Combination Products Coalition

Industry Perspective of US Combination Product Rule: Postmarket Safety Reporting Challenges and Proposed Solutions

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With credit to the CPC Postmarket Safety Working Group

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1. Executive Summary

Combination products by definition are therapeutic and diagnostic products that combine drugs, devices, and/or biological constituent parts to achieve the intended use. While innovative solutions have leveraged a combination of these constituents, providing a multitude of options for patients, they pose postmarket safety regulatory and implementation challenges for both the Food and Drug Administration (FDA) and the medical device and pharmaceutical industry.

This paper takes a deep dive into some of the challenges and preparation necessary for the implementation of the 2016 final rule, 'Postmarketing Safety Reporting (PMSR) for Combination Products.' The initial expectation of the rule is that combination product and constituent part applicants are already compliant with the requirements of their respective application upon the rule's effective date of January 19, 2017. While each constituent part of a combination product is governed by one of three differing sets of postmarket safety reporting regulations, and while each set of regulations have similar provisions, there are significant differences among these regulations which address the unique characteristics of the product type. The FDA has identified six such provisions specific to drugs, biologics, or devices that need to be supplemented to ensure appropriate PMSR for combination products. The requirements for cross-labeled combination products are clearly outlined in the rule,[1] so this paper does not address in depth the applicability of the rule to cross-labeled combination products.

The least burdensome approach for compliance with the rule will require combination product and constituent part applicants, as defined in the final rule, to leverage their existing systems and manually add to the final report details related to the other constituent part by the compliance date of July 19, 2018 (i.e. information entered in narrative text as opposed to specific data fields; e.g. using the narrative section of the Individual Case Safety Report (ICSR) form as needed to ensure completeness of report[2]). While this seems theoretically simple for immediate implementation, it poses significant challenges. High volumes for certain products will make it very challenging to sustain a manual process that is also prone to errors given that the current forms and fields do not easily accommodate field elements from a different type of report. For organizations with global reporting responsibility, manual addition of details of the other constituent part will also pose a significant challenge to maintain and submit different versions of the ICSR/medical device report (MDR) based on differing combination product regulations. Additionally, for manufacturers who market more than one type of product (e.g. drugs, devices), company reporting expertise will need to be enhanced. Beyond July 2018, there exists a bigger challenge for the industry, as well as the FDA, related to the inability to review the data for all the constituent parts in a holistic manner due to lack of structured fields to accommodate the required information.

Building the right infrastructure, collectively with collaboration between FDA's various centers (Center for Biologics Evaluation and Research [CBER], Center for Drug Evaluation and Research [CDER], and

[1] 21 CFR §§ 4.102(b) & 4.103.

[2] John Barlow Weiner, US FDA Final Rule on Postmarketing Safety Reporting For Combination Products, Webinar presented on 03 February 2017, https://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm537047.htm.

Center for Devices and Radiological Health [CDRH]) and industry including device, drug, and biologic manufacturers representing various organizational sizes, therapies, and technologies may lead to a sustainable solution that allows for continuously evolving patient-centric safe therapies.

2. Introduction and Scope

The Combination Products Coalition (CPC) is a group of companies representing the drug, device and biologics industries. On 20 December 2016, the FDA published the 'Postmarketing Safety Reporting for Combination Products' final rule.[3] The CPC is grateful the final rule provides several clarifications from the proposed rule[4] and extends the implementation to 18 months from the rule effective date of January 19, 2017. This white paper conducts a comprehensive review of the final rule and includes challenges and preparation activities for implementation. It also provides an annex of simple examples to help illustrate how reporting scenarios associated with drug, device or biologic constituent parts would unfold when they are part of a combination product under the new rule.

The PMSR requires combination product applicants to comply with the reporting requirements applicable to the type of marketing application used to approve or clear their combination product. Additionally, combination product applicants must comply with a subset of six specified reports based on the other constituent parts (drug, device or biological product). The rule also defines additional information sharing requirements for cross-labeled combination products with individual market authorizations held by different manufacturers. These requirements are highlighted in the newly proposed Subpart B of 21 Code of Federal Regulations (CFR) 4 (§ 4.100 to § 4.105).[5]

The duties for both combination product and constituent part applicants under §§ 4.102(a) and (b), and for constituent part applicants under §§ 4.104(a) and 4.105(a)(1), are generally the same as for any other entity holding such an application. Effective January 19, 2017, the FDA expects that all applicants subject to this rule be in compliance with existing provisions based on their filing status, recognizing that per FDA's direction manufacturers have been requested to comply only with PMSR requirements associated with their application type at this time (prior to the July 2018 deadline).[6] For the new requirements of § 4.102(c) and (d) for combination product applicants, of §§ 4.103 and 4.105(a)(2) for constituent part applicants, and of §§ 4.104(b) and 4.105(b) for combination product applicants, the compliance date will be 18 months following the effective date of this rule.[7]

The purpose of the final rule is to build consistency and avoid duplicate reporting. Though conceptually possible, some reporting requirements for drugs, devices, and biologics are unique and these requirements create significant implementation challenges related to electronic submissions. Since

[3] 81 Fed. Reg. 92603 (Dec. 20, 2016).
[4] 74 Fed. Reg. 50744 (October 1, 2009).
[5] 81 Fed. Reg. 92625-92626.
[6] John Barlow Weiner, US FDA Final Rule on Postmarketing Safety Reporting For Combination Products, Webinar presented on 03 February 2017, https://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm537047.htm.
[7] 81 Fed. Reg. 92619.

2009, when the draft rule was proposed, FDA centers have established different electronic reporting mechanisms, e.g. E2B, HL7 for each product modality adding complexity that will require resolution prior to implementation of the final rule.

