Combination Products Coalition

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FDA-2008-N-0424

VIA ELECTRONIC SUBMISSION

June 18, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2008-N-0424: Postmarketing Safety Reporting for Combination Products

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff" ("Draft Guidance"). Although we greatly appreciate that FDA appears to have considered previous CPC feedback in the development of this Draft Guidance, we have several suggested revisions and requests for clarification, as detailed below. In addition to our specific comments, we request that FDA ensure alignment between its field inspectors and the Office of Combination Products on the key principles reflected in the Draft Guidance.

We are thankful for the opportunity to provide input on the Draft Guidance and are happy to meet with the Agency to clarify or discuss any of our suggestions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues.

Section, Line(s)	Guidance Text	Proposed Changes/Comments	Rationale
General Edits			
III.A., Lines 169-171	*"…a company that holds an application for a product is a Constituent Part Applicant* ***only if that entity holds an application to market that product as a constituent part of a combination product.****" (emphasis in the original)*	Please explicitly state that this language applies only to cross-labeled combination products and not to single entity or co-packaged combination products.	Clarification to distinguish requirements that apply to co-packaged, single entity versus cross-labeled combination products. Currently, many of the examples utilized in the Draft Guidance are for cross-labeled combination products.
III.A., Line 178, Footnote 7	*"Although outside the scope of this guidance, it is worth noting that, under this example, PharmaCo is required to establish and maintain procedures to ensure that supplied syringes meet all required specifications…."*	The footnote indicates that constituent applicants that do not hold an application to market that product as a constituent part of the combination product are outside the scope of the Draft Guidance. However, the reference made on line 31 to Appendix 3 listing entities not covered by the rule does not include such an entity. Please add as an example to Appendix 3.	Inconsistent information between body of the Draft Guidance and Appendix 3.
III.B., Lines 240-246	*"Constituent Part Applicants must share with the other Constituent Part Applicant(s) for the combination product, within 5 calendar days from initial receipt, information on the following if associated with the use of the combination product:* • *Deaths or serious injuries as described in 21 CFR 803.3 or* *Adverse experiences as described in 21 CFR 314.80(a) or 600.80(a)."*	*"Constituent Part Applicants* ***for cross-labeled products*** *must share with the other Constituent Part Applicant(s) for the combination product, within 5 calendar days from initial receipt, information on the following if associated with the use of the combination product:* • *Deaths or serious injuries as described in 21 CFR 803.3 or* • *Adverse experiences as described in 21 CFR 314.80(a) or 600.80(a)."*	Clarification for requirement to share information based on classification of combination product.

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		Please clarify or explicitly state throughout the document that Constituent Part Applicant only pertains to cross-labeled combination products. Rephrase Constituent Part Applicant with "Device" or "Drug/Biologic" Constituent Part Applicant for cross-labeled combination product.	
IV.A.1., Lines 349-356	*"A Combination Product Applicant for a combination product marketed under a Device Application may receive a report of an event that triggers a Fifteen-day report but not a death or serious injury report under 21 CFR Part 803, if the event is associated with the use of the combination product but the applicant does not believe the information reasonably suggests that the product may have caused or contributed to the event. FDA anticipates that such circumstances would be rare, but should they arise and the event is both a serious and unexpected adverse experience, the Combination Product Applicant must submit a Fifteen-day report even though a death or serious injury report is not also required."*	Please provide example(s) for this section to clarify scenarios where this may occur. Please clarify further in this section that in such scenarios, the Fifteen day report can be submitted within 30 calendar days.	Clarification
IV.A.2., Lines 369-376	*"For combination products that contain a device constituent part…Remedial action includes 'any action other than routine maintenance or servicing…where such action is required to prevent recurrence of a reportable event' (21 CFR 803.3(v))."*	*"For combination products that contain a device constituent part…Remedial action includes "any action other than routine maintenance or servicing…where such action is required to prevent recurrence of a reportable event' (21 CFR 803.3(v)).* ***FDA considers the 5-day time frame to begin the day after an employee with management***	Additional clarity regarding 5-day reports to align with FDA's guidance on "Medical Device Reporting for

