ACRP
ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS

MISSION:
ACRP promotes excellence in clinical research.

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June 8, 2015

Division of Documents Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

In reference to docket number: **FDA-2014-D-1747-0001**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the FDA with our comments on the Risk Evaluation and Mitigation Strategies: Modifications and Revisions; Guidance for Industry as this issue has a significant impact on our membership. The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

We applaud the FDA's efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Terri Hinkley, RN, BScN, MBA, CCRC
Interim Executive Director

FDA-2014-D-1747-0001 : Risk Evaluation and Mitigation Strategies-Modifications and Revisions			
Page Number	**Text Line**	**Reference** *(if applicable)*	**Comments**
cover	NA	Title Page	Cover indicates this document is "for comment purposes only" and the document refers to a draft guidance from 2009 on page 3 lines 71-72. Suggest to edit the 2009 guidance to meet the current regulations.
1	20	Introduction	The guidance opens with a statement about this guidance describing how "FDA will define and process submissions" for modifications and revisions to REMS - as such, this guidance would seem to be more appropriate as part of the CPGM for FDA not as a guidance for industry. Perhaps the tone and information in this guidance can be refocused to help industry by describing how industry can successfully submit REMS changes to the FDA using a least burdensome approach.
1	20-25	Introduction	The intro might be improved by first describing what a REMS is and then discuss the types and ways to submit changes to REMS. We do not believe we need the confusing naming convention of "revisions" to REMS as these are not really separate entities from "modifications." Unless this naming creates a "least burdensome" approach, perhaps the separation of these two types can be re-considered. The terms are so similar as to be confusing. Why not just say "Any REMS changes that are editorial in nature or are appropriate for submission in an annual report will be considered notifications when they arrive in the annual report. Other types of REMS changes require FDA review depending on whether they are minor (CBE-30) or major (PAS) modifications to the REMS." (in this way, consider moving footnote 13 on page 3 of the guidance into the text)
2	33-35	Introduction	Please consider changing this guidance to INCLUDE any and all additional work needed for changes to REMS for "single shared system drugs" (ANDA and listed drugs) and do not wait to do this in the future. The proliferation of guidance documents including these guidance on top of guidance documents are not entirely helpful. Please note: sometimes the multiple guidance confusion can be worse than no guidance at all.

2	40-41	Introduction	This guidance needs a strong rationale about why FDA should replace one draft guidance with another one. This is not all that helpful to industry because the changes are confusing (the new draft starts the review cycle all over again) and may lack substance (e.g. "revisions" into a special group vs. modification, etc). Also the 2009 guidance is still available on the website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf
2	44-45	Introduction	The sentence about major and minor modifications is out of place in this paragraph. A better approach would be to explain what major and minor modifications are in the introduction in a separate paragraph inserted after line 32.
2	45-50	Introduction	This Section is particularly confusing: "It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Insofar as this guidance establishes the modifications to an approved REMS that may be implemented following notification to the Secretary under section 505-1(h)(2)(A)(iv) — here referred to as REMS revisions — it has binding effect, except for the portions of the guidance setting forth the submission procedures for REMS revisions, which will, when final, have binding effect." When does binding effect occur?
3	75-78	Background	The wording in this paragraph is confusing since a draft guidance does not have the effect to require action; therefore, terms like "must be submitted" and "must include" and "may not be implemented" seem misleading and less than accurate because they are linked to a 6 year old draft guidance that was not finalized and is now abandoned in this document (see lines 39 and 41). This circular logic with potentially faulty information sources adds to the confusion and obfuscation of the message here. Consider stating what the Act requires and separately explaining in clear language why the 2009 guidance needed to be entirely abandoned (and remove the incorrect info from the website).
4	100-101	Background	The last sentence in the background can be deleted.

4	110-111	Policy	Consider removing the "revisions" terminology and replace with "…List of REMS changes that are editorial in nature or are appropriate for submission in an annual report (i.e. notifications)..." or similar wording to avoid having another official name to remember for a trivial issue like edits. Consider refocusing the message on the important higher risk issues without belaboring edits with their own category and special table of editing examples (since this document cannot possibly capture all of the potential editing examples).
4	135-136	Policy	These lines can be deleted
5 to 8	137-173	REMS REVISIONS	Consider removing the "revisions" terminology and replace simpler information like "editorial changes to the REMS should be submitted with and summarized in the annual report with an attached redlined document." If necessary, a bulleted list of the types of changes that would be considered editorial can be provided but should not duplicate information provided earlier in the guidance and need not be spread out across multiple pages / sections in the document.
5 & 9	152-153 & 191-192	REMS REVISIONS	Since this document list/table cannot possibly capture all of the potential editing examples, the clause that anything not listed in Table 1 seems particularly unwise. For example, the table may not cover all of the regulatory requirements for an annual report, etc. Also, the approach to make tables 2 & 3 "representative" but table 1 "exhaustive" seems inappropriate due to the undue emphasis on LOW risk issues and causes significant added burden. We request that the FDA provide specific details about why this low risk information is critical to the public health or remove this unnecessary LOW RISK "revision" burden from the guidance.
8	161-173	Table 1	Suggest to move footnotes to the applicable pages where they are referenced. For example, footnotes a & b are used on page 6; footnotes a, c, d, e, f, g are used on page 7 and footnote a is used on page 8 but not defined there.
9	191	Table 1	Suggest to add a footnote to “Proposed changes to approved REMS that are not listed in Table 1 will be considered REMS modifications” to be consistent with the information on lines 152-153
9	201	Table 2	Why does FDA need to review issues like "prescriber's medical specialty" or "providers unique identifier"? Without justification for the need for this specific CBE-30 need, such changes seem unduly burdensome and without merit. These types of changes would be better captured in the