This white paper summarizes industry understanding of the PMSR rule and discusses challenges in more detail and provides recommendations for addressing the gaps including long term solutions that will require FDA and industry collaboration. Recommendations include changes to process and procedures supporting the existing provisions related to coding, data processing, and reporting of a serious adverse event (SAE)/serious injury (SI)/reportable malfunction to regulatory agencies for combination products.[8]

This document is relevant to the FDA requirements for PMSR. Specific requirements defined by other regulatory authorities are out of scope for this document. However, as applicable, practices of the World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) were considered in the assessment of the final rule.

3. Background

In the United States (US), medicinal or therapeutic products are regulated as drugs or biologics by either the CDER or CBER, and devices by the CDRH within the FDA.

The first combination products were pre-filled syringes, which became available in 1943.[9] The fields of radiobiology and in-vitro diagnostics (IVD) began to develop combination products in the 1970s and set the path for what we see as complex combination products leveraging multiple constituent part capabilities. As delivery system technology and medical device advances continue, the combination of drug-device and device-drug modalities is rapidly growing and the distinction between the modalities is becoming blurred. In some situations it is difficult to discern the application type of the final product.

In the US, combination products refer to products comprised of a combination of a drug and a device; a biologic and a device; a drug and a biologic; or a drug, biologic and device. It includes single entity, co-packaged and cross-labeled combination product types, as defined in the CFR.[10]

The FDA's final rule for PMSR for Combination Products[11] is currently the primary regulatory document guiding the reporting of death, serious adverse event, serious injury, and reportable malfunction for a combination product with the suspected constituent drug, biologic, and/or device malfunction of the combination product. The rule requires industry to comply with the requirements associated with the

[8] *See* CPC Comments on the Proposed Rule for Postmarketing Safety Reporting for Combination Products, available at http://combinationproducts.com/images/CPC-Adverse-Event-Proposed-Rule-Comments-FINAL.pdf.
[9] Sacha G, Rogers JA, Miller RL, Pre-filled Syringes: A Review of the History, Manufacturing and Challenges, 20 Pharm Dev Technol 1 at 1-11 (2015).
[10] 21 CFR §§ 3.2(e)(1) – (4).
[11] 21 CFR § 4 Subpart B (published rule).

application used to approve or clear their combination product,[12] [13] [14] in addition to meeting the following six unique specified reporting provisions based on other constituent part(s):

1. 5-Day Reports (combination product with device constituent part);
2. Malfunction Reports (combination product with device constituent part);
3. Correction or Removal Reports (combination product with device constituent part)
4. Field Alert Reports (combination product with drug constituent part)
5. 15-Day Reports (combination product with drug or biological constituent part); and
6. Biological Product Deviation Report (BPDR) (combination product with biological constituent part)

Additionally, for periodic safety reporting of combination products with a device constituent part that received marketing authorization under a new drug application (NDA), biologic license application (BLA) or abbreviated new drug application (ANDA), the combination product applicant must also include a summary and analysis of the 5-day [device] reports and 30-day device malfunction reports that were submitted during the reporting interval. An overview of these requirements, along with traditional reporting requirements expected for drugs, devices and biological products, is presented in Table 1 below. Various scenarios discussing reportability decision making based on application status are available in Appendix A.

[12] Drugs: 21 CFR §§ 310 & 314: Reports concerning adverse drug experiences on marketed prescription drugs for human use.
[13] Medical Devices: 21 CFR § 803: Reports concerning adverse events with approved devices for human use.
[14] Biologics: 21 CFR §§ 600 & 606: Reports concerning adverse experiences on marketed biologics for human use.

Table 1. Overview of Reporting Requirements for Combination Product Applicants as Required by the Combination Product Postmarketing Safety Rule*

	Application Type		
Constituent Part	**ANDA/NDA**	**BLA**	**Device Application**
Standard Filing Requirement	• 15-day report (initial & follow-up) • Field alert report • Periodic report	• 15-day report (initial & follow-up) • BPDR • Periodic report	• Malfunction report (initial & supplemental) • 5-day report (initial & supplemental) • Correction or removal report/record
Drug	• Refer to standard filing requirements	• Field alert report	• 15-day report requirements to be submitted within 30 days (initial & follow-up) • Field alert report
Biologic	• BPDR	• Refer to standard filing requirements	• 15-day report requirements to be submitted within 30 days (initial & follow-up) submitted • BPDR
Device	• Single malfunction report with available information in 15 days **or** 15-day initial report and follow up report. • 5-day report (initial & follow-up) • Correction or removal report/record • Periodic report with summary & analysis of 5-day & malfunction reports	• Single malfunction report with available information in 15 days **or** 15-day initial report and follow up report. • 5-day report (initial & follow-up) • Correction or removal report/record • Periodic report with summary & analysis of 5-day & malfunction reports	• Refer to standard filing requirements

*Gray-shaded boxes indicate current reporting requirements and orange-shaded boxes indicate new reporting requirements.
ANDA indicates abbreviated new drug application; BLA, biologic license application; BPDR, biological product deviation report; NDA, new drug application.

Outside the US, the product modalities may be registered differently and several SAE/SI reporting pathways exist for commercial products that have more than one type of constituent part. Mostly, these reporting pathways follow the requirements of the constituent part that provides the application status. For example, in the European Union, a product having drug and device constituent parts and having a drug application status follows the drug SAE reporting requirements per ICH E2B. In addition, some health authorities have provided specific postmarket reporting guidance for combination products or products comprised of drug and device constituent parts.[15] [16] Currently, countries such as the US,

[15] Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan, Q&A on Adverse Drug Reaction and Malfunction Reports of Combination Products, Administrative Notice (31 October 2014).
[16] Therapeutic Goods Administration, Australia, E2B Reports: Frequently Asked Questions, accessed on 28 November 2016 at https://www.tga.gov.au/e2b-reports-frequently-asked-questions.