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		or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or a person whose duties relate to the collection and reporting of adverse events, 'becomes aware' of the event [21 CFR 803.3]. We do not expect employees such as non-technical staff to recognize that an adverse event(s) requires remedial action to prevent a risk of substantial harm to the public."	Manufacturers" (Nov. 8, 2016).[2]
IV.A.3., Lines 427-429	*"After submitting the Fifteen-day report, the applicant determines that failure of the infusion set to meet its specifications could have caused or contributed to the event. In this case, a Malfunction report must also be submitted (see 21 CFR 803.3(k) and 803.50)."*	*"After submitting the Fifteen-day report, the applicant determines that failure of the infusion set to meet its specifications could have caused or contributed to the event. In this case, a Malfunction report must also be submitted (see 21 CFR 803.3(k) and 803.50)* ***no later than 30 calendar days after the day the applicant becomes aware of the reportable malfunction.****"*	Provide clarity that the 30-day report time frame should start when the applicant becomes aware of the reportable malfunction, not when the event is deemed a 15-day report.
IV.D., Line 665	*"In addition to sharing information with each other, Constituent Part Applicants must report events to FDA as required by the PMSR regulations applicable to their respective constituent part (see 21 CFR 4.102(b)). Such reports to FDA should address how the event is related to the constituent part and the combination product as a whole."*	Confirm this language only applies for cross-labeled combination products. If so, we recommend the clarifying language below. *"In addition to sharing information with each other, Constituent Part Applicants* ***for cross-labeled products*** *must report events to FDA as required by the PMSR regulations applicable to their respective constituent part (see 21 CFR 4.102(b)). Such reports to FDA should address how the event is related to the constituent part and the combination product as a whole."*	Clarify whether this applies only to cross-labeled combination products.

[2] *Available at* https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm359566.pdf.

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IV.D., Lines 674-676	*"However, we note that the purpose of 21 CFR 4.103 is to ensure sharing of adverse event information between entities who are collaborating to market products intended for use with one another, to help ensure timely, complete reporting to FDA. Accordingly, we encourage such applicants to share such information with one another regardless of whether the products necessarily comprise a combination product."*	This section of the Draft Guidance is encouraging entities holding separate applications (but not considered a combination product) to share information with one another per 21 CFR 4.103 even though they are not subject to the rule. It's unclear which types of products this is referencing and thus should be either removed or expounded upon to describe applicable situations.	Clarify intended purpose of this section in the Draft Guidance when it does not relate to combination products.
V.A.1., Line 755	*"Death/Serious Injury/Malfunction Reports - No later than 30 calendar days after the day that you become aware of the event (see 21 CFR 803.50)"*	*"Death/Serious Injury/Malfunction Reports - No later than 30 calendar days after the day that you* ***receive information on or otherwise*** *become aware of the event (see 21 CFR 803.50)"*	Align Draft Guidance with the regulation (21 CFR 803.50).
V.A.3., Lines 829-831	*"A Combination Product Applicant who holds an approved NDA for a drug-device combination product must submit both a Fifteen-day (see 21 CFR 314.80) and Malfunction (see 21 CFR 803.50) report for an event that triggers both duties."*	*"A Combination Product Applicant who holds an approved NDA for a drug-device combination product must submit both a Fifteen-day (see 21 CFR 314.80) and Malfunction (see 21 CFR 803.50) report for an event* ~~***that triggers both duties that***~~ ***meets the respective reporting requirements.****"*	Refine the text to ensure clarity, indicating one Individual Case Safety Report ("ICSR") submitted in 15 days and follow up in 30 days.
Appendix 2, Lines 1127-1128	*Chart 2.1. ICSR Reporting Requirements for Combination Products Marketed Under NDA/ANDA/BLA*	For clarity, after the boxes for Fifteen-day Report and Malfunction Report, we recommend that a single output line exit the box then have a distinct "AND" split in order to indicate that both pathways must be followed in order to assess the need for additional ICSRs. In the current diagram, the two exit points from the boxes can be missed.	Clarification
Appendix 3, Lines 1134-1135	*Combination Product Postmarketing Safety Reporting Considerations for Entities that are not "Applicants"*	Appendix 3 listing entities not covered by the rule does not include constituent applicants that do not hold an application to market that product as a	To ensure consistency with Footnote 7.

