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Request for Agency to Publish Second Draft of FDA Draft Guidance on Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

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The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international non-profit association comprised of companies that develop, manufacture, market, and support research and development of inhaled and nasal drugs and biologics (INDBs), with substantial experience and interest in drug delivery and combination product topics. Current IPAC-RS member companies are listed at https://www.ipacrs.org/about.

In recent years, IPAC-RS has been engaged with the Agency on the topic of Essential Drug Delivery Outputs, including submitting extensive public comments[1] on the June

[1] IPAC-RS 2024 Comments on the FDA Draft EDDO Guidance, https://www.regulations.gov/comment/FDA-2024-D-2560-0011

2024 FDA draft Guidance on *Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products*[2] (draft EDDO Guidance).

We are writing today as the Agency has signaled its intention to finalize the draft Guidance on *Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products* in 2026-2027[3]. In the intervening time since the issuance of the draft EDDO Guidance, the document has been further assessed and analyzed by individual companies and industry consortia and has been the subject of a number of public presentations on fundamental issues on the draft Guidance. It is our firm hope that the Agency will take public comments onboard in earnest, and revise the draft Guidance such that it better aligns with existing tenets of medical device and combination product development, manufacturing, and application submissions. However, IPAC-RS also recognizes that if the Agency makes the updates we see as required to ensure successful implementation of the guidance, core tenets and content of the document will need to fundamentally change.

Given the extent of changes expected to the draft Guidance, IPAC-RS recommends that the Agency issue a second draft version of the Guidance rather than progressing the document to final in one revision. We believe this approach is consistent with Good Guidance Practices[4] for controversial topics and potential conflicts with recognized standards and will ultimately produce a better outcome for the Agency and the combination products and medical device industry, ultimately better serving the patients that rely on these products for improved health and wellbeing.

Additional information supporting the IPAC-RS recommendation is provided within the paragraphs below.

Background

In June 2024, the FDA released a draft Guidance on Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products[2] (hereafter referred to as the Draft EDDO Guidance). The draft EDDO Guidance described Agency expectations on

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[2] Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products | FDA OCP/CBER/CDRH/CDER June 2024

[3] OCMO Guidance Agenda. January 13, 2025. https://www.fda.gov/about-fda/ocmo-guidance-documents/ocmo-guidance-agenda

[4] US FDA. Food and Drug Administration Report and Plan on Best Practices for Guidance. 2024. https://www.fda.gov/regulatory-information/guidances/background-fda-good-guidance-practices

identification of essential drug delivery characteristics for certain medical devices and combination products, including expectations for marketing applications and implications for quality management system. The Agency's guidance was highly anticipated amongst the combination product industry, and subsequently received hundreds of comments[5] from 31 entities, including IPAC-RS. In public meetings, the Agency has stated they are examining comments received on the draft EDDO Guidance and according to recent updates to the FDA's Office of the Chief Medical Officer (OCMO) Guidance Agenda, the draft EDDO Guidance is intended to be finalized in calendar years 2026-2027 as resources permit[3].

Key Issues Identified with the Draft EDDO Guidance

In the intervening time since the issuance of the draft EDDO Guidance, the document has been further assessed and analyzed by individual companies and industry consortia and has been the subject of a number of public presentations. Several concepts in the draft Guidance have emerged that represent fundamental divergence from industry current practice, expectations and experience in developing and submitting devices intended to deliver drugs and biological products for Agency's review.