Canada and Japan recognize combination products as a class of therapeutic products and in the future, other countries such as India and Malaysia will also address combination products. Thus, FDA's final rule adds to the existing heterogeneity of reporting requirements with regard to SAE/SI of combination products.

4. Implementation Challenges and Proposed Solutions

The FDA's PMSR final rule for combination products brings unprecedented challenges with implementation and incorporation into the safety and quality systems and procedures that already exist in industry today. The most impactful challenges and solutions, including long-term options (beyond the 18 months to July 19, 2018) are outlined in Tables 2 and 3 below. Table 2 outlines the challenges related to data architecture, infrastructure and organizational structure and proposes some solutions. More detailed challenges that are specific ICSR reporting are presented in Table 3, along with proposed solutions. As seen from these tables, it is evident that considerable amount of time and resources will be required on behalf of the industry to plan and implement all the requirements of the final combination product PMSR rule in a compliant manner.

Table 2. Data Architecture, System Infrastructure, and Organizational Challenges and Proposed Solutions	
Issue/Challenge	**Solution**
Data Architecture Lack of established data structure for medicinal product & Medical Device reporting, & inadequacy of the 18-month timeframe to establish new data structures (device forms do not have drug fields & vice-versa). The FDA submission scheme for E2B (R2) or (R3) & HL7 cannot currently accept both drug & device structured data in a single report. A drug submission via E2B does not contain structured fields for FDA 3500A sections D, F or H, while a device submission would not require completion of section C. Currently, FDA systems can accept structured data that is defined in E2B (R2) or (R3) & HL7, but these electronic systems do not contain all fields on paper form FDA 3500A. It is essential to have a common methodology to allow data to be used for signal detection and safety evaluation.	In the near term, in order to meet the rule compliance date of 19 July 2018, companies could provide data for the other constituent part that is not available in the E2B (drug) or HL7 (device) scheme as unstructured free text data within the narrative section, differences in the character limit between unstructured text for the drug report & device submissions, notwithstanding. Long-term solutions: (i) FDA to revise relevant reporting forms, with updates including aspects related to data architecture for all constituent part types. (ii) Industry & FDA work together to establish data architecture acceptable to both parties in order to optimize the data elements (structured fields) across devices, drugs & biologics in a manner that helps extract useful information.
System Infrastructure Integration of independent drug & device reporting systems within companies for meeting combination product reporting rule requirements. A variety of global safety and quality system applications utilized by industry that are selected & validated[17] to support the specific registered product regulatory class (device, drugs/biologics, &/or diagnostics) they manufacture. For organizations that have more than one product regulatory class (for example, markets drugs & standalone devices), often two distinct systems are set up to handle independent reporting. These independent systems will need to be integrated for reporting per combination product reporting rule requirements. Additionally, industry infrastructure is not set up to produce a single unified report & companies would need to develop systems to generate a unified report should FDA implement such an approach.	In order to accommodate the final combination product reporting rule requirements, industry will need to conduct a gap assessment of their existing global safety applications and Quality system applications (i.e. complaint, batch distribution, risk management) to determine if functional enhancements can be made or a change to a different global safety application may be required. FDA & industry should work together to define the functional requirements for a unified report (ICH E2B (R3), HL7 is a possibility). Both parties should work together to ensure an optimal infrastructure with compatible output that helps signal detection. Such a system should be designed & validated for submission with the corresponding updated FDA system. Once the requirements are defined, commercial systems would be available. In the near term, to be compliant to the rule, a manual system can be put in place.
Organizational Organizational alignment, retraining & resourcing within combination product applicant companies: (i) Differing functional responsibilities: Industry experience & knowledge of regulatory requirements & data handling processes are often aligned with the regulatory class of products marketed. Due to	Industry & FDA work on adoption of terminology that harmonizes device & drug adverse event reporting (e.g. adoption of & expansion of MedDRA SOC 27 by the device community on both industry & FDA side). Based on organizational needs & product portfolio, companies should set up a combination product organization that includes

[17] FDA, Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application (2003).

the nature of the information required to be reported & associated regulatory requirements, many device companies utilize their quality organizations to support AE case management (processing/reporting) under the oversight of a medical device safety physician, while most pharmaceutical companies utilize their safety organization for AE case management. Even for those companies that support both medical device & pharmaceutical case management in their safety organizations, there is usually a separation of responsibilities with distinct sub-teams to support each regulatory class. (ii) Differences in terminology: MedDRA coding & terminology are used as AE classification dictionary for drug reporting while FDA medical device codes are used in device reporting. (iii) Differences in processes & procedures: Traditionally different terminology, processes & procedures are utilized for surveillance (drugs/biologics) & trending (devices). While safety and quality govern all decisions, there may be additional objectives. For example, devices will also focus on user errors and device design in addition to safety and quality. For combination product applicants who hold an NDA or BLA license, in order to meet the new requirements associated with certain reporting types such as PSURs, additional controls & communications between functions, such as quality & PV, need to be put in place to handle the additional reporting requirements.	personnel from regulatory affairs, safety, quality etc., who are trained on combination product regulations.
Organizational Update/redefinition of relationship between combination product applicants & GMP exempt device manufacturers: The scope of the rule only includes constituent part applicants that have received FDA approval & not manufacturers of Class I devices, particularly those that are GMP exempt, such as measuring cups, droppers, etc. While these are low-risk devices themselves, in combination with drugs or biologics (single entity, co-packaged, or cross labeled) device malfunction or quality defect & its impact to patient safety needs to be considered (e.g. overdose due to erroneously marked volume levels in a measuring cup). Depending on the nature of the drug product & the indication, a device constituent part malfunction could cause an AE.	The least burdensome approach to addressing the issue would involve: (i) Combination product applicant, with input from the constituent part supplier, should conduct an assessment of risks related to the interaction of the drug & the device as it relates to the functioning of the combination product. (ii) Institute risk appropriate robust supplier quality agreements that emphasize risks related to device constituent part malfunctions.
AE indicates adverse event; BLA, biologic license application; FDA, food and drug administration; GMP, good manufacturing practices; MedDRA, Medical Dictionary for Regulatory Activities; NDA, new drug application; PSUR, periodic safety update report; PV, pharmacovigilance; SOC, System Orphan Class.	

