Dear Ms. Roth:

The Coalition of PET Drug Manufacturers (the Coalition) was organized in November 2010 to help manufacturers of drugs for positron emission tomography (PET) understand requirements related to the implementation of 21 CFR part 212, and to communicate with the Food and Drug Administration (FDA) on behalf of this community. Since that time, the Coalition has played an instrumental role in numerous policy issues on the behalf of PET drug manufacturers. Coalition members represent the majority of the PET drug manufacturing facilities in the US and strive to represent the interests of the entire PET community. We appreciate the opportunity to provide comments on conducting Remote Regulatory Assessments (RRAs).

**Background on Positron Emission Tomography (PET)**

PET is an imaging technique that is used to assess the biochemical processes that define the physiology of living organisms. Since diseases first manifest themselves as changes in “normal” physiology, and then later by changes in “normal” anatomy, PET imaging provides earlier detection than traditional anatomical imaging techniques such as x-ray, CT, and MRI. PET imaging is also a very sensitive technique, which can often detect diseased tissue before it is apparent anatomically. For these reasons, PET imaging is frequently referred to as “molecular imaging,” and offers individualized treatment based on the specific disease state in the patient. From a practical standpoint, PET imaging studies are performed in combination with CT scans to provide more precise information about various diseases in neurology, oncology, and cardiology. PET imaging is a relatively simple procedure that employs small doses of radioactive tracers (i.e., PET drugs). PET scans are commonly performed in hospitals and routine outpatient settings.

**Background on PET Drug Manufacturers**

PET drugs are necessary to perform a PET scan. Due to their very short radioactive half-life and unique manufacturing methods, PET drugs are inherently a different class of drugs compared to traditional drug products. The inherent differences of PET drugs impact all aspects of the PET drug manufacturing environment. For example, instead of one or two production facilities that may be required for the nationwide supply of a traditional drug product, the Coalition estimates that approximately 150 manufacturing facilities are required to provide nationwide coverage of currently approved PET drugs. This
is due to the short radioactive half-lives of PET products which range from 10 minutes to 110 minutes and longer. Each PET drug facility is a small operation staffed by two to twelve employees. Two subsets of manufacturers supply PET drugs in the US: self-producers and commercial suppliers. The terminology varies, but self-producers are often associated with academic or hospital-based centers that manufacture PET drugs for use within their own radiology or nuclear medicine department and do not typically market to third-party PET imaging centers. On the other hand, commercial suppliers manufacture PET drugs from one or several locations for use by third-party PET imaging facilities.

Self-producers and commercial suppliers are often involved as contract manufacturers for innovators in the development and commercialization of new PET drugs. Since most innovators lack manufacturing capabilities for PET drugs, innovators rely on contract manufacturing agreements with academic and commercial producers for support during the FDA approval process and for commercial distribution after FDA approval.

The inherent differences of PET drugs were recognized by Congress through the passage of the 1997 FDA Modernization Act\(^1\) and later by the FDA through the development of good manufacturing practice standards (GMPs) for PET drugs, 21 CFR Part 212.\(^2\) The FDA has recognized these differences in other areas as well, most notably with regard to inspectional practices for PET drug manufacturers\(^3\) and reductions in user fees.

**General Comments Related to Remote Regulatory Assessments (RRAs)**

In general, the Coalition supports and recognizes the value of RRAs when the FDA cannot conduct inspections due to travel limitations resulting from pandemics, natural disasters, and other unstable situations that make travel infeasible. In these cases, RRAs are an important tool for the Agency’s mission to protect public health and oversee PET drug manufacturers. In addition, the Coalition supports the use of RRAs for investigations into consumer complaints.