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		constituent part of the combination product; as noted above, we understand that such entities are outside the scope of the Draft Guidance. Please add as an example to Appendix 3.	
Appendix 4.B.Scenario 1, Line 1218, Footnote 34	N/A	Footnote 34 is missing and instead footnote 35 is repeated on both pages 38 and 39.	Correct footnote number under Scenario 1 on page 38.
FR Notice Related to Draft Guidance (83 Fed. Reg. 12292, 12293 (March 21, 2018))	*"There may be events that would be reportable for a Combination Product Applicant as a malfunction and/or a Field Alert Report ("FAR") and/or a Biological Product Deviation Report ("BPDR")…FDA requests feedback on circumstances under which such reporting may be redundant or otherwise unnecessary and, if so, alternative reporting approaches that will assure timely and complete reporting of information to FDA. FDA encourages the use of example scenarios to illustrate circumstances under which submitting one or a subset of such reports may be sufficient to ensure timely and complete reporting."*	In such cases, filing a single report would be sufficient (with timing to be discussed – either 30 days for malfunction, 15 days for FAR, and 45 days for BPDR). Please see attached as Appendix A the case studies used in the May 31, 2018 RAPS Postmarketing Safety Reporting Workshop.	Clarification and consistency
Throughout Draft Guidance	N/A	We also recommend that FDA: • Provide examples and scenarios for single entity/co-packaged combination products. • Clarify that FAR/BPDR cannot be combined with ICSR.	Clarification

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		• Clarify handling of subsequent ICSR after a correction or removal.	
Criteria for Defining Same/Similar Combination Products			
Throughout Draft Guidance	*Same/Similar applicability to combination products*	Please clarify approach to be taken for identifying same/similar for combination products when product contains multiple device constituents. We recommend the following approach based on Medical Device regulation for assessment of same/similar devices: • Assessment is based on devices that have the same: basic design and performance characteristics related to device safety and effectiveness, intended use and function, and device classification and product code (if applicable). Devices that differ only in minor features unrelated to safety or effectiveness can be considered similar devices. Other factors that we recommend to be used to determine whether devices are similar include: brand name, common name, and whether the devices were introduced into commercial distribution under the same pre-market notification ("510(k)") (see 21 CFR Part 807) or the same pre-market approval ("PMA") application number. • In addition, the devices must be used with the same drug/biologic product.	Clarify and consider CPC-recommended approach for identifying same/similar combination products.
N/A (new request)	***Expectedness Assessment***	Labeled malfunction – "expectedness"	Least burdensome approach and more robust

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		Consider inclusion of expected malfunction similar to AEs addressed in the label or IFU, related to device malfunction that are collected during clinical trials. These may be included in the Periodic safety reports.	holistic data analysis of product as a whole.
IV.A.1., Lines 323-328	*"Whether an event is "expected" for purposes of fifteen-day reporting is based on whether the event is listed in any current labeling for the combination product including the labeling accompanying each of the constituent parts. For example, if a Combination Product Applicant is marketing a cross-labeled combination product, the labeling accompanying each of the constituent parts would collectively constitute the labeling for the combination product."*	*"Whether an event is "expected" for purposes of fifteen-day reporting is based on whether the event is listed in any current labeling for the combination product***. *****including the labeling accompanying each of the constituent parts.*** *In the case of* ~~***For example, if a Combination product applicant is marketing***~~ *a cross-labeled combination product, the labeling accompanying each of the constituent parts would collectively constitute the labeling for the combination product."* The language in the Draft Guidance could be interpreted to be applicable to constituent parts of co-packaged products or single entity products. Potential events disclosed in the labeling are specific to the combination product. There are no regulatory requirements to include expected list of events for the device constituent for these combination products. We recommend making the edits above to ensure clarity.	Clarification to ensure applicability of the Draft Guidance.
IV.A.6., Lines 501-503	*"Likewise, Combination product Applicants for combination products containing device constituent parts should submit other ICSRs to FDA for otherwise reportable events for the same or similar*	Please provide specific guidance on how to submit a case for same/similar combination products that are not under NDA or BLA. For example, using the NDA/BLA # in submission for ex-U.S. combination product.	Please provide reporting guidance.

