CPC COMBINATION PRODUCT COALITION

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CPC Comments On
FDA Adverse Event Concept Paper

March 23, 2006

The members of the Combination Products Coalition (CPC) have spent considerable time assessing several possible approaches to the reporting of post-market adverse events associated with combination products. Attached at Table 1 is a brief summary of six different approaches that the CPC considered. Hopefully the general idea of those approaches is at least somewhat apparent from the summary, so we won't go through all of them here. We realize that there are an almost endless number of possibilities, but these six seemed to capture some distinctly different conceptual approaches.

The first four options are all available to the agency without a change to either the statutes or the regulations. The fifth option we believe may well require a change to the regulations, and the sixth option may require a change to the statute, depending on what exactly is to be done. Ironically, of the first four options currently available within the existing regulation, we were not able to identify which if any of them best captures the agency's existing approach. There is, we are afraid, a significant gap in the agency's existing guidance with regard to explaining the applicability of the adverse incident reporting rules in the context of combination products.

As we worked through comparing the various alternatives, in order for us to come to consensus, it was necessary to distinguish between short-term, intermediate-term and long-term objectives. Some changes cannot realistically be made in the short term because (1) there is further, complex policy development that needs to occur, (2) there are huge implications for the agency's information technology systems, as well as for training and staffing the work that needs to be done and (3) ultimately statutory amendments may be required before such changes can be fully implemented. As a result, we will break our comments into three sections: short term, intermediate term and the long-term changes. But before we do that, we want to state clearly what we perceive the challenge to be on the industry's side, and comment on how FDA frames the issues in its concept paper.

Industry's Challenge

We recognize that FDA has challenges that it is trying to address in its concept paper, so it can better protect the public health, and we enthusiastically support efforts to address those challenges. At the same time, we want to make sure that the agency understands the challenges we face in trying to comply with the agency's regulations.

In summary, our primary concern is understanding which regulatory requirements apply to a given regulated article, and in particular which deadlines govern the timing of required reports. Using form 3500A makes it easy for manufacturers to supply all of the information that may be required under any set of reporting regulations, but it does not help us determine how quickly we must respond. We are usually pressed for time in gathering the information needed to respond, so understanding clearly the deadline becomes essential. Currently, we often do not. The agency gives an instructive example of the ambiguity surrounding timeframes in its concept paper. Specifically, adverse event reporting for devices requires 30-day reports for serious injuries, while drugs and biological products require 15-day "alert" reports for serious and unexpected events. For products with drug or biological device components that are regulated by the device regulations, manufacturers may be confused as to whether and when the alert reporting requirements come into play.

FDA's concept paper

We generally agree with the way FDA frames the issues in its concept paper on adverse event reporting. For example, we agree that FDA has appropriately identified the major differences between the reporting schemes. We also agree that for the most part following the approval pathway identifies the appropriate adverse event reporting scheme. Generally, for example, if a product is appropriately approved under drug regulations, adverse events associated with the product should be reported under the drug reporting regulations. While the general rule is easy to state, specific instances cause unique challenges. We find that the greatest challenges are with combination products that we refer to as kits (separate products packaged together)[1] or virtual combination products (products not packaged as a unit but required to be used together to achieve the intended use, indication or effect).[2] And unfortunately, at times even single entities (combination products that are "comprised of two or more regulated components" that are "combined or mixed and produced as a single entity") create challenges.[3]

Short-term changes

After analyzing options 1 through 4 in the attached concept paper, the CPC concluded that option 4 -- manufacturer discretion -- represents the best approach for the near term. In defining the various options, it was usually important to describe separately how the process would operate when there is one premarket submission compared to when there are two. In this particular option, however, the same basic rule could be applied in either case, revealing its simplicity.

Under this manufacturer discretion option, the starting "presumption" would be that both sets of adverse event regulations that correlate to the two components apply unless the

[1] *See* 21 C.F.R. § 3.2(e)(2).
[2] § 3.2(e)(3) and (4).
[3] § 3.2(e)(1).

manufacturer can "reasonably" determine that the specific adverse event is related to one of the regulated components and not the other.