These concerns included, but are not limited to, the following:

- confusion over framing and identification of EDDOs as a 'design **input'** vs 'design **output'**,
- ensuring that only the appropriate outputs (rather than all outputs) are identified as EDDOs,
- mix-up of key concepts such as 'validation' of EDDOs vs support for acceptance criteria for EDDOs and design validation for finished devices,
- insufficient articulation of reasonable design validation evidence for drug delivery devices,
- disconnect surrounding EDDO submission content recommendations within the context of existing FDA eCTD Technical Conformance Guide and ICH Guidance,
- inconsistencies in identification paradigm and definitions for EDDOs vs existing recognized international consensus standards (e.g., ISO 11608 "Primary

[5] Public Docket with Comments on the "Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products; Draft Guidance for Industry". Availability Notice in the Federal Register on July 1, 2024 at https://www.federalregister.gov/documents/2024/07/01/2024-14409/essential-drug-delivery-outputs-for-devices-intended-to-deliver-drugs-and-biological-products-draft

Functions", ISO 20072 "Device Functionality Profile"), and long-established industry terminology (*e.g.*, Essential Performance Requirements),
- misaligned nomenclature conflicting with design control terminology,
- lack of clarity around acceptable implementation of control strategy, including suitable upstream controls versus release test requirements,
- inconsistencies in post-approval change management for EDDOs vs existing FDA draft Guidance on ICH Q12[6] Established Conditions / Primary Characteristics for drug delivery devices,
- EDDOs as a submission construct vs an implementable quality system concept with EDDO expectations relating to each design control stage.

In response to the 2024 draft Guidance, several industry groups have called for the concept of EDDOs to be aligned with those from established ICH and international consensus standards (such as ICH Q12, ICH M4Q, ISO 11608-1, ISO 20072, and others) rather than the Agency introducing a wholly new, inconsistent and internally contradictory construct.

Request to Issue a Second Draft EDDO Guidance

It is IPAC-RS's firm hope that the Agency will take public comments onboard in earnest and revise the draft Guidance such that it better aligns with existing tenets of medical device and combination product development, manufacturing, and application submissions. However, IPAC-RS also recognizes that if the Agency makes the updates we see as required to ensure successful implementation of the guidance, core tenets and content of the document will need to fundamentally change.

Under the assumption that the Agency makes the suggested and necessary improvements to the draft Guidance, we are envisioning that the content will need to change so substantially that it may not be appropriate to transition the document to a final guidance in one revision. The Agency's Good Guidance Practices[4] recognize the importance of clear connection and cohesion between draft guidance documents and their eventual final versions, and in some instances the Agency has determined that a second draft release is required. The Agency opined on this scenario as part of responding to comments on past rules amending 21 CFR part 10 and has cited examples "when the first draft Guidance on a medical or scientific topic is highly controversial and when the

[6] U.S. Food and Drug Administration. (March 2, 2020). ICH Q12: Implementation considerations for FDA-regulated products (Guidance for industry). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ich-q12-implementation-considerations-fda-regulated-products

first draft Guidance is in conflict with other widely recognized sources of scholarly guidance (International Conference on Harmonization guidance, pharmacopeial standards)" as valid reasons to support the publication of a second draft guidance[7].

Given that the comments raised by industry suggest several fundamental updates to the draft EDDO Guidance will be needed to better align with current industry practice and international consensus, IPAC-RS believes that publication of a second draft version will provide the public and the Agency with additional opportunities for collaboration before the underlying concepts are finalized.

Conclusion

Public feedback on the 2024 Draft EDDO Guidances identified a number of significant concerns. The issues raised in public comments deserve careful attention and further discussion before the EDDO Guidance is finalized. A Revised Draft of the Guidance should therefore be published for public review and analysis.

As stated in the 2024 IPAC-RS Comments[1], IPAC-RS would be willing to participate in further discussions with the Agency and any other interested parties, including through a public workshop, as appropriate.

IPAC-RS remains committed to advancing the science and science-based regulation of orally inhaled and intranasal drugs and biologics, and to collaborating with all stakeholders in ensuring the timely availability of critical and life-saving medicines to the patients.

[7] Administrative Practices and Procedures; Good Guidance Practices: A Rule by the Food and Drug Administration on September 19, 2000. https://www.federalregister.gov/documents/2000/09/19/00-23887/administrative-practices-and-procedures-good-guidance-practices