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	combination product marketed outside of the U.S. by that applicant."	Clarify which field is expected to contain identification that suspect product is considered same/similar to a U.S. marketed combination product.	
Data Elements: Technical Specification Document			
V.B.1., Line 848	*"PMSR reports for combination products must contain all information required for the report under the applicable regulations, including relevant information on the entire product (including constituent part). Also, in situations where the Combination Product Applicant submits multiple types of reports for the same event or product problem, the reports should include cross-references to each other."*	Please clarify what types of reports for same event or product problem need to be cross-referenced.	Unclear what requires cross-referencing.
Appendix 4 & Technical Specification	*N/A*	The current E2B(R2) schema used to define the contents of E2B(R2) files for Global exchange of cases between partners does not contain the additional fields listed in Appendix 4. This functionality is not currently available in any commercially available safety database. Has the FDA defined how the existing schema could be updated to incorporate these changes, and has FDA provided these specifications to software vendors for development? Will a new document type be created by FDA and is this an interim solution until E2B(R3) is implemented? Specifically: • What are the mandatory 'new FDA' fields? • Has a testing plan been established and, if so, what are the details of the testing plan and	Clarification for electronic submission schema changes, testing plan, use of null flavours, and naming of xml files.

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		will industry be notified when available for testing? • Will there be new E2B business rules on device fields with impact on E2B acknowledgement? • Is there also a document outlining how E2B(R3) format will be used to capture the additional data? • Can null flavours identified for E2B(R3) be used for mandatory fields if information is unknown, unavailable or masked? • Is there a specific naming convention to be utilized for the xml files being submitted for combination product reporting? Please note that the E2B data elements in FDA's "Specifications for Preparing & Submitting Electronic ICSRs & ICSR Attachments (Feb. 2018)"[3] and guidance on "Medical Device Reporting for Manufacturers" (Nov. 8, 2016) differ – which is accurate.	
V.B.2., Lines 858-911; Appendix 4 & Technical Specification	N/A	A number of the fields in this section, such as Suspect Medical Device and Device Problem Code, are not currently included as part of the AE reporting process for drugs. These fields have not been captured in AE reporting, but even if they were included in drug AE reporting system, there is no guidance on how these fields are to be transmitted	Clarification

[3] *Available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM601820.pdf.

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		for reporting to FDA. We recommend this Draft Guidance include how these fields are to be incorporated and transmitted using the E2B reporting schema.	
Cross-Referencing Between FAR/BPDR and ICSR			
IV.B.1., Lines 530-532	*"For combination products, a FAR is submitted for any of the issues described above that could have resulted from <u>any</u> of the constituent parts of the combination product or the manufacturing process for the combination product" (emphasis added).*	Wording suggests that FAR is required for a device malfunction or for significant chemical, physical, or other changes to the device even if it does not affect the drug. Does FDA intend that all malfunctions require FAR or is it the intention that the FAR pertains to the drug constituent part even if the contamination came from the device?	Please clarify intent.
IV.B,1., Lines 542-544	*"…the Combination Product Applicant must submit a FAR and should also communicate with the drug product supplier to enable any additional actions and reporting by the drug product supplier as appropriate."*	Typically, the supply site of the drug product would initiate and file a FAR. If the issue resulted from a material supplied to the applicant by another party, the other party should share information.	To prevent duplicate reporting.
V.B., Lines 913, 962 & 970	*"Cross-reference to Other Reports"*	Please clarify if the intent of the cross-reference is for the FAR or the BPDR to reference the applicable ICSRs. Similarly, is the intent that a correction removal refer to the applicable ICSRs?	Clarify intent of cross-reference.