You might be wondering in that paragraph what we mean by that term "presumption." In our parlance, the term "presumption" simply means that in the absence of any facts, the stated presumption would hold. In baseball, for example, you need a rule that defines what happens in the case of a tie, when the ball and the player reach the plate at the same time. In this area, we need a presumption which says what happens when the facts are either unknown or don't point to one component or the other. In our proposal, when the manufacturer has enough information that the manufacturer can reasonably conclude that one component was more likely the source of the adverse event, at that point it is no longer necessary to follow both sets of adverse event regulations, but rather only the set for the component at issue.

We deliberately picked the word "reasonably" to convey a fairly low threshold of assurance (as opposed, for example, to the word "clearly") because the choice is not between reporting or not, but rather under which set of regulations the reporting obligations would be assessed. Because at stake is only the choice between two different regulations at issue, we do not think that the manufacturer should be required to meet a very high level of proof. Indeed, to state our concept more concretely, when a manufacturer has evidence that suggests that the adverse event was more likely caused by one component than the other, they should follow the reporting obligations for the more likely component. Also, because a reporting deadline usually arises before the investigation of the event is complete, typically manufacturers would make a judgment on reporting prior to the root cause analysis. If the root cause analysis changes the manufacturer's assessment of causation, the manufacturer should outline, summarize, and document any conclusions, and update its adverse event report as appropriate.

Examples

Some examples might help to clarify our proposed approach.

- Take, for example, a prefilled syringe without a natural rubber stopper. Assume that the patient has an adverse reaction of a kind that is occasionally observed with regard to the drug component (for example, it is an allergic reaction). In addition, the manufacturer of the drug knows that because they have seen it in a number of instances, and it occurs regardless of the specific kind of drug delivery device. Assume further that the manufacturer can understand scientifically why this adverse event might occur with the use of the drug, but they can see no connection between the particular device and the event. Further, the company sees no evidence of any device malfunction or a design issue. In essence, the company can see no reason why the device would be responsible for the adverse event, and on the contrary the company does know enough to associate the adverse event with the drug. In that instance, the company would follow the regulations for reporting adverse drug events, and not be required to follow the process specified under the medical device reporting regulations.

The analysis does not change much even when two manufacturers are selling the product separately to the customer.

- Consider, for example, a dedicated drug delivery device that is not prefilled, but rather sold directly to the customer without the drug. It is, however, cross labeled specifically for use with a particular brand of drug. The branded drug is likewise specifically cross labeled for use with the device. An adverse event occurs in which the needle breaks off during delivery of the drug, and the patient is in fact injured. After an investigation, no evidence exists pointing to the drug as the culprit for the adverse incident. Instead, the device manufacturer, and only the device manufacturer, would need to report the event.

The one difference in the second example from the first is that we do believe the two manufacturers have an obligation to talk to each other. In the example we gave, the cause is arguably crystal-clear. If instead of crystal-clear it is simply more likely one component over the other, the two manufacturers should communicate to share information and to make sure that they agree on who should file. (As previously explained in our January 2006 comments on the cross-labeling issue, we believe that cooperation between manufacturers – especially those co-marketing virtual combination products – is essential, and that these manufacturers typically will contractually assign responsibility for initiating and responding to communications.) If they do not agree, each thinking that the other should file, we believe both of them should file within the time period associated with their component. In other words, if the one manufacturer believes based on their investigation that the other company's product is responsible for the event, the other company should file, and vice versa. Likewise, if for whatever reason the manufacturers do not communicate about the event, we believe that both of them should file to the extent they have information suggesting that filing is required.

The reasoning behind our recommendation quite simply flows from the last couple of rows from the table in which we identify the pros and cons of the various approaches. We believe this approach gives manufacturers much greater clarity regarding which set of regulations it needs to follow, at the same time meeting the public health objectives that industry and the agency share. While this manufacturer discretion option does not offer the simplicity of options 1 and 2 -- which are in effect just rote rules that do not require any real assessment or decision-making -- we think the advantages are worth the extra effort by companies. This approach does call upon manufacturers to make judgments -- judgments that might be second-guessed by the agency – but we believe it is industry's responsibility to assess the meaning of information that we receive in the first instance.