Table 3. Implementation Challenges and Proposed Solutions Related to Individual Reportable Events (ICSR/MDR)	
Issue/Challenge	**Solution**
Definition of event and potential discrepancy in number of reports: An event is defined differently in drug & device industries. For example, if a patient experiences multiple symptoms such as nausea, dizziness, nose-bleed, & hospitalization, each symptom is treated as an AE by drug companies; however, the totality of the AEs are considered an event by device companies.	(i) Follow application type requirement for reporting (refer to Table 1). (ii) Utilize follow-up reporting as an option to report other constituent part related events.
For device-drug combination products filed under a device application, in case of a suspected, unexpected, serious (unlabeled) adverse drug reaction, an investigation by the device combination product applicant may not identify the device correlation to the reportable event. Similarly, in case of a device constituent part malfunction for a drug/biologic-device combination filed as an NDA/BLA/ANDA, the lack of an AE may not trigger a drug safety report due to not identifying the potential serious injury that may occur should the malfunction reoccur. Also, drug & device reporting differ in that the serious injury criteria for devices are not the same as seriousness criteria for drugs which creates changes in assessing malfunction &/or SAE reporting	Responsible quality & drug safety functions within combination product applicant's organization need to be trained on identifying drug or device constituent part specific events. Based on organizational needs & product portfolios, companies should define criteria for identifying events and set up a combination product organization that includes personnel from regulatory affairs, safety, quality, etc., who are trained on combination product regulations.
In cases of non-serious AEs, there is no mechanism for devices, & consequently for the device combination product applicant, to update the drug label in case the non-serious AE is "associated" with the drug.	FDA needs to clarify how non-serious AEs that are "associated" with the drug for device combination product applicants will be communicated to the drug label.
Risk to aggregate reports, safety signaling & risk management due to lack of readiness of safety systems in combination product applicant companies to assess device & drug/biologic labeling. Both constituent part labels need to be evaluated for determining causality. In practice, due to organizational processes & functional differences, teams generally do not evaluate both labels.	Within combination product applicant companies processes should be implemented so that teams look at both labels in evaluating expectedness.
Processes need to be put in place for 5-day reporting between constituent part applicants. For cross-labeled products that have different marketing applicants, the final rule clarifies the responsibilities for the constituent part applicants.	Processes need to be set up in constituent part applicant companies to trigger marketed product evaluation & communication for events in scope of the notification.
Challenges reporting SAEs across multiple health authorities due to geographic differences in product designation. (i) If an expedited report needs to be submitted to multiple geographies, the data content requirements will be unique to FDA which may be challenging to meet using a single unified AE database. (ii) Addition of relevant device investigation information to the AE database will trigger unsolicited reports to ex-US health authorities & affects reporting volume. (iii) Products that are approved in the US under a specific designation (drug or device) may be approved in other geographies under a different designation. For example, a product that is approved as a drug in the EU may be approved as a device or a drug-device combination product in the US. Vitamin K is a device in Italy & a drug elsewhere. (iii) A product with different approvals in different regions will have to comply with various timelines across the regions. (iv) FDA & certain other geographies require notification of reportable events outside their country.	(i) Processes will need to be developed within organizations to comply with notification of reportable events outside the US for combination products. The process may not be easily amenable to IT solutions & may be manual. (ii) Agency should clarify how device reportability involving similar/same devices apply to device constituents of combination products, given the potential for increased volume of reporting.

