backbone File Specification for Study Tagging Files*
  - FDA *eCTD Backbone Files Specification for Module 1*

Pre-Submission Considerations

- Before making the first electronic submission to an application, you must obtain a pre-assigned application number by contacting the appropriate Center
  - Information on obtaining a pre-assigned application number may be found on the eCTD web page (https://www.fda.gov/ectd)

Submission Structure

- Document granularity, or the level for which the submission content is broken out into separate files, must be consistent with the *Granularity Document* found in the ICH guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* (October 2017) unless otherwise specified in the ICH M2 technical specification *eCTD IWG Question and Answer and Specification Change Request Document*

File Formats and Versions

- Files within an eCTD submission must adhere to the formats and versions specified in the associated FDA technical specification *Specifications for File Format Types Using eCTD Specifications*
- Portable Document Format (PDF) files submitted must adhere to the FDA technical specification *Portable Document Format (PDF) Specifications*

Document Life Cycle

- If a document replaces a document previously submitted with an eCTD backbone file within the same application, you must use the eCTD replace operation to indicate this, rather than submitting the file as new
- You must not indicate that files are new if they are in fact replacing files already submitted. If you intend to remove a file, you must use the delete operation
- For instructions, see the ICH M2 technical specification *Electronic Common Technical Document Specification*

Summary of Clinical Efficacy and Summary of Clinical Safety

- When submitting a Summary of Clinical Efficacy and/or Summary of Clinical Safety, the location of these documents within the eCTD must adhere to the FDA guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (April 2009)

Datasets and Study Information

- Datasets must only be provided in modules 3, 4, or 5 and not in modules 1 or 2
- When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification *eCTD Backbone File Specification for Study Tagging Files*
- Datasets must be referenced in an STF using the appropriate STF *file-tag* describing the document's contents

Transmitting Electronic Submissions

- For all submissions that are 10 gigabytes (GB) or smaller, you must use the FDA ESG
- For submissions that are greater than 10 GB, refer to the FDA technical specification *Transmitting Electronic Submissions Using eCTD Specifications*

FDA Forms

- Electronic submissions must include only FDA fillable forms (e.g., Form FDA 1571 or Form FDA 356h) and electronic signatures to enable automated processing of the submission
- Scanned images of FDA forms will not be accepted

Session IV – Session IV: Changing Landscape of PET Drugs, Labeling Requirements, and Electronic Filing Requirements
Q&A Discussion Points

- In the past FDA has indicated that:
  - Stability data for three batches at the upper range of proposed radio concentration should be provided to support expiration dating period. Three batch release data from each site should be provided to support that site is able to manufacture the drug product.
  - We are not looking for site-specific stability data. So as long as the manufacturing process is the same, uses the same synthesizer, same source of raw materials, the data from a central site should be okay, and stability data from each site is not necessary.
- Can the PET community rely on this guidance?

Session IV: Electronic Filing Requirements

- When will the new version be published and what happens following its publication?
- How long would it take to respond to a request for a long term waiver?
- How would such a request be verified?
- What do we anticipate as a reason for possibly denying the request?
- Does FDA recommend a particular format for a non-e-CTD submission? Should we expect additional information in this regard?

Session IV – Session IV – Session IV: Changing Landscape of PET Drugs, Labeling Requirements, and Electronic Filing Requirements

Q&A Discussion Points

Can a PET drug manufacturer with approved ANDA do additional clinical studies which would allow label changes for the ANDA drug product?

A NDA holder updated their FDG labeling on 1 July 2019 for the breastfeeding requirements of 2014. For those organizations that have based their ANDA applications on that NDA as RLD, How can the ANDA holder update their labeling? Will it be annual report, a CBE-0, CBE-30 or a prior approval supplement?

Session IV – Session IV: Changing Landscape of PET Drugs, Labeling Requirements, and Electronic Filing Requirements
Q&A Discussion Points

- If a QC method for a PET drug product is a compendial (USP monograph) method, does the method needs to validated / verified for use?

- What are the FDA's expectations regarding method transfer for newly developed products being transferred to multiple manufacturing locations? What are the expectations around site staff training?

Session IV – Session IV: Changing Landscape of PET Drugs, Labeling Requirements, and Electronic Filing Requirements
Q&A Discussion Points

- How can the PET community be kept up to date with changes in FDA expectations? Could the FDA create a webpage to communicate PET-specific recent changes?