			annual report unless FDA can stipulate why they need to review this specific type of information to better assess risk.
10	203	Table 2	Suggest to revise such that a change to manufacturer logo is a REMS revision rather than a REMS modification as the change in a manufacturer's logo does not impact content of a REMS.
10	204-206	Table 2	Suggest to move footnotes to the applicable pages where they are referenced. For example, footnote a and * are used on page 9 but not defined there.
11	211	Table 3	The line about changes to a Medication guide needing a CBE-0 is a new concept in this document and needs clarification. When is a CBE-0 required? This row is quite confusing.
11	210	Table 3	Suggest to revise the statement found in the 2nd column, 2nd row, 3rd line: "Changes related to drug administration ~~that affect patient safety~~" by removing the qualifier 'that affect patient safety' as all changes to drug administration can affect patient safety in some capacity.
11	210	Table 3	Suggest to add the word "type" to the last statement in 2nd column, 2nd row: "Changes to reflect a change in the <u>type</u>, frequency and/or timing of patient laboratory testing required to ensure documentation of safe-use conditions" as the type of laboratory testing performed may be an element that changes and would constitute a major modification.
12	213-217	Table 3	Suggest to move footnotes to the applicable pages where they are referenced. For example, footnotes a and * are found on page 10; footnotes a, b, c are on page 11 and footnote a is on page 12 but not defined there.
12	224-228	Procedures	Consider allowing the reasons for edits to be grouped and not specified one at a time as should be required for major modifications. Also minor modifications probably should not require a rationale when a simple description of the minor modification should suffice.
12&13	245-250	Procedures	The information about electronic submissions gateway appears "out of the blue" and does not seem appropriate in this part of the document.
13	268-274	Procedures	These lines do not make sense
13	268-273	Submission Procedures for REMS Revisions	Suggest to update the spacing/formatting as there are many extra lines.

13	279-280	Procedures	This sentence does not make sense because it implies a CBE-0 when the changes are allowed to occur during the year and are simply reported in the annual report AFTER THE FACT, not "can be implemented following receipt by the FDA."
13	283	Procedures	CONSIDER DELETING THIS PARAGRAPH or at least clarify, why each submission should include ALL "previously implemented REMS revisions" - what is the regulatory need to submit the same information to the FDA multiple times? Why does the FDA need to see ALL the prior versions and why is the history not sufficient since the FDA has already received the prior versions of the REMS?
14	309-319	Procedures	FDA should consider a less burdensome approach than having REMS submitted separately from the labeling changes driving the REMS
14	320-323	Procedures	FDA should consider a less burdensome approach than related REMS information sent in separate types of submissions: annual report, CBE-30, PAS. Potentially, can one REMS submission be forwarded to include CBE-30 changes together with PAS when the issues leading to the REMS changes are inter-related. For example, when doing a PAS for a REMS change, it would not make sense to separate out the editorial changes or the CBE-30 types of changes for separate submissions. The least burdensome approach might be to send them all in at one time so the REMS will maintain good integrity and clarity.
16	380-386 & 395-400	Procedures	The 30-day wait period for FDA to notify the applicant of an inappropriate submission seems inappropriately lengthy and a 2 week timeframe seems more appropriate (esp. for high risk situations where changes should be made in a more time-sensitive manner).
16	402-406	Procedures	FDA should not extend their review time beyond the 30 days already provided in the CBE-30. It does not make scientific or ethical sense to allow a product on the market for 30 days while the FDA is still reviewing the REMS after waiting 30 days for the FDA to review the REMS. This doubling of the review time does not seem appropriate for REMS.

17	412-422	Procedures	The information about waiting 60 days for "conforming REMS modifications and for 180 days for a review of "*not considered conforming* REMS modifications" and 180 days for labeling changes meeting CBE-0 (see footnote) is confusing.