Short Term Path Forward

As already alluded to, members of the coalition believe that FDA has not provided complete guidance on this topic. We are also unclear on how FDA makes decisions regarding what adverse event regulations apply in a given instance, as well as how the adverse reporting systems for drugs, biologics and devices work and interact with one

another. That said, we would suggest that FDA as promptly as possible develop and finalize guidance that describes this option and affirms that it agrees with this interpretation of existing authorities. The guidance would have to delineate in general the rules for attributing an adverse event to one component over another, parsing carefully what it means for one component to be more likely the cause, and the level of evidence necessary to reach that conclusion. Indeed, for the guidance to be useful, it will probably need to include numerous, specific examples of adverse incidents and how the attribution should be resolved.

In this area, FDA still obviously will be tied to the existing regulations. So attribution of a device malfunction is different than the attribution required for a serious health consequence. And, when we contrast that with the standard for attributing an adverse event to a drug, it does become quite complicated. Nonetheless, we do believe that under existing regulations it is up to the manufacturers to exercise those judgments in the first instance.

The examples that we recommend be included in the guidance would be perhaps one of the most important features of the guidance. Those examples might be best obtained by putting an informal notice out to industry representatives that the agency is looking for particularly difficult or problematic examples of combination product adverse event reporting incidents. These examples would help illustrate issues such as timing of reports and what regulatory requirements apply. For example, in addition to the interplay between adverse event and MDR reporting requirements, how should annual reports for drugs and corrections and removals for devices be applied?

We also think it would be extremely valuable to work through adverse event reporting examples with the agency at an industry-wide meeting. Speaking for ourselves, we would be glad to supply some of those examples, and indeed we would be glad to help frame the guidance document itself in the form of a proposal for the agency to consider under its Good Guidance Practices.

Intermediate-Term Initiatives

One of the key challenges to combination product adverse experience reporting relates to how a report is reviewed once it is submitted. As mentioned above, though, we have observed that the agency's adverse event reporting systems simply lack transparency to the outside world, which can make it difficult for industry to comment on agency proposals. For example, currently we are not aware of an adverse event database specifically dedicated to combination products. It is also not clear to us how the review process is or can be coordinated among the various centers. Our understanding is that the device MDR database is not compatible with those for drugs and biologics, and device reporting does not mandate the use of the MedDRA coding system. Given these assumptions, we observe that FDA may not have the ability to use the data to its full potential.

That said, we have looked for an intermediate-term approach that would ensure the rapid review of reports by the appropriate centers and comply with existing statues. In our assessment, the requirements for this approach would be as follows:

- FDA should create an adverse event database for combination products and port data from approved combination products into it. We think this is feasible in the near term.
- FDA should expand the MedDRA dictionary to include device-specific terminology. The MedDRA MSSO is already doing this at the request of clients involved in drug-eluting stents and pacemakers.
- CDRH may be using the MedDRA terminology hierarchy, but should adopt a set dictionary of MDR terms.
- FDA should develop a guidance document for industry and the agency on these elements and train everyone.
- FDA should explain how each adverse event reporting system works and how the systems interact, if at all.

This approach would enable the industry and FDA to implement a unified reporting system in advance of the statutory change suggested in the next section over the long term and help ensure the rapid review of adverse event reports by the agency.

Long-term solution

In our chart, options five and six represent candidates for a longer term solutions in the sense that either one of them would require at least a change to the regulations to implement. In comparing the two, we believe it is most sensible to aim for option six, which is a truly unified reporting process. We believe that technology will continue to drive the convergence of drug, device and biological products, and that it will be more and more difficult to separate out the effects of one component over another. Thus we see this technology convergence as necessarily leading to a convergence of the reporting processes.