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V.B.5., Lines 962-963 & 970-971	*"[When submitting a FAR]… Cross-reference to the identifier(s) for any related PMSR reports (i.e., related ICSRs, correction and removal reports, BPDRs, if applicable)."* *"[When submitting a BPDR]…Cross-reference to the identifier(s) for any related PMSR reports (i.e., related ICSRs, correction and removal reports, FARs, if applicable)."*	FARs are submitted based on quality defects associated with a particular lot. Does this mean any PMSR associated with that lot should be referenced? Or should we reference any PMSR that "could be" attributable to the quality defect, regardless of lot? And for what time period before or after the FAR submission? We propose removing or defining the requirement to cross-reference FARs with "any related PMSR reports." This could be problematic without further definition of what the Agency feels should relate a FAR with PMSR.	Clarification
Applicability of Combination Product PMSR to Clinical Studies			
Section II.A., Lines 67-71	*"Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (another basis for cross-labeled combination product status)."*	This extends the scope of PMSR to non-approved constituents which are not reported to marketing authorization licenses. Please update section to reflect that postmarket reporting applies only if (i) an approved combination product (single entity or co-packaged) is utilized in an investigational study, and (ii) approved constituent parts (cross-labeled) of a marketed combination product are utilized in an investigational study. Move second paragraph in footnote 4, to line 67.	Consistency with PMSR regulation and with footnote 4 on line 124.
Section III.A., Line 124, 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 products*	The labeling for a marketed constituent used in an investigational co-packaged or single entity combination product would not reflect its use in the combination product. Please clarify why the PMSR would apply in this scenario. Also, please clarify if	Reporting to an approved marketing authorization would not apply since the marketed constituent is not approved for use within

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	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 the marketed combination product or constituent part."	requirement applies to ongoing studies or only to studies approved after compliance date of PMSR.	that combination product. Please clarify scope.
Medical Device Constituent Information			
V.B.2., Lines 883-885 & Footnote 25	*"Combination Product Applicants should select the procode that most closely aligns with the device constituent part (include regardless of whether or not you believe the device constituent part was implicated in the event)."*	Per lines 883-885 and footnote 25, a procode needs to be selected even if one is not assigned to the device constituent (i.e., in a co-packaged combination product where the device constituent is not separately marketed). Although some common procodes are provided, this is still a significant concern for NDA/ANDA/BLA combination products where device constituents may not have a procode assigned. We recommend including further examples and a more complete listing of common device constituents within NDA/ANDA/BLA combination products in an additional appendix along with a discussion of how to best select a code without FDA involvement. This will also address comments on procodes included in CPC's response to Federal Register Number 2017-27650 on voluntary summary reporting, where selecting a procode will be a challenge for such products. Specifically, we recommend the following: • In Scenario #1 within Appendix 4, lines 1206-1208, the example indicates that if an appropriate procode cannot be found, it does	Clarify process for selection of procodes and provide examples in an additional appendix.

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		not need to be included. We encourage such direction to be included in the body of the document along with lines 883-885. • In scenario #2 within Appendix 4, lines 1242-1243, the example of being unable to find an appropriate product code for a vial adapter is not a good example since such a code exists (ONB). We encourage this to be updated to provide an example where an appropriate code is unavailable (or include this procode). Additionally, providing an appendix with additional guidance on selecting a procode as indicated above will help address this situation. For example: Prefilled syringe and autoinjector are commonly used drug-device combination products. The Agency should provide the most closely matched product codes for these commonly used device constituent parts. • Combination Product Applicants should select the procode that most closely aligns with the device constituent part. For example: o Pen injectors: NSC or KZH o Needle or needle-free injectors: KZE	
Use Errors			
IV.A.3., Lines 409-413	*"Caused or contributed" means that an event "was or may have been attributed to" the product or that the product "was or may have been a factor" in the event,*	Please clarify if user errors that do not implicate design or quality labeling defect are out of scope for PMSR. In some companies, this would not be captured as a complaint.	Clarification for how to apply device caused and contributed user error.