The Coalition and its members are concerned about the more extensive use of RRAs for routine oversight of existing PET manufacturing establishments, preparations for planned inspections, follow-up to corrective actions, and responses to previous inspections, without further definition of information collection and use by the Agency to provide the necessary level of assurance that RRAs will not increase the overall regulatory burden of manufacturers without commensurate operational benefits. The Coalition is especially concerned about a potential increased regulatory burden given the small staffing levels and small scale of operations in typical PET manufacturing facilities. Specifically:

- The Coalition recommends an explicit definition of Voluntary RRA be added. Voluntary is currently defined indirectly as non-mandatory (i.e., not 704(C) requests).
- The Coalition recommends language to ensure that declining a Voluntary RRA will not lead to delayed approvals and authorizations, and avoid the perception of coercion or indirect increased regulatory burden placed on manufacturers.

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\(^1\) Public Law 105-115, Title I, Subtitle B, Section 121, Positron emission tomography (1997).


\(^3\) See: Positron Emission Tomography (PET) CGMP Drug Process and Pre-Approval Inspections/Investigations, Compliance Program Guide, 7356.002 and 7346.832.
• The Coalition recommends incorporating language that defines the type and scope of RRA requests made to accelerate regulatory approvals without creating a net increase in overall regulatory burden.
• The Coalition requests further operational clarification about communication modalities, such as real time feedback mechanisms, closure process, timeframes around reviews and communications, and a formalization of various steps along the process flow.

Specific Comments Related to Remote Regulatory Assessments (RRAs)

In this section, the Coalition makes recommendations with references to specific line numbers in the Guidance.

1. Line 131-132 (FDA use of RRAs) – suggest insertion of the following clarifying sentences on line 132: “Although RRAs do not replace FDA inspector establishment visits (“site inspection”), their use by the Agency supplements overall risk management programs and regulatory decisions and actions regarding specific establishments. The Agency may use RRAs as partial evidence supporting regulatory actions and decisions”.

2. Line 171 (RRAs complement FDA’s authority to conduct inspections) - To what extent are RRAs expected to reduce onsite inspections (line 258-9) and over what timeframe would this reduction occur? Is it supporting internal FDA business goals (e.g., fewer inspections per review cycle) or FDA staffing goals (e.g., fewer inspectors per applications)?

3. Line 171 (shift of data collection) – using pre-COVID as a baseline, can FDA elaborate on the data shift expected by FDA under the RRA program, based minimally on the projected use of mandatory RRAs alone?

4. Line 176-79 and 185-194 (when is an information request an RRA) – how can a sponsor identify an FDA request for information that does not reference 704(a)(4) as either a voluntary RRA (177-179) or not an RRA at all (191-194)? What identifies a request as RRA (line 211), specifically is it only the explicit request by FDA for an RRA per line 289-290?

5. Line 229-231 (FDA discretionary power vs need for stakeholder transparency) - If FDA explicitly mentions a request as being RRA, does FDA anticipate providing the rationale/justification for using the RRA process with the (initial) establishment request (lines 209-222), especially regarding (non-mandatory) participation requests?

6. Line 233 (RRA use and compliance inferences) – As FDA will not use RRAs and on-site inspections concurrently (line 236-7), can a sponsor infer that the mark of a successful RRA process is the absence of - or reduction of need for - on-site inspection? Conversely, does initiating an RRA process convey a perceived stronger compliance history and lower compliance risk for the establishment?

7. Line 243 (post inspection and 483 follow-up) – does FDA intend to perform post-inspections follow-up via RRA as much as possible? In what way would this be different from current controlled communication correspondence?

8. Line 265 (risk-based approach) – this speaks to FDA benefits, however, to what extent will industry benefit from the higher information level available to FDA, including to what extent will FDA make elements of risk assessment available to industry (this information has been unavailable historically)?
9. Line 267 (RRAs for compliant manufacturers follow up) – as noted earlier, this statement again infers a more intensive use of RRAs for manufacturers with favorable history of compliance. Is this accurate?

