Chemistry, Manufacturing and Control Issues

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SPEAKER DISCLOSURES

Dr. Daniel Yokell is an employee of Telix Pharmaceuticals (US), Inc. The views he expresses in this presentation are his own and do not reflect the views and positions of Telix Pharmaceuticals (US), Inc. or its affiliates.

Dr. Peter Scott has no relevant disclosures.
STABILITY TESTING: HOW ARE INSPECTORS TRAINED TO ASSESS ADEQUACY OF STABILITY PROGRAMS? FOR PET MULTI-SITES/NETWORKS, SUBMITTING STABILITY DATA PER PRODUCT FROM ONE REPRESENTATIVE SITE IS CONSIDERED COMPLIANT.

CAN FDA PROVIDE SPECIFIC EXAMPLES WHERE SINGLE SITE STABILITY ANNUAL SUBMISSION ARE CONSIDERED INADEQUATE?

Perspective: For PET drugs which are made on the same synthesis platform and validated via comparability protocol under an application which demonstrates "equivalence" of the processes at the different manufacturing sites, single site annual stability is believed to be adequate.

PET drugs are manufactured on a daily (or multiple times per day) and having each site perform stability can interfere with doses being available to patients as stability runs often use a patient batch manufacturing slot.

CAN THE FDA COMMENT UPON INCONSISTENCIES IN APPLICATION OF GUIDELINES AROUND, FOR EXAMPLE, RESIDUAL SOLVENTS. WHEN A SITE FILED THEIR IND THEY WERE ASKED FOR A 10 PPM TFA LIMIT, DESPITE THE OTHER TWO SITES ON THE STUDY NOT TESTING FOR RESIDUAL TFA. THE PROCESS GAVE TFA IN THE 100s OF PPM, ALTHOUGH THE pH WAS FINE. THE FDA HAD SAID THAT THEY KNEW IT WAS POSSIBLE SINCE OTHER PLACES HAD DONE IT, BUT PROVIDED NO DETAILS. CLINICAL WORK IS SEVERELY DELAYED NOW BECAUSE SITE IS STILL REDESIGNING THE SYNTHESIS TO TRY AND GET THE TFA NMT 10 PPM

Perspective: Inconsistent application of regulations between sites, especially multiple sites on the same study like in this case, causes confusion and frustration amongst the community. Moreover, setting overly conservative release criteria without rationale (e.g. TFA is not a Class I solvent, so why request residual limits akin to benzene (2 ppm) or carbon tetrachloride (4 ppm)?), is making it extremely difficult for academic PET Centers to develop and translate new PET tracers on short grant timelines, while also managing busy production schedules, and is ultimately slowing progress, stifling innovation and reducing the competitiveness of the United States PET Community compared to other nations (e.g. Germany, where PSMA and DOTATATE were developed).
WHAT REQUIREMENTS MAY BE USED BY PET DRUG DEVELOPERS IN SUPPORT OF IMPURITIES, SUCH AS IDENTIFICATION, CHARACTERIZATION AND QUALIFICATION? DOES ICH Q3A AND ICH Q3B APPLY TO RADIOPHARMACEUTICALS? HOW CAN PET DEVELOPERS BEST LEVERAGE SUCH GUIDANCE DOCUMENTS?

Perspective: Applying commercial standards to IND products which most likely will never be commercial (e.g. C-11 compounds) is overly burdensome and hampering translation of new radiotracers to first-in-human studies. Moreover, there are general issues around expectations of literature compounds, and the fact that manufacturing under <823> guidelines are sometimes scrutinized like commercial 212 products.

PET drugs are inherently safe and have an excellent track record of safety – millions of doses are administered each year without adverse events. Microdosing of C-11 compounds, however, and particularly literature compounds such as C-11 acetate that have been used for decades, appear to be under enhanced scrutiny of late. In one instance, a group was told the impurity profile using the established SPE purification was no longer acceptable, despite having been used around the world for a long time, and needed to develop an HPLC purification. This can be done, but again takes time away from other activities and appears to be unnecessary given the small numbers of research subjects (10s) and the well-established low risk profile of radiopharmaceuticals.

CAN THE FDA PROVIDE GUIDANCE ON WHEN A QC TEST CAN MOVE FROM PER BATCH TO A PQIT, HOW A COMPANY SHOULD EVALUATE AND JUSTIFY, AND ALSO IS THERE ANY GUIDANCE ON THIS TRANSITION PROCESS?