In a related vein, partly in response to the activities under ICH and the CDRH e-MDR initiative, we see FDA moving increasingly toward electronic reporting of adverse events. If that trend continues, and manual completion of paper forms disappears, it will be even more important to have the system constructed so that the information is included in a sensible way that makes it useful to the agency.

In our parlance, the unified reporting process means having just one type of report that asks for all of the relevant information for a regulated article whether it is comprised of a device, biological or drug and one integrated set of time periods for reporting. Obviously there are concepts such as malfunction that may only make sense in the context of one of

those component articles, but that can be addressed as the MedDRA vocabulary incorporates more "device-specific" terminology.[4]

The benefits of such approach seem significant both for the agency and for the industry. From an agency perspective, the system becomes administratively much easier to operate in the sense that there is simply one system collecting and analyzing all of the information. That should better enable the agency to protect the public health by spotting trends in a way that would not be masked by over-reporting duplicative information, and avoid gaps as well.

While there may be some field in the report through which it is necessary to ascribe, if possible, the component of the article that caused or led to the adverse event, good faith mistakes in such assessments would not produce liability for the industry. Industry would have an easier time complying if it only had to worry about one unified system with unified time frames, for which it could train its people. There would certainly remain issues that need to be worked out, for example when more than one company is responsible for producing separate components of a virtual combination product or kit, but presumably the system could be designed in such a way that it catches any duplicate information inadvertently submitted by two companies.

Given that recommendation, and given the possibility that a statutory amendment will be necessary, we stand ready to work with the agency toward that statutory change. While we do not necessarily see any provisions in the current Federal Food, Drug & Cosmetic Act that preclude unified reporting, it may well be necessary to obtain further statutory authority, depending on the kind of unified reporting that ultimately is sought. It seems that we are now in a legislative cycle process where significant changes to the Federal Food Drug & Cosmetic Act occur in five-year intervals as user fees are reauthorized. We believe that the factors that will slow the move toward a unified reporting process -- including the substantial information technology issues as well as the complex policy development issues -- suggest that this issue might be ripe for legislative change in about seven years, corresponding to the next anticipated renewal of the medical device user fees after the next one.

Given the complexities of the administrative tasks necessary to implement the truly unified system, as well as the IT challenges, we should probably all anticipate working on and beginning the implementation of a system well in advance of any actual legislative change. Working together, the agency and industry can begin to design systems that will most effectively gather the needed public health information, and begin to design the hardware and software systems necessary to accomplish that task, even before legislation is in place. If the system can be developed through consensus, conforming legislative change can become a relatively simple process.

[4] FDA should also evaluate the impact of SNOMED (Systemized Nomenclature of Medicine) on a unified reporting process, considering issues such as how FDA will handle adverse event reports that are coded in SNOMED.

Finally, to state the obvious, this subject represents a complex mixture of issues surrounding the public health needs, the practice of medicine, the manufacturing industry's systems, and administrative challenges for the agency. It seems to us that a substantial and ongoing dialogue among the stakeholders would be very fruitful toward moving these enhancements forward. We applaud the agency for its leadership in publishing its concept paper, and we would suggest that as a next step a public meeting at which some of the data and logistical issues are discussed would be quite helpful. Perhaps for expediency, we would suggest that we all work with an organization such as RAPS or FDLI in order to organize such a public meeting reasonably soon.

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Table 1:
Options for Reporting Adverse Events Associated with Combination Products[5, 6]

	Option 1—Submission (Or Center) Type Approach	Option 2—Always File Two	Option 3—FDA Discretion Approach	Option 4—Manufacturer Discretion Approach	Option 5—Supplemental Report Approach	Option 6—Unified Reporting Process
What does this option look like--						
A. When there is one premarket submission	Always just follow the regs that correlate to the type of premarket submission (or center of jurisdiction)	Always follow both sets of regs	Follow the regs that correlate to the type of premarket submission (or center of jurisdiction), except when FDA specifically advises that sponsors need to potentially file both types of reports; in that case evaluate whether the incident is	Follow both sets of regs unless the incident is reasonably related to only one component	Always follow the regs that correlate to the type of premarket submission (or center of jurisdiction) plus supply supplemental information based on the second type of report that only includes the information not required under the first set of regs, unless the incident is	Have just one set of integrated regs that asks for all the relevant information for all three types of products

[5] This Table omits reporting obligations for vaccines.
[6] Our proposals in Table 1 assume that the reporting obligations for a product include any annual reporting requirements. For example, for a drug-device combination approved under an NDA, the relevant reporting obligations would include those under 21 C.F.R. § 314.81. Likewise, Option 6, the Unified Reporting Process, would take into account what annual reporting would be necessary for products.

