TransCelerate BIOPHARMA INC.

FDA PMSR Drug Device Combination Implementation Guide

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1. Introduction and Scope

Scope

This guide attempts to identify the challenges associated with interpreting the relevant guidances (see below) and offers suggestions for practical application. It provides points to consider for combinations products approved under a NDA/ANDA/BLA that contain a device constituent part.

The following regulations and guidances are considered in this document:

- FDA Final Rule 21 CFR Part 4 *December 2016*
- FDA's Postmarketing Safety Reporting for Combination Products DRAFT Guidance for Industry and FDA Staff *March 2018* (referred to in this document as "the draft guidance")
- FDA's Compliance Policy For Combination Products Postmarketing Safety Reporting *March 2018*

NOTE: A BLA or Device Application for a combination product that contains a drug constituent part and ANDA/NDA or Device Application for a combination product that contains a biological product constituent part are out of scope for purposes of this Implementation Guide.

1. Introduction and Scope

Problem statement

Historically, drugs, devices and biological products each have their own set of post-marketing safety reporting regulations. As such, applicants typically have had individual approaches to each. With the issuance of this FDA draft guidance, applicants are tasked with identifying new approaches to ensuring consistent and complete reporting, as well as avoiding duplicate reporting.

Applicants describe the existence of a quality system for MDR reporting and one for adverse event reporting for drugs /biologics. With the issuance of the draft guidance, applicants are required as a practical matter to take a holistic view of patient safety for combination products and their quality systems now must consider each other in an integrated manner.

In the context of this document, "Quality System" refers to an applicant's processes and procedures for post-marketing safety reporting for both devices and drug/biologics.

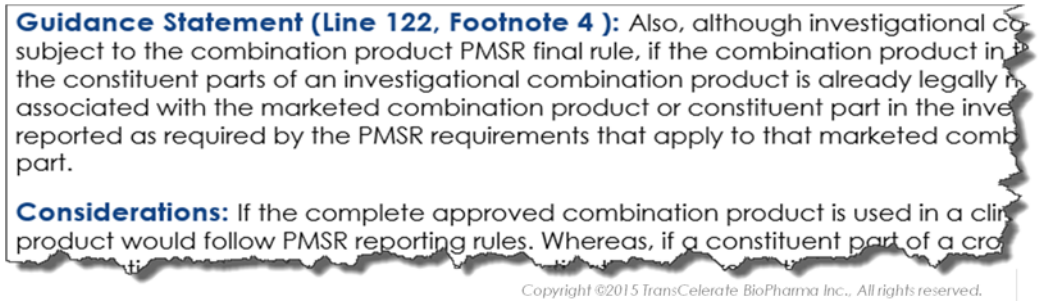
1. Introduction and Scope

Project Methodology

With issuance of the draft guidance, the TransCelerate IPVR initiative identified a team of SMEs to interpret and provide points for consideration on the new draft guidance. As such, the team highlighted areas that were ambiguous. This document is the results of discussions to address those ambiguous areas. It is not meant to repeat what is in the guidance or describe all sections of the guidance. It should not be considered as legal guidance.

How to Use This Guide

The TransCelerate team authoring this guide considered various sections of the draft guidance and focused on those that were ambiguous. These ambiguous areas were identified through the collection of Member Company pain points. For each, the section, the specific provision of the draft guidance is listed "(Guidance Statement"), along with the specific line in question. Following the guidance statement, the team provides considerations, visuals and thoughts on this specific line in question.



2. Defining a Combination Product and Information Sharing

Guidance Statement (Line 40): Per the draft guidance, a combination product is a product comprised of any combination of a drug, a device and a biological product. Each drug, device and biological product included in a combination product is referred to as a "constituent part" of the combination product. A complete definition can be found in 21 CFR 3.2(e).