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	including events occurring as a result of: (1) failure, (2) malfunction, (3) improper or inadequate design, (4) manufacture, (5) labeling, or (6) user error (see 21 CFR 803.3(c)).”	In addition, please clarify that serious events occurring as a result of user error will qualify as reportable.	
Aggregate Reporting			
V.B.1., Lines 848-852	*“PMSR reports for combination products must contain all information required for the report under the applicable regulations, including relevant information on the entire product (including constituent part). Also, in situations where the Combination Product Applicant submits multiple types of reports for the same event or product problem, the reports should include cross-references to each other.”*	Please clarify what types of reports for the same event or product problem need to be cross-referenced.	Clarify cross-reference requirement and types of reports.
V.B.4., Lines 927-932	*“When NDA/ANDA/BLA Combination Product Applicants submit a periodic adverse drug experience report (PADER) or periodic adverse experience report (PAER), information from any initial and follow-up Five-day and Malfunction reports, in addition to any Fifteen-day reports, submitted during the reporting interval must be addressed in the section that contains summary and analysis of reports submitted during the interval (see 21 CFR 4.102(d)(1), 314.80(c)(2)(ii) 931 and 600.80(c)(2)(ii)).”*	What FDA means by “…contains summary and analysis of reports submitted during the interval” is not defined in the Draft Guidance. CPC interprets the “summary” to include a list of applicable ICSRs. Since the details of each ICSR is submitted to the Agency previously, a summary of each ICSR is redundant. We recommend that the Agency clarify the interpretation of “summary” in the Draft Guidance and provide focus areas to be covered in analysis.	Provide clarity as to how the ICSRs summary should be addressed in the periodic reports.

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V.B.4., Lines 936-937	*"Such information may be included in the body of the report or as an appendix….."*	The Draft Guidance should contain details on the required information to be added to the body or appendix of periodic reports for the Five-day and Malfunction reports.	Clarify specific required information to be added to periodic report for Five-day and Malfunction reports.
Reporting Timelines			
IV.A.4., Lines 449-455	*"<u>Submission timelines</u>. A follow up report must be submitted within…30 calendar days for Five-day, Malfunction, and death or serious injury reports, of receipt of the new information…For example, if a Combination Product Applicant for an NDA-approved combination product receives reportable new information related to a previously submitted Fifteen-day report, the information must be submitted as a follow up report within 15 calendar days of receipt of the new information."*	Wording implies that Five-day reports are due within 30 calendar days and contradicts line 393 (reportable malfunction due in 30 calendar days) in that follow up information for Drugs or Biologics is due in 15 calendar days.	Align wording in Draft Guidance with rule to indicate that reportable malfunctions in a drug or biologic approved combination product are due within 15 calendar days.
IV.A.4., Lines 467-475	*"For example, if a Combination Product Applicant for an NDA-approved combination product submits a Fifteen-day report, and later determines that a Five-day report must also be made regarding the need for remedial action, the Five-day report should be submitted as a follow up report to the previously submitted Fifteen-day report, and must be submitted with 5 work days after the day the applicant becomes aware that remedial action is needed. In contrast, if the applicant*	Definition for Five-day report in this example is not complete. We suggest addition of remedial action **to** prevent an unreasonable risk of substantial harm to the public health as reflected in 21 CFR 803.53. Specifically, we note that section 803.53 states that a manufacturer "must submit a 5-day report to [FDA] with the information required by 803.52 in accordance with the requirements of 803.12(a) no later than 5 work days after the day that [manufacturer] becomes aware that:	Consistency with 21 CFR 803.53