Perspective: The guidance "Changes to an Approved NDA or ANDA" notes that changes in product specifications to comply with compendial changes can be a CBE-30 – for example the FDG and NH₃ USP monographs have been updated since many sites had initial application approval.

For sites which seek to move a compendial test from per batch to PQIT or to move to a longer PQIT test frequency i.e. quarterly to annual, this could be justified with data and appropriate risk assessment of the change according to the guidance, with submission potentially as a PAS.
FOR CMC, IF THE EQUIPMENT CHANGES, BUT THE TESTING AND SPECIFICATIONS DO NOT CHANGE, CAN THIS BE SUBMITTED AS PART OF THE PRODUCT’S ANNUAL REPORT?

Perspective: The guidance "Changes to an Approved NDA or ANDA" notes that changes to equipment which produces an equivalent product can be submitted in the annual report.

There is lack of clarity in the community around FDA expectations here – some sites are submitting CBE’s for this, while others are submitting in the annual report. For example, if a synthesis module is replaced with a new manufacturer and/or model can this change be documented in the next annual report?

WHAT IS FDA’S EXPECTATION REGARDING VENDOR QUALIFICATION FOR PET MANUFACTURERS? ARE ONSITE AUDITS REQUIRED FOR CRITICAL VENDORS OR CAN THEY BE QUALIFIED BY ALTERNATIVE MEANS?

Perspective: PET cGMPs provide for reliance on vendor performance and COAs since many firms are academics or networks with multiple sites which may require use of local vendors. Onsite audits of critical vendors has been raised during inspections and the industry believes this is will be a challenge for many firms, especially academic sites to comply with.

A more acceptable approach is continued reliance on the vendor history and COAs and documentation of key vendor qualifications in local QMS.
WHAT ARE THE EXPECTATIONS FOR TRENDING NO/LOW SYNTHESIZER YIELDS FOR MANUFACTURING EQUIPMENT?

Commerical Perspective (NDA/ANDA): Applications may not have yield specifications, in the event of no specification for yield in an approved application, trending of yields is not required.
Trending of no yield batches should occur in the local QMS with CAPA investigations as no yield is most likely considered under a site QMS as a quality event to identify root cause and remediate if possible. Since the PET industry relies in CMOs and equipment manufacturers for synthesis sequences and cassettes which are "locked", manufacturers may not have ability to immediately remediate the root cause if related to consumable/synthesis sequence. This requires working with suppliers to remediate the cause while tolerating an acceptable failure rate due to daily production requirements which does not impact quality or safety of the PET drug since no product was manufactured.

IND Perspective: Given that even multi-center IND studies frequently involve low numbers of research subjects at a given site (10s), n values are typically too low to meaningfully track / trend.

PRECURSORS ISSUES
i) TESTING BEYOND THE COA ACCEPTANCE
ii) STANDARDS FOR PRECURSOR SYNTHESIZED IN HOUSE TO VERIFY NEW PRECURSOR, UPON RECEIPT, MEETS TEST/RELEASE SPECIFICATIONS

Perspective: There is ongoing ambiguity and confusion over what standards are required to receive components intended for manufacture of PET radiopharmaceuticals. 21CFR212 states “If you conduct finished-product testing of a PET drug product that includes testing to ensure that the correct components have been used, you must determine that each lot of incoming components used in that PET drug product complies with written specifications by examining a certificate of analysis provided by the supplier. You are not required to perform a specific identity test on any of those components.”

However, sites have been requested to synthesize samples of precursor themselves to confirm identity of incoming lots ((A)NDA), while more stringent GMP criteria are even being asked for precursors in Phase 0/1 IND applications. These inconsistencies between the regulations and site experience are complicated translation of radiopharmaceuticals.
WHY IS FDA MANDATING THROUGH INSPECTION THAT HOT-CELLS ARE WIPPED DOWN WITH STERILE IPA WHEN IT IS A CLOSED SYSTEM WITH TERMINAL STERILIZATION?

Perspective: A number of sites have reported this issue arising. There is no requirement to have ISO 5 for synthesis in 21CFR212 and EM is not conducted. Hot-cells themselves are not LAFs, and synthesis modules themselves are not sterile, or necessarily even compatible with solvents like IPA. Syntheses frequently involve a closed-system and all PET drugs are terminally sterilized. Indeed, given this latter point, use of non-sterile reagents is also typical/necessary for some radiosyntheses.