Considerations: TransCelerate identified a best practice pursuant to which a company creates a list of its US approved products which are or would have been approved as a combination product based on the definition in the guidance. The list could also include

- Type of application (NDA/aNDA/BLA)
- Type of Combination Product (single entity, co-packaged, cross-labeled)
- Reporting requirements (in addition to 15-Day reporting requirements)

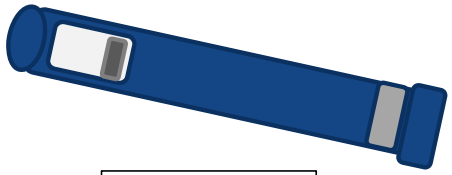
It is highly advisable that companies consider employing a cross-functional team with expertise in (for example) Safety, Regulatory, Legal, Device Engineering and Quality to ensure alignment. If needed, the applicant may wish to consult FDA.

2. Combination Product Examples

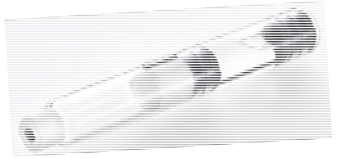
Example Single Entity Combination Product (Line 46)

Example Co-Packaged Combination Product (Line 52)

Example Cross-Labeled Combination Product (Line 57)



Pen
+
Cartridge



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2. Defining a Combination Product and Information Sharing

Guidance Statement: A Combination Product Applicant holds the only application or all applications for a combination product **(Line 134).** A Constituent Part Applicant holds an application for a constituent part of a combination product, the other constituent part(s) of which is marketed under an application held by a different applicant **(Line 148).**

Consideration: The obligation of the combination product applicant is to notify FDA of any reportable event and the presumption is that the FDA will notify the manufacturer of any constituent part, as applicable. Any existing contractual agreements may further define information sharing obligations.

If 2 different companies hold marketing approvals for a combination product (constituent part applicants), they should notify each other of reportable events.

2. Defining a Combination Product and Information Sharing, continued

Guidance Statement (Line 122, Footnote 4): Also, although investigational combination products are not subject to the combination product PMSR final rule, if the combination product in the clinical investigation or one of the constituent parts of an investigational combination product is already legally marketed, any adverse events associated with the marketed combination product or constituent part in the investigational setting must be reported as required by the PMSR requirements that apply to that marketed combination product or constituent part.

Considerations: If the complete approved combination product is used in a clinical investigation, the combination product would follow PMSR reporting rules. Whereas, if a constituent part of a cross-labeled or co-packaged combination product is used in clinical investigation, only reporting rules for the commercially approved constituent part are applicable.

Combination Product Reportable Event

Approved single entity with new auto-injector. Events that meet criteria for combination product reportable event, must be reported because complete approved combination product is used in clinical investigation.

Single entity combination product + new autoinjector = Reporting required for single entity combination product

Not a Combination Product Reportable Event

Parts of approved combination product used in clinical investigation but not entire combination product therefore events are not reportable to **combination product application**.

Drug product as part of co-packed combination product + new pump = no combination product reporting

3. Considerations for Implementation of Draft Guidance

Guidance Statement (Line 494): Fifteen-day reports for combination products must address foreign experiences consistent with the requirements for drugs and biological products.

Considerations: All combination product applicants need to ensure that affiliates in rest of world can capture and report foreign experiences so that these can be reported to FDA in alignment with the PMSR rule.