10. Line 289-90 (awareness of voluntary RRA participation) – Can it be clarified that for an RRA to be voluntary the following must occur: a) FDA must request it and the manufacturer acknowledge it (line 287-290), and b) FDA and establishment will together define the logistical needs around the scope of the RRA (line 291-294).

11. Line 298-300 (awareness of mandatory RRAs): establishments will always be aware of being subject to a mandatory RRA by receiving Form 4003 following a request pursuant to 704(a)(4), which will always be stated in writing by FDA. Can this be confirmed?

12. Lines 304-305, 320, 480 and 502-507 (FDA Feedback under RRAs) - For remote interactive evaluation as part of the RRA process, a clearer definition of FDA feedback during and after the RRA is recommended. Although RRAs do not lead to issuance of 483, the RRA process (especially remote interactive evaluations) involves dynamic and real-time interactions similar to on-site inspections. As such, there should be similar opportunities for real-time feedback and real-time minor establishment corrections, as well as for the opportunity of a real time (e.g., daily) “debrief” meeting. In addition, an establishment may feel the need for formalization of findings to support accurate and actionable source material for the establishment. This appears especially relevant since such information is then made publicly retrievable (question 16, lines 489 and 495, and line 507). Lines 320, 480 and 502 should be revised (i.e., remove the term “may” and “ordinarily”) to include minimally a closure meeting and the issuance of a report.

13. Line 320, question 7 (FDA Feedback under RRAs) – For Documentation Request conducted under 704(a)(4), the potential benefits are direct to FDA, but generally indirect and inferred to establishments. Of note, FDA notes that the process “may enhance the establishment’s preparedness for their next FDA inspection” (line 255-256). Many establishments experience no FDA feedback at the closure of a mandatory request under 704(a)(4), generally described as a “black hole” activity. As stated in paragraph # 12, we request the ability to receive feedback on the FDA reviews of documents provided in order to meet the stated goal of supporting establishment preparedness. Specifically, we reiterate the requests in the above paragraph for lines 320 and 480. We also request that the RRA report be made available to the establishment (line 502).

14. Line 485 (FDA Documentation Format) – For US based establishments, what form will the written report take (it is 483s for foreign establishments per note 29)? If a memorandum, please briefly address how these may be compiled/aggregated by FDA and rendered searchable by 3rd parties under public information request?

15. Line 333-342 (contribution to review delays of RRAs vs on-site inspections) – the paragraph implies that on-site inspections will be secondary tools, occasionally tools of last resort, in assessing establishment compliance. Can FDA articulate the possible perception of coercion around RRAs in spite of the term “voluntary”.

16. Line 357 (technological expectations) – regarding live streaming of videos, has FDA incorporated the needs and restrictions around specific businesses to ensure enforcement equity, such as the extensive shielding of nuclear medicine manufacturing that inherently shields WIFI signals and degrades video communication?
17. Line 364 (technology/quality of remote connection) – remote viewing capabilities may not be possible in some areas of PET manufacturing facilities due to poor connectivity that results from shielding for purposes of radiation protection

18. Line 360 (submission approach) – can FDA refine the vague statement of submission “electronically or through other means”?

19. Line 454 (data submission format) – are electronic submissions made via email or through the electronic gateway? Many PET manufacturing facilities do not have access or capabilities to use the electronic gateway.

20. Line 494 (establishment response) – Unless there are reasons for FDA to ignore the establishment response provided in due time, the term “generally” should be omitted. It is noted that considering a response does not mean agreement with its content, however the response should minimally be a relevant document pertaining to the RRA process (as recognized in note 8).

Thank you for the opportunity to comment on this important matter. Please contact Charles Metzger, Coalition Executive Director, if you need additional information or have any questions. Charles can be reached at cmetzger@petdrugmanufacturers.org.

Sincerely,

Henry VanBrocklin, Ph.D.                         Steve Zigler, Ph.D.
Co-Chair                                Co-Chair
Coalition of PET Drug Manufacturers         Coalition of PET Drug Manufacturers