There is ambiguity around this point, and it is unclear to the community what expectations are. Clarity about the FDA’s thinking would be helpful.

CLARIFICATION IS REQUESTED ON ISSUES SURROUNDING RADIONUCLIDIC IDENTITY AND PURITY TESTING:

I) TWO SOURCES ON CONSTANCY FOR DOSE CALIBRATORS WITH Co-57 AND Cs-137?
II) NEED FOR 2 METHODS OF RADIONUCLIDIC PURITY FOR SHORT- AND LONG-LIVED IMPURITIES?
III) HPGE FOR RNP FOR DECAYED SAMPLE; NEED FOR SPECTRUM?

Perspective: These issues are not clearly delineated in 21CFR212 but have cropped up for multiple sites during inspections and application reviews. It is unclear what issues the FDA is trying to solve for with all of this added work, expense and need for additional complex/ expensive equipment such as HPGE detectors. Use of 2 sources for daily constancy not in alignment with NRC regs that require 1.

PET drugs are inherently safe and have an excellent track record of safety – millions of doses are administered each year without adverse events. The PET community is unaware of a single batch of radiopharmaceutical that has failed RNP testing.
DUAL TEMP INCUBATION FOR EM MEDIA?

Perspective: Environmental monitoring (EM) remains an essential detection tool for clean environments within radiopharmaceutical-manufacturing facilities. During monitoring, plates are incubated at a specific temperature for a set time. There appears to be no single approach to incubation currently used, and some industry partners have begun asking for dual temperature incubation (TSA) or dual media (TSA/SDA).

Clarity from FDA on their thinking around this issue would be helpful as we aspire for some level of standardization throughout the industry.

LABELING ISSUES
I) ACTUAL STRENGTH (mCi/mL) AND EXPIRATION (TIME/DATE) SHOULD APPEAR ON THE DOSE VIAL LABEL
II) REPLACE THE WORD “MUTIPLE-DOSE VIAL” WITH “SINGLE-DOSE VIAL”

Academic Perspective: Strength and expiration information is not available until after the vial has been filled, and that is the reason we use Outer Container labels in PET. It is not industry practice to edit labels on vials containing radioactivity as it violates ALARA principles. Moreover, expecting PET Technologists to read expiration information on a radioactive vial and irradiate their eyes is also an egregious violation of ALARA principles. There are provisions for outer container labels in both FDA and USP regulations.

With regards to multi-dose vs single-dose vials, while it is true that most research vials are for a single subject, it is not always the case.

Perspective from FDA on what issues they are trying to solve for with these repeated requests would be helpful.
LABELING ISSUES

1) ACTUAL STRENGTH (mCi/mL) AND EXPIRATION (TIME/DATE) SHOULD APPEAR ON THE DOSE VIAL LABEL

Industry Perspective: Strength and expiration information is not available until after the vial has been filled. Some sponsors have a reduced format label approved for the vial with drug name, strength range, batch number and firm information/caution statement.

An outer shield label with full batch information (total activity, EOS, strength at EOS, expiration date/time, etc.) have been accepted as a balance between batch information on the dose and ALARA, since the drug product is stored and transported inside of a radiation shield.

INSPECTIONS FINDING ISSUE WITH SPONSOR’S CMC DURING INSPECTION AT CMOs AND ISSUING 483s

Industry Perspective: The Sponsor’s CMC is reviewed by the Agency review division(s) during application or supplement approval. CMOs are not responsible for the content in the Sponsor’s application and are often not privileged to have access to this information.

It would be helpful to clarify why CMC issues are being identified during CMO inspection and resulting in 483s when the CMO has no control over the content in the application.

Are there alternative mechanisms for the Agency to review and communicate the concerns inspectors may raise which would not result in 483s issued to the CMO?
REGULATION OF BIOLOGICS LABELLED WITH PET ISOTOPES FOR IMAGING

Perspective: There are several biologic based diagnostics in late stage development which are labelled with PET isotopes intended for imaging purposes.

There is a novel combination from a regulatory prospective; there have been no biologic imaging agents approved labelled with PET isotopes.

While it is acknowledged the drug would be regulated under the Public Health Service Act(PHS)/BLA under 21 CFR 610, there is no clear reference to 21 CFR 212 in the PHS or biologic CFRs.

21 CFR 212 definition of a "PET drug":

*PET drug* means a *radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images*. The definition includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug. “PET drug” includes a “PET drug product” as defined in this section.

QUESTIONS / DISCUSSION?