Further clarification will be needed to comply with these requirements for combination products. (v) For medical devices, reportable malfunctions that occur outside the US require reporting to the FDA for same or similar products, while this is not the case for drugs/biologics. For combination product applicants, this may result in significant increase in the volume of reports in the US. Also, inclusion of details related to device investigations also significantly increases the reporting burden for NDA/BLA combination product applicants.	
Differences in reckoning date of awareness, i.e., the day the organization becomes aware or 'day 0' for AE/complaints in drug & device companies/communities can cause delays in reporting or cause additional follow-up reporting (if the most conservative approach is used). For devices first day of awareness is day 1, but for drugs it is day 0. There is a potential gap of 1 day. Also, for FAR, the day of awareness is day 1 & submission is required within 3 calendar days.	Alignment of a common 'day 0' to introduce consistency in reportability timelines.
Expansion of seriousness criteria to include some device malfunctions without patient exposure. Unlike drug or biologic products, for devices, patient exposure isn't required for a reportable event. A malfunction likely to cause or contribute to death or SI, even though not observed in actual use of the device with a patient, is a reportable event in the case of medical devices. An example is an out of box failure. It also becomes difficult to trigger an ICSR report to the FDA for a non-AE identified as a near-miss that is related to the product.	Proposal for Industry: Retraining of organizations including staff from both drug safety & device quality. Need to establish processes to a priori codify/clarify malfunctions that need to be reported to drug safety as soon as possible. Proposal for FDA: Provide guidance on how industry should process cases where there is no patient AE & mandatory data fields in the current drug reporting forms will not be available. Currently it is not clear how the reporting could be done. The updated forms should include the option of multiple product reporting in case of platform device malfunctions.
Confusion related to multiplicity of lot numbers associated with constituent parts: Selection of the appropriate lot number (drug or device) applicable to the reportable event may create confusion if one is filing a drug report but the event is related to the device (particularly relevant for co-packaged combination products). There are 2 lot number fields in E2B & it is difficult to differentiate & determine the correct field. In the MDR for a device application status there are fields & options to include additional lot numbers & additional drug product fields. Additionally, for device constituents that may be in a co-packaged combination product & carry a UDI, or combination products that may themselves have a UDI, this creates additional complexity in terms of numerical identifiers.	Align ICH E2B forms with MDR forms to include specific sections for lot numbers & other product identifiers for drug & device constituent parts.
Additional complexity due to multiple reports: For follow-up reports, medical device follow-up submissions require that only the new information is reported, which is different from reporting for other regulatory classes (drug/biologic). For other classes, an entire report including any new information is required. While this causes volume burden for NDA/BLA combination product holders, it also adds burden to device combination product applicants.	In line with least burdensome approach, the follow-up reporting should follow the type of constituent part impacted, i.e., full report if the follow-up report is related to a drug & only new information if the follow-up is related to a device.
The concept of "same/similar" devices will increase the burden of reporting & add complexity for combination products with device constituent parts. Recognition or awareness of the "same/similar" concept usually does not exist in the pharma/biologic industry. For platform devices that are used across	Agency should consider single malfunction reporting by NDA/BLA combination product applicants across multiple drug products using same or similar devices. Additionally, FDA should confirm

multiple therapies, identification & assessment of "same/similar" products (e.g., PFS) may result in significantly added reporting burden for the pharma/biologic manufacturers. Also, "the same or similar" device constituent may be a part of other manufacturers' products (single-entity or co-packaged) which creates added complexity for defining when this provision applies.	that "the same or similar device" indeed applies only to device constituents in products marketed by the application holder & not to device constituents marketed independently.
Addition of reporting complexity due to differences in constituent part coding nomenclature. Different constituent parts have different coding hierarchies. Examples include the MedDRA, FDA device codes, & ISO codes. This adds complexity to the analysis & potential double-counting of events. Product defect classification criteria are used by device quality divisions in product quality complaint reports for reportability of device malfunction. Quality complaint reports do not follow the coding defined in MedDRA. Instead, other coding standards are used to capture product investigation & action on the postmarketing safety section H6 of FDA 3500A, CIOMS, or other electronic equivalency reports.	The addition of MedDRA SOC 27 may provide an alternative solution for combination products with a drug/biologic application status for coding for reporting purposes for device related issues. Additional agreement across industry & regulators to use MedDRA coding for all patient codes even for devices may further help gain alignment at least for applications approved as ANDA/NDA/BLA. Device evaluation/investigation & root cause analysis may continue to use FDA codes that can be captured in the narratives.
Lack of clarity on details of device reportable events that need to be included in drug/biologic Periodic Safety Reports. Prescriptive aggregate reporting requirements are applicable to drugs/biologics. Devices require a review & trend analysis of complaint data as predefined by internal processes with a need to take action should a trend be noted. Although the final rule clarifies that the summaries & analyses of 5-day & 30-day malfunction reports should be included in the periodic reports of combination product applicants under NDA/BLA, clarity does not exist around the details of device reportable events that need to be included in the periodic reports.	Some best practices, such as a device annex,[18] have been considered to meet the need for overall product safety oversight, & may be incorporated into the proposed guidance in order to clarify the contents of device reportable event summaries & analyses in drug/biologic periodic reports. Use of an annex helps customize the reports according to local health authority requirements. Also, for certain device classes quarterly reporting will be an option in the future should they qualify for periodic reporting of malfunctions.[19] [20] [21]

AE indicates adverse event; ANDA, abbreviated new drug application; BLA, biologic license application; CIOMS, Council for International Organizations of Medical Sciences; EU, European Union; FAR, Field Alert Report; FDA, food and drug administration; ICSR, individual case safety report; ISO, International Organization of Standardization; IT, information technology; MDR, medical device report; MedDRA, Medical Dictionary for Regulatory Activities; NDA, new drug application; PFS, prefilled syringe; PV, pharmacovigilance; SAE, serious adverse event; SI, serious injury; SOC, System Orphan Class; UDI, Unique Device Identifier; US, United States.

[18] Roman X, Reder R, Barch D, Bano K, An Approach to Aggregate Safety Reporting of Drug and Device Constituent Parts of Combination Products, Poster Presentation at DIA (2015).

[19] 76 Fed. Reg. 12743 (Mar. 8, 2011).

[20] FDA, Medical Device Reporting for Manufacturers: Guidance for Industry and FDA Staff at 4-5 (2016).

[21] FDA, Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry and FDA Staff (2016).

5. Discussion/Future State

The 18 month timeframe for compliance with the final rule will necessitate a manual process to be utilized for reporting the required information. Industry would submit a single report driven by application status with addition of missing fields in the narrative for the other constituent part including description of the event, applicable coding, lot information, and follow-up information following applicable report submission timelines. Pros and cons include the following:

- PROS: Limits duplication, complete information as all data is in one place, and can be implemented in specified timeframe since no infrastructure change is needed for FDA or industry.
- CONS: Critical information may not be adequately highlighted, the process is very manual for the industry, and incorrect constituent part issues may get tagged to the primary application status constituent. Also, there are differences in character limits for free text narrative between drug reports (20K characters) and device reports (35K characters).