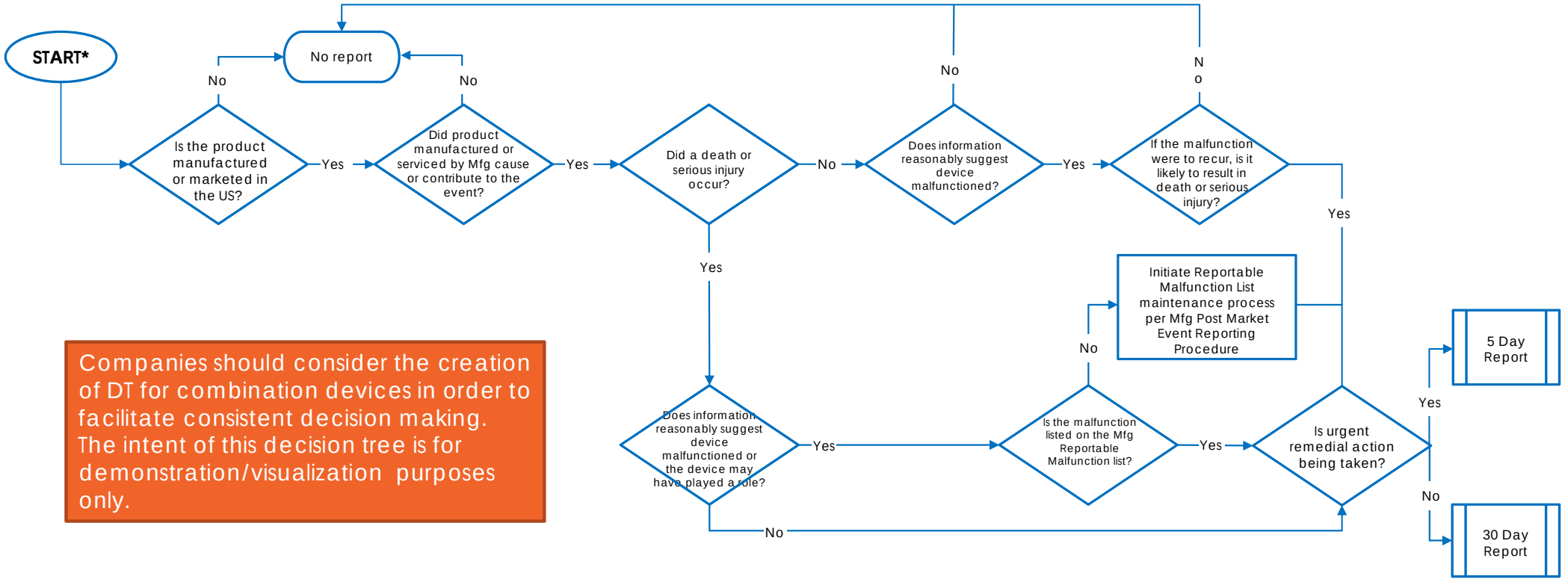
Guidance Statement (Line 396): Malfunction reports are required when the applicant receives or otherwise becomes aware of information that "reasonably suggests" that the product has malfunctioned and the product, or a similar product marketed by the applicant, "would be likely to cause or contribute to a death or serious injury if the malfunction were to recur".

Considerations: Best practices include:

- Conducting risk management leveraging ISO 14971 for combination products with device constituent parts to determine potential sources of harm (hazard), potential failure modes and related harms. For each harm, determine severity and probability of occurrence. Following this analysis, applicants should be able to identify malfunctions that "would be likely to cause or contribute to a death or serious injury."
- Creating a list of all malfunctions including reportable, non-reportable, and those that require evaluation, to allow a more efficient and consistent approach to making the reportability decision. Consideration should be given to who contributes to the list. At minimum, include Engineering and Drug Safety.
- Decision trees to help manage the reportability decision for new malfunctions. The decision tree can include when to escalate for medical judgement. The following slide provides an example of a Device Decision Tree

3. Example of a Medical Device Only Decision Tree

Example Decision Tree For Medical Device Only



Companies should consider the creation of DT for combination devices in order to facilitate consistent decision making. The intent of this decision tree is for demonstration/visualization purposes only.

4. Receipt of a Serious and Unexpected event

Guidance Statement (Line 319): An unexpected adverse experience is any adverse experience that is not listed in the current labeling for the product as a whole

Considerations: The expectedness should be assessed per the drug labeling.

Guidance Statement (Line 396): Malfunction reports are required when the applicant receives or otherwise becomes aware of information that "reasonably suggests" (see 21CFR 803.20 reference below for definition) that the product has malfunctioned and the product, or a similar product marketed by the applicant, "would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

21CFR 803.20 "Any information, including professional, scientific, or medical facts, observations, or opinions, may reasonably suggest that a device has caused or may have caused or contributed to an MDR reportable event."