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	receives information that a reportable malfunction also occurred, the Agency does not intend to object if the applicant submits the malfunction report as a follow-up report to the previously submitted Fifteen-day report within 30, rather than 15, calendar days after the day the applicant receives the malfunction information."	(a) An MDR reportable event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health. [Manufacturer] may become aware of the need for remedial action from any information, including any trend analysis or (b) [FDA has] made a written request for the submission of a 5-day report. If [manufacturer] receives such a written request from [FDA], [manufacturer] must submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request. [FDA] may extend the time period stated in the original written request if [FDA] determines it is in the interest of the public health" (emphasis added).	
IV.B.3., Lines 602-605	*"The Combination Product Applicant must submit a written report to FDA of any reportable correction or removal of the combination product, unless the information about the correction or removal has already been provided through an ICSR required for the combination product, in which case a separate correction or removal report is not required…"*	The 5-day report is not specifically mentioned as an alternative ICSR means of reporting corrections/removals, even though based on the similarity of scenarios provided in this section with those provided in Section B.2., it is the ICSR that would most likely satisfy the correction and removal reporting requirement. We recommend the following revision: *"The Combination Product Applicant must submit a written report to FDA of any reportable correction or removal of the combination product, unless the information about the correction or removal has already been provided through an ICSR required for the combination product,* ***such as a 5-day report***	Clarification

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		<u>under 503.3(v),</u> *in which case a separate correction or removal report is not required…"*	
V.A.1., Line 755	*Timelines for Various Combination Product PMSR Requirements*	Please explicitly state FDA reporting timeline for malfunction reports for combination product applicants whose products were approved under NDA, ANDA or BLA (including what is considered day 0 for investigation results). The proposal is that follow up reports to 15 day reports are submitted within 15 days of new information becoming available. This includes information received external to company as well as internal (e.g., investigation results). Day 0 for investigation results should be stated as the date that the investigation is closed.	The phrase "FDA does not intend to object" is not explicit and may be misinterpreted and lead to inconsistent compliance approaches.
V.A.3., Lines 831-834	*"That applicant could satisfy both requirements by submitting a single report within 15 days that includes all of the information that would be required in both types of reports for the event."*	This section is more explicit than prior sections in the Draft Guidance with respect to reporting timelines. Please explicitly state what is considered day 0 for a combination product applicant approved under NDA, ANDA or BLA for investigation results. Consider defining day 0 for investigation results as the date the investigation is closed as this represents the date that all investigation results are available. This information would be submitted as a follow up to initial report.	Clarity on day 0 for investigation results. Consistency throughout Draft Guidance.
VI.B.2., Line 1088	*"The reporting timeline for both the Fifteen-day and serious injury report is 30 calendar days."*	Recommend that the same concept of consistent reporting timelines used for Device manufacturers is extended to Drug/Biologic products approved under NDA/ANDA/BLA, i.e., submit within a consistent	Consistent timelines for drug/biologic submissions is practically easier for initial/follow up submissions.

Section, Line(s)	Guidance Text	Proposed Changes/Comments	Rationale
		15 calendar days regardless of reason for submission.	
IV.A.1., Lines 302-305	*"Fifteen-day reports must be submitted for "adverse experiences" that are both "serious" and "unexpected" within fifteen calendar days (see 21 CFR 314.80(a) and (c) and 600.80(a) and (c)) or within 30 calendar days for combination products marketed under a Device Application as explained below."*	*"Fifteen-day reports must be submitted for "adverse experiences" that are both "serious" and "unexpected"* ***and if there is a reasonable possibility that the product caused the adverse experience. These reports must be submitted*** *within fifteen calendar days (see 21 CFR 314.80(a) and (c) and 600.80(a) and (c)) or within 30 calendar days for combination products marketed under a Device Application as explained below."* Per FDA's draft guidance entitled "Post Marketing Safety Reporting for Human Drugs and Biologic Product including Vaccines" (March 2001),[4] for clinical trials, patient registries, company-sponsored patient support programs and disease management programs, adverse experiences are only required to be reported if there is a reasonable possibility that the drug or biologic *caused* the adverse experience (VI.B., p. 774-785). We recommend the edit above to clarify this requirement in the Draft Guidance.	Additional clarity to align with FDA's "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" draft guidance, which states there must be a causal association.
IV.B.2., Lines 569-570	*"BPDRs should be submitted as soon as possible and must be submitted no later than 45 calendar days from the day of acquiring information..."*	*"BPDRs should be submitted* ~~***as soon as possible and must be submitted no later than***~~ ***within*** *45 calendar days from the day of acquiring information..."*	Edit requested to clarify Agency expectation.

[4] *Available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080538.pdf.