Ideally, as a long-term solution, a single form and a unified system (i.e. E2B R3 or HL7) supporting submission of a single report that includes relevant information for all constituent parts with a single set of codes will enhance safety oversight for combination products as a whole. This will help identify the potential role of the applicable constituent in causing the reportable event and allow capturing information across constituent parts in a format amenable to searching and analysis that would yield important safety information in a timely manner. Pros and cons include the following:

- PROS: Robust and sustainable, limits duplication, complete information as all data is in one place with proper emphasis on the components, automated process allows for fewer errors, information sharing between branches of FDA, and provides proper oversight to ensure public safety.
- CONS: Significant infrastructural and organizational changes requiring resource investment for FDA and industry and longer implementation times.

Additional dialogue between industry and FDA to address some of the challenges of developing a unified system would be helpful. Additionally, guidance clarifying specific requirements is also needed.

6. Conclusion

The PMSR final rule provides the vision for combination product reporting to ensure a holistic approach to obtaining and analyzing adverse events (AEs) and product malfunctions. The new process may pose challenges for both FDA and industry that will need to be resolved potentially in a phased approach. The implementation of the final rule may initially require portions of the reporting process to be manual. As the process matures, and clarity is obtained through an accompanying guidance, collaborative workshops between FDA and industry and an understanding of industry best practices will evolve this process. The backbone for success is the development of updated infrastructure that allows for adequate capture and analysis of AEs and malfunctions related to both or multiple components for

combination product reporting. The infrastructure changes need to occur both within industry and at the FDA. As science and technology evolve to provide patients with novel medical therapies involving multiple modalities, the final rule provides the framework necessary for a patient-centric approach to AE and malfunction reporting.

Appendix A: Combination Product Scenarios

Registration Pathway 1: Drug/Biologic as the Registration Status

The following discussion is specific to the electronic submission of AEs for combination products registered using an NDA, BLA, ANDA, or biosimilar pathway. ***The scenarios discussed are deliberately overly simplistic in order to explain the assessment process, and may not reflect complex real world scenarios. Individual organizations, their infrastructure, specific product risk profiles, and assessment approaches may dictate reporting outcomes***.

For drugs/biologics approved as a combination product, AE reporting may occur under four possible options. These include an event associated with the following constituents:

1. Drug/biologic
2. Device (including malfunctions likely to cause a SI)
3. Both drug/biologic and device
4. Non discernible: drug/biologic or device as the event is not discernible

Drug/biologic SAEs are required to be submitted as E2B reports. Based on the final rule, the report should comply with NDA/BLA reporting requirements and include any applicable device constituent data required to fulfill the device specific 5-Day Report and the 30-Day Medical Device "Malfunction" reporting requirements (to be filed as a single report within 15 days from awareness or an initial report filed within 15 days with a follow-up malfunction report).

Drug/biologic as alleged or suspected cause of SAE:

A drug/biologic report, where the drug/biologic is the suspected cause of the event is assessed for submission as an ICSR with no additional device related fields included, and if applicable, as a product quality complaint for investigation. Case assessment to evaluate seriousness (SAE), causality (assumed or assessed), and expectedness is conducted. Additional supplemental filing of field alert reports (FAR), BPDR, and other required reports are completed as appropriate. The problem coding used for ICSR may vary from the product quality complaint report product defect classification.

Example: A pre-filled syringe (PFS) used to treat an autoimmune disease resulted in an allergic reaction requiring hospitalization. Additionally, the solution is reported to have looked cloudy. Upon investigation, it was determined that the product did not meet stability criteria at time point T1. Please note that in this scenario, device related causes are ruled out (e.g. no impact from leaching of silicone from the PFS walls and associated denaturing of the product).

- Seriousness: Yes
- Labeledness/Expectedness: No (if yes – not reportable)
- Causality/Contribution/Association/Relatedness: Drug
- Malfunction: No
- ICSR: Yes
- Field Alert Report Requirement: Yes (if drug constituent part is involved)
- Biologic Product Deviation Report: Yes (if biologic constituent part is involved)

- Periodic Safety Report Inclusion: Yes

Device constituent as suspected cause of SAE:

Where the device constituent is the suspected cause of the event, the reporting is assessed for submission as an ICSR via E2B. Although the drug/biologic is not suspected, the event would be reported against the drug/biologic. In this scenario, the ICSR would primarily contain device information elements. Of note, ICSR E2B schema does not include device fields and for a complete submission these data are required.

Individual case safety reports may (E2B R3) or may not (E2B R2) allow for attachments. A product quality complaint report is submitted in a quality system for device constituent part investigation and results are reported in the ICSR and submitted in a 15-Day Report or a follow up report. For example, a manufacturer number would not be assigned, but all sections would need to be populated as the product is registered as a drug (A, B, C, E and G). Additionally, information will need to be incorporated in D and H into either the narrative or manufacturer's additional narrative.

While this reporting allows for complete data to be submitted to the agency, the data would be unstructured and difficult to analyze as signal detection activities would not be supported by electronic signaling tools and data mining.

Example: While using an autoinjector used to treat an autoimmune disease, the needle misfired and caused injury requiring intervention.