Considerations: A product sample is not needed to determine if an event is reportable under the combination product rule. The sample is required to ***confirm*** if a malfunction actually did occur. Day 0 of a device malfunction could be on the day that the complaint is received.

5. Case Processing

Guidance Statement (Line 1180): The table below identifies which ICSR elements identified in section V.B.2 of this guidance should be included in which data field in combination product ICSRs when using the FDA Adverse Events Reporting System (FAERS) or eMDR (Electronic Medical Device) reporting system. This information is current as of the date of this guidance.

Considerations: Per footnote 31 of the draft guidance, the FDA is considering options for providing further assistance to Combination Product Applicants on the issues addressed in this Appendix and welcomes comments on the content of Appendix 4 and whether additional examples and other mechanisms to communicate this content would be helpful.

Data elements specified by FDA are not recognized as standard ICH E2B fields.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM601820.pdf

Some companies are considering MedDRA event coding, for instance device malfunction, to be able to identify these reports for aggregate periodic safety reports. Others are identifying the reports by case type (i.e. adverse events vs. adverse event with product problem).

Other companies have added the device constituent products to the company drug dictionary. This is allowing all device fields to be visible and present within the case and available for reporting. This will allow these companies to update/implement auto-narrative technology which is pulling all device related fields from the device constituent tab into the narrative of the case so they are available for reporting to FDA if the fields are not available for E2B transmission to FDA.

6. Reporting to FDA

Guidance Statement (Line 494): Fifteen-day reports for combination products must address foreign experiences consistent with the requirements for drugs and biological products

Considerations: Foreign (outside the US) adverse event experiences that meet the criteria for reporting under 21 CFR 314.80, 600.80 and/or 21 CFR 803 must be reported. See Lines 490-511 for additional details.

Guidance Statement (Line 445): Follow-up reports are required when the ICSR submitter becomes aware of reportable new information related to the event that was not available at the time of the initial report (see 21 CFR 314.80, 600.80, and 803.56).

Considerations: Follow-up reports are required when the ICSR submitter becomes aware of reportable new information related to the event that was not available at the time of the initial report. Companies should pre-determine what they consider to be “reportable new information” for instance investigation results, new information surrounding the reported event, complaint sample evaluations, and cross-references to other reports submitted for the event.

7. Periodic Reports: Summary and Analysis of 5-Day and Malfunction Report

Guidance Statement (Line 477 & 927): Under the combination product PMSR rule, periodic reporting is required for combination products marketed under an NDA, ANDA, or BLA. If such a combination product includes a device constituent part, these periodic reports must include a summary and analysis of the Five-day and Malfunction reports submitted during the reporting interval for the periodic safety reports required under 21 CFR 314.80(c)(2) and 600.80(c)(2) (see 21 CFR 4.103(d)(1)).

Considerations: Some companies plan to add US specific annex to be included in periodic safety reports (PBRER, PSUR, PADER) for combination products. This would include a summary of any 5 Day reports and Malfunction reports and highlight if any updates were made to labeling or any actions were taken as a result of these reports to minimize risk and improve safety. If there are no 5-Day or Malfunction reports during the period, this should be noted.

8. Business and Supplier Agreements

Guidance Statement (Line 625): Constituent Part Applicants must share information with the other Constituent Part Applicant(s) for the same combination product regarding an event associated with the combination product that involves a death or serious injury as described in 21 CFR 803.3, or an adverse experience as described in 21 CFR 314.80(a) and 600.80(a).

Considerations: Business partners should ensure safety data exchange agreements and other types of applicable agreements for combination products include clear delineation of responsibility for collection, assessment, information sharing, and reporting of events if applicable.

Ensure mechanism is in place for rapid notification to responsible parties so that evaluation for potential reportability can be accomplished within required timelines.

If each partner is responsible for separate regional/country-specific submissions, ensure partner notification timeframes accommodate preparation of report in time to meet most conservative regional/country requirements.

Ensure agreements contain clear definitions of terms to avoid confusion (e.g., malfunction, complaint, incident, etc.)