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	Option 1—Submission (Or Center) Type Approach	Option 2—Always File Two	Option 3—FDA Discretion Approach	Option 4—Manufacturer Discretion Approach	Option 5—Supplemental Report Approach	Option 6—Unified Reporting Process
			reasonably related to only one component.		reasonably related to only one component.	
B. When there are two premarket submissions (assume two sponsors)	Always follow both sets of regs that correlate to the premarket submissions (or centers of jurisdiction)	Always follow both sets of regs	Follow both sets of regs that correlate to the premarket submissions (or centers of jurisdiction), unless FDA specifically allows the sponsors to determine whether the incident is reasonably related to only one component	Follow both sets of regs that correlate to the premarket submissions (or centers of jurisdiction) unless the incident is reasonably related to only one component	Supplemental duties: Situations where a sponsor receives an adverse event report about a constituent part that was approved or cleared under the marketing application held by the other sponsor. Various possibilities include: 1. If the initial safety report received by the sponsor clearly identified the constituent part thought to be associated with the event, and if that	Have just one type of report that asks for all the relevant information for all three types of products

	Option 1—Submission (Or Center) Type Approach	Option 2—Always File Two	Option 3—FDA Discretion Approach	Option 4—Manufacturer Discretion Approach	Option 5—Supplemental Report Approach	Option 6—Unified Reporting Process
					constituent was held by the other sponsor, the sponsor who received the report would send the report to the holder of the other marketing application for assessment of whether the report should be submitted to FDA. 2. The sponsor who initially received the report would submit the safety report to FDA with a cover letter indicating the manufacturer and application number for the suspect constituent part. 3. If the initial safety report did not contain	

	Option 1—Submission (Or Center) Type Approach	Option 2—Always File Two	Option 3—FDA Discretion Approach	Option 4—Manufacturer Discretion Approach	Option 5—Supplemental Report Approach	Option 6—Unified Reporting Process
					enough information to identify which constituent part may have been associated with the event, then the sponsor who received the report would submit the report to FDA as it would for other reportable events concerning its product and provide a copy of the report to the application holder of the other constituent part.	
Short term or long term—are changes to regs or statutes involved	No statutory or regulatory changes required, but guidance	No statutory or regulatory changes required, but guidance	No statutory or regulatory changes required, but guidance	No statutory or regulatory changes required, but guidance	May require changes to the regulations.	Statutory and regulatory changes may be necessary.
What are the pros of this approach	Simple	Simple Low risk for	• Usually simple • Includes a safety valve the	Satisfies the public health need for data	Reduces the data redundancy	Simple No duplication of

	Option 1—Submission (Or Center) Type Approach	Option 2—Always File Two	Option 3—FDA Discretion Approach	Option 4—Manufacturer Discretion Approach	Option 5—Supplemental Report Approach	Option 6—Unified Reporting Process
		companies	agency can use when it can predict the need for greater reporting			data Avoids manufacturer risk
What are the cons of this approach	Gaps in the data needed to protect the public health	• Too much data—hides true problems • Added cost of multiple reports	• Administrative burden on FDA to identify technologies that require greater reporting • Needs to be an opportunity for FDA review, such as during assignment in response to RFD • Risk that FDA will fail to ask for reporting when it should	• Can be too much data because manufacturers tempted to over report to avoid risk—also wasted resources • When not over reporting, manufacturers have more risk	• More burdensome on manufacturers as they must report more data • More risk for manufacturers as they decide what needs to be reported	More data for manufacturers to collect