- Seriousness: Yes
- Labeledness/Expectedness: No (not in instruction for use (IFU) or drug/biologic label). Note: If this was a labeled event, it would not be reportable.
- Causality/Contribution/Association/Relatedness: Device
- Malfunction: Yes (only if this is a non-labeled event)
- ICSR with device constituent part investigation: Yes (only if this is a non-labeled event)
- Field Alert Report Requirement: No (unless reportable quality defect is identified)
- Biologic Product Deviation Report: No (unless reportable quality defect is identified)
- Periodic Safety Report Inclusion: Yes

Both (1) Drug/biologic and device and (2) Non discernible drug/biologic or device as suspected cause of SAE:

Similar to the situation where a device is suspected as the cause of an SAE/SI, an ICSR would be submitted with the drug and biologic fields completed in its entirety. In addition, a product quality complaint report is submitted for an investigation of the suspected constituent parts and results are reported in the ICSR. In certain cases submission of a FAR, BPDR, and correction and removal report may be required.

Additional points to consider on Registration Pathway 1: While it is possible for companies to develop a work around to meet the requirements related to ICSR reports that include device information, the work around does not utilize structured data and manual signaling processes would need to be developed.

Most common safety databases have the capability to accommodate data elements for both drug and device products; however, organizations may need to upgrade and validate their systems to accommodate use for both drugs and devices in one report with structured fields. This may result in internal process enhancement but the FDA system receiving data into various centers, as set up currently, may not be able to accommodate the combined data.

The manual workaround may not effectively alert the market authorization holder (MAH) and/or FDA to issues related to devices in a timely manner, unless appropriate systems are set up, as information may be buried within unstructured data fields making it hard to analyze. For scenarios where the AE is purely related to the device constituent part, the drug report submission would imply drug causality and submission of a valid ICSR may be challenging, due to missing mandatory data elements.

Periodic safety reports are required for drugs/biologics but not for devices. The combination product rule requires inclusion of 5-day and malfunction report summaries in the periodic reports. Inclusion of defined device related data helps provide the overall product safety profile on a periodic basis.

Registration Pathway 2: Device as the Registration Status

When considering the final rule for safety reporting of a combination product where the registration status is a device, an organization must still consider the reporting requirements of each individual constituent part. The reporting requirements for drugs and devices differ resulting in multiple safety reporting scenarios depending on the constituent part suspected to contribute to the safety event. Table 1 above presents the different safety reporting types for a combination product with a device application status. It also demonstrates the complexity associated with safety reporting for combination products in that a company will be reporting a 30-Day device report regardless of the constituent part contributing to the safety event. If both constituent parts (device and drug) contribute to the safety event a 30-Day report is required. Additional supplemental filing of FARs, including a 5-Day report, and other required reports are completed as appropriate. Please note: The applicability of reportability requirements based on same or similar device constituent part is not clearly outlined.

Organizations that market different types of medical products (drugs, devices, or combinations) often use different software for medical device and AE reporting. An MDR can accommodate drug related narrative and additional information. FDA device codes will be used for coding of AEs. No data scheme is available for Medical Dictionary for Regulatory Activities (MedDRA) coding, causality assessment, expectedness, and multiple AEs with their codes on one report. Reconciliation between an AE database and medical device database for AEs will pose a challenge as demonstrated in the example below. ***As stated previously, the scenarios discussed are deliberately overly simplistic in order to explain the assessment process, and may not reflect complex real world scenarios. Individual organizations, their infrastructure and approach may dictate reporting outcomes.***

Drug/biologic as alleged or suspected cause of SAE:

A device report, where the drug/biologic is the suspected cause of the event, is assessed for submission as an MDR with only drug related information in MDR fields and, if applicable, as a product quality complaint for investigation. Case assessment to evaluate seriousness, malfunction/root cause analysis,

returned product investigation, causality (assumed or assessed), and expectedness (evaluated or not considered) will need to be conducted. For scenarios where the AE is purely related to the drug constituent part, the manufacturer report number would imply device causality. As a device combination product applicant typically licenses the use of the drug/biologic constituent part from a pharmaceutical manufacturer, it would be challenging for the pharmaceutical manufacturer to conduct aggregate review of AEs for drug related periodic safety reports due to lack of adequate MedDRA coding. Additional filings of FAR, BPDR, and other required reports are completed as appropriate. The problem coding used for the MDR will be based on FDA device/patient codes. Even though the device performed as expected, the report will be filed against the device.

Example: A drug-eluting stent used to treat a coronary artery stenosis resulted in an allergic reaction requiring hospitalization right after the procedure. Upon investigation, it was determined that the device constituent part (stent/catheter system) had no malfunction.

- Seriousness: Yes
- Labeledness: No. Note: If this was a labeled event, it would not be reportable.
- Causality/Contribution/Association/Relatedness: Drug
- Malfunction: No
- Field Alert Report Requirement: No (unless reportable quality defect is identified)
- Biologic Product Deviation Report: No (unless reportable quality defect is identified)
- Device remedial action report: No
- Periodic Safety Report Inclusion: N/A
- MDR filing: Yes, MDR filed within 30 days (SI) only if this is a non-labeled event.

Device constituent as suspected cause of SAE:

A report where the device constituent is the suspected, the event is assessed for submission as an MDR via HL7. In this scenario, the MDR would primarily contain device information elements. Drug/biologics related information does not need to be included in the report.

Example: While using a drug-eluting stent to treat a coronary artery stenosis the stent failed to deploy resulting in the need to remove and deploy another stent causing procedural complications due to prolongation of procedure.