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Table 2: Unified and Interim Safety Reporting

Requirement	Drugs (21 CFR 314.80) and Biologics (21 CFR 600.80)[7]	Device (21 CFR 803)	Blood Derived (21 CFR 606.170)	Interim Safety Reporting	Unified Safety Reporting System
Early Reports		*5-day report* An MDR reportable event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health must be reported within 5 days or in response to a written request from FDA.	*7-day report* Complication of blood collection or transfusion is confirmed to be fatal must be submitted within 7 days after the fatality.	*5-day report* Any AE that necessitates immediate or remedial action to prevent an unreasonable risk to public health must be reported within 5 days. This includes AE resulting in death related to Combination Products derived from blood.	*Public Health Risk Report* Any AE that necessitates immediate or remedial action to prevent an unreasonable risk to public health must be reported within 7 days. This includes AE resulting in death related to Combination Products derived from blood or tissue, or there is a

[7] We have observed, though, that in some cases FDA is requiring manufacturers whose *in vitro* diagnostic products are approved under a BLA to follow MDR reporting requirements.

Requirement	Drugs (21 CFR 314.80) and Biologics (21 CFR 600.80)[7]	Device (21 CFR 803)	Blood Derived (21 CFR 606.170)	Interim Safety Reporting	Unified Safety Reporting System
					suspicion of contamination or tampering.
Mid term reports	*Postmarketing 15-day "Alert reports".* Serious and unexpected AEs reported within 15 calendar days of initial receipt of the information with a follow-up within 15 calendar days	*30 day report* All non-5-day MDRs. (NOTE: User facilities must submit annual reports to the FDA on Form 3419. Manufacturers would have the option of submitting an annual report under the Intermediate-term approach)		*Alert Reporting 15-day* Serious and unexpected AEs not constituting a public health risk must be reported within 15 calendar days of initial receipt of the information with a follow-up within 15 calendar days, 30 days for non-5-day MDRs	*Alert Reporting* Serious and unexpected AEs not constituting a public health risk must be reported within 30 calendar days of initial receipt of the information. 30 days would be allowed for the compilation of a complete repot.
Periodic reports	*Periodic adverse drug event reports* Reported quarterly for first 3 years	Periodic reports may be required as a condition of approval for a PMA device. (21 CFR 814.82(a)(2), (7); 814.84(b))		*Non-alert adverse experiences* All AEs reported quarterly for first 3 years post-approval,	*Non-alert adverse experiences* All AEs reported quarterly for first 3 years post-approval,

Requirement	Drugs (21 CFR 314.80) and Biologics (21 CFR 600.80)[7]	Device (21 CFR 803)	Blood Derived (21 CFR 606.170)	Interim Safety Reporting	Unified Safety Reporting System
	post-approval, then annually.			then annually. This includes Combination products comprised of Drugs, Devices, Biologics, Blood and Tissue-Derived Products approved under an NDA or BLA.	then annually. This includes Combination products comprised of Drugs, Devices, Biologics, Blood and Tissue-Derived Products irrespective of the approval route.
Records		*Not submitted to the FDA* AEs not considered device-related are not reported. Reports are maintained by the manufacturer and often reviewed by the FDA during inspections.	*Not submitted to the FDA* Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion.	*Device and Blood-derived non-alert AEs* All AEs reported annually on a voluntary basis. This includes Combination products comprised of Drugs, Devices, Biologics, Blood and Tissue-Derived Products approved under a PMA or	

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Requirement	**Drugs (21 CFR 314.80) and Biologics (21 CFR 600.80)[7]**	**Device (21 CFR 803)**	**Blood Derived (21 CFR 606.170)**	**Interim Safety Reporting**	**Unified Safety Reporting System**
				510(k) or blood derived, where annual reporting is not a condition for approval.	
Form to Use	FDA Form 3500A	FDA Form 3500A	Form 3500A or CIOMS I	*FDA Report Form 3500A*	*FDA Report Form 3500A*