- Seriousness: Yes
- Labeledness: No (not in IFU or drug/biologic label). Note: If this was a labeled event, it would not be reportable.
- Causality/Contribution/Association/Relatedness: Device
- Malfunction: Yes
- Field Alert Report Requirement: No
- Device remedial action report: No
- Periodic Safety Report Inclusion: N/A
- MDR filing: 30-day malfunction report (only if this is a non-labeled event)

Both (1) Drug/biologic and device and (2) Non discernible drug/biologic or device as suspected cause of SAE:

Similar to the situation where a device is suspected as the cause of an SAE or SI, an MDR would be submitted with the drug/biologic information completed in its entirety. In addition, a product quality complaint report is submitted for investigation of the suspected constituent parts and results are reported in the MDR. In certain cases submission of a FAR, BPDR, and correction and removal report may be required as applicable.

The MDR report submission would imply device causality. Additionally, information related to MedDRA codes and expectedness assessment may be missing.

Periodic safety reports are required for drugs/biologics but not for devices. Inclusion of drug/biologic related data during annual safety review helps provide the overall product safety profile on a periodic basis.

Refer to the same section under Registration Pathway 1 Section for additional information.

Registration Pathway 3: Certain Stand-alone Device Constituent Part Used in Co-packaged Combination Product and Not Covered Under the Combination Product PMSR Rule

There is no requirement outlined in the final rule for reporting related to certain Class I devices that require no pre-market registration (e.g. Liquid oral dispensers). Often these devices are low-risk and may not require the full Current Good Manufacturing Practice (cGMP) or Quality System Regulation (QSR) and risk management documentation for devices. These device constituent part manufacturers face a unique challenge when considering the final rule for safety reporting. They may not be aware of how the constituent part is used in the final combination product. Depending on how it is used in the finished product, the same issue with the constituent part can result in variable severities of impact. Therefore, the constituent part manufacturer may not be in a position to determine whether the adverse event resulting from the device constituent meets the definition of a reportable safety event. Thus, the constituent part manufacturers may not have identified all potential malfunctions that could occur with their products in the finished form in various possible applications.

The intent of the final rule can be met by recommending that Class I device constituent part manufacturers notify the MAH of the finished product upon discovery of a constituent part malfunction, and this requirement is usually a part of the Quality Agreement. It is then incumbent upon the MAH, as the combination product applicant, to evaluate the malfunction as it relates to the finished product. The MAH knows the product, labeling, actual use, and potential impact of the component malfunction and is in the best position to understand the event and determine whether the event meets the requirement for reporting. In this case, the 'aware' date of the event is unclear (date the constituent part manufacturer notifies the MAH of the malfunction or the date impact assessment is completed by MAH). In most situations, the MAH initially receives the report of the malfunction from the market. A supporting investigation from the supplier may be requested, however, determining the date of awareness may be challenging. In addition, the constituent part manufacturer may be required to share

investigation results as assessed by the MAH. Device constituent part manufacturers may not have the infrastructure to complete a thorough safety assessment and file individual reports. A potential solution would be for the MAH to file events as ICSRs or MDRs based on regulatory pathway after assessment of impact due to malfunction referencing the MDR number from the component manufacturer.

Appendix B: Definitions

Adverse event (device): Defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device.

Adverse event (drug): Defined in the CFR[22] as an untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

Applicant: The person holding an application under which a combination product or constituent part has received marketing authorization, and there is a combination product applicant if there is one applicant that either holds the application for a combination product or, holds the applications for each constituent part if the constituent parts of the combination product are marketed under separate applications (as could be the case for the constituent parts of a cross-labeled combination product).

Combination products are defined in the CFR.[23] The term combination product includes:

(1) Single entity products: two or more regulated components physically or chemically combined to produce a single entity. Examples include: PFS, drug eluting stents, and medicated patches.

(2) Co-packaged products: two or more regulated components packaged together. Examples include: convenience kits that include drug and delivery system and device implantation kit with medication to prepare the area.

(3) Co-labeled products: two or more regulated products packaged separately and intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect. Example include: diagnostic/screening test required prior to use of a drug/biologic product.

(4) Co-labeled investigational products: two or more investigational products packaged separately and intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect. Example include: diagnostic/screening test required prior to use of a drug/biologic product. The assumption is that the rule is referring to investigational products that are marketed and being investigated for new indication

A combination of two products of the same modality (for example two combined medications) are not considered combination products.

Constituent part: A constituent part is a drug, device, or biological product that is part of a combination product.

Constituent part applicant: Applicant for a constituent part of a cross-labeled combination product the constituent parts of which are marketed under applications held by different applicants.

[22] 21 CFR § 312.32(a).
[23] 21 CFR §§ 3.2(e)(1) – (e)(4).

Device Problem Code: Device failures or issues related to the device that are encountered during the event. Each MDR should include at least one code.

E2B - R2/R3: The international standard for transmitting medicine AE reports specified by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use .

FDA Device Code: The 4-digit code number assigned by FDA for each component, device problem, patient problem and investigation code for data entry purposes.

Malfunction: Defined in the CFR[24] as the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Medical Devices: A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

(1) recognized in the official National Formulary, or the US Pharmacopoeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

MedDRA: Terminology for AE reporting used globally by the biopharmaceutical industry and regulators to promote consistent reporting and data analysis.

Monograph products: Products meeting a compendia monograph.

PADER: Periodic adverse drug experience report; cumulative reports of AEs after approval of the product. Their purpose is to present a cumulative understanding of the safety of a product at defined time points.

PMA: Premarket approval (PMA) is the FDA's process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. A successful PMA submission results in approval of the new device.

Serious Injury: Means an injury or illness that:

(1) Is life-threatening,

[24] 21 CFR § 803.3(k).

(2) Results in permanent impairment of a body function or permanent damage to a body structure, or

(3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

XML (Extensible Markup Language): Type of markup language that defines a set of rules for encoding documents in a format that is both human-readable and machine readable. This format is used to transmit E2B files.

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