Combination products are therapeutic or diagnostic medical products that combine drugs, devices, and/or biological products with one another. FDA developed a regulation (final rule) on Current Good Manufacturing Practices (CGMP) for combination products that became effective July 22, 2013 (21 CFR Part 4). AAMI recently developed a technical information report (TIR) that provides information on how to effectively implement FDA’s regulation. The overall goal of the TIR is to aid informed, risk-based decisions in establishing CGMP operating systems that support development, manufacture, premarket regulatory evaluation, and ultimately commercialization of combination products. This article, a result of an discussion with industry and FDA representatives, explores the landscape of combination products, highlights important considerations in developing and seeking marketing clearance for these innovative products, and provides insight on trends in the area.

Jena Passut: Welcome to our roundtable discussion on combination products. How are combination products reviewed by the FDA?

Stephanie Del Paine: One option is for companies to confer with FDA’s Office of Combination Products (OCP) and OCP will determine the lead center. That determination is largely based on the primary mode of action (PMOA) of the combination product. A lead center is selected based on the mode of action, and the application goes to that Center. A potential additional consideration now is that since there’s a “lead center,” there will also be a non-lead center, and both centers will likely have to connect and communicate. Manufacturers may need to communicate with both lead and non-lead centers, and the logistics can be challenging.

John Barlow Weiner: As Stephanie explained, there is a lead center to which the product is assigned based on its “primary mode of action” (whether the drug, device, or biological product in the combination product contributes most to the therapeutic effect). The lead center is the primary point of contact for regulatory questions for the combination product but typically works closely with the secondary center on premarket review and other issues, including CGMP requirements. Other components play an active role, such as ORA [Office of Regulatory Affairs] for facility inspections. Typically, the primary mode of action for a combination product is clear, and sponsors just go directly to the lead center with their applications. If it’s not clear which center should have the lead or there is disagreement between the sponsor and a center about this, the sponsor can come to OCP for a determination. OCP is basically responsible, by the way, for ensuring FDA regulates combination products in an efficient and consistent as well as effective manner. So, in addition to making assignment determinations, OCP is available to assist the centers and sponsors with regulatory questions, facilitate interactions, and help resolve differences of opinion when they arise. We really are here to help. I’d like to thank AAMI for putting this discussion together. It’s great to have experts from industry come together to share their experiences, perspectives and advice.

FDA gets to say what it thinks through rules and guidance, etc. So, I’m going to listen here more than talk, but am very glad to be included.
Jena Passut: AAMI recently published TIR48, a companion document to the FDA rule. Can you tell us about its development and scope? How will it eventually help industry?

Rosemary Gonzales: About five years ago, I contacted AAMI and proposed it develop guidance to help industry understand what quality system regulations applied to the manufacturers of combination products. There are several ICH, ISO standards and regulations, but there wasn’t an umbrella or overarching document that companies could use to determine which requirements were applicable. The proposal requested the guidance be written from a global perspective. AAMI agreed that a global guidance would be beneficial, but the initial scope of TIR48 would be U.S. focused. AAMI brought in experts from industry, including representatives from CBER, CDER, and CDRH to develop TIR48—a technical guidance that would provide additional insight to companies establishing quality systems for the development of combination products.

Nolan Baird: Here are my thoughts on what we put together for the TIR48. It started out as a comparison of the device, drug, and biologic quality management systems requirements. The TIR evolved into recommendations for how to apply the final rule for combination products—essentially, how companies can start implementing aspects of the final rule, like the “streamlined” approach. There are product examples in TIR48; excellent graphics addressing the challenges between a combination product; and device and drug development processes. I’ve used the TIR and accompanying strategy extensively here at Abbvie. The TIR is a useful guide for getting to “how” an organization can develop combination products. It’s not the answer for everything, but it’s an important step in that direction.

Rosemary Gonzales: Another part was that industry is really moving into the combination product arena. It’s all aimed at innovative ways to address unmet needs. There are ever more devices out there that are helping patients, and there is competition toward innovation, mobile devices, mobile apps, and, in addition, biosimilars in combination products. So, TIR48 helps companies make sure they are doing the right thing. Ultimately, this helps patients.

John Barlow Weiner: In terms of its scope, I actually heard a little bit of the answer on this from Nolan. I agree with what I was hearing in terms of it evolving. It was initially proposed before the final rule was published, and the concern was to make sure that industry had a basic understanding of what the rule was about, since it was potentially a new concept, although the issues had been addressed previously in draft guidance from the FDA. As the AAMI process progressed, the rule was finalized and work on a draft guidance was underway. So the thinking shifted a bit. From the FDA’s perspective, a big part of what made the TIR development process worthwhile was the substantial engagement from industry and the willingness of industry participants to discuss what they had learned, were doing, and using to help other members of industry to understand how to apply the rule. Fundamentally, the TIR attempts to address development of a sound manufacturing approach for combination products. We’re very excited about the AAMI TIR. We think it dovetails nicely with our guidance efforts.

Jena Passut: How do you get a decision on whether a product is a combination product?

Steven Binion: Either through informal conversation and discussion with OCP, or with a formal submission of a request for designation (RFD). Those are the two processes that are currently used to my knowledge.

Roundtable Participants

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“Fundamentally, the TIR attempts to address development of a sound manufacturing approach for combination products.” — John Barlow Weiner
Jena Passut: How do I comply with the FDA rule on combination products?

Nolan Baird: One of the important elements about complying with the FDA rule and understanding what the FDA was trying to accomplish with the rule, is that the rule is not new in terms of regulations. Instead, it brings together the device and drug regulations into one rule that provides guidelines to industry about how they can apply what they’re already doing and bring those elements together to achieve compliance for a combination product.

Stephanie Del Paine: But, to be accurate, there is more for companies to address than in the past. There are additional considerations for drug and device companies, even though CGMP rules existed for drug and device realms.

Rosemary Gonzales: Another important element to implementing the final rule is to clearly understand the roles and responsibilities of all parties involved in the manufacturing of the combination product(s). It allows the manufacturer to identify which aspects of the regulations are applicable.

Jena Passut: It sounds like that could be potentially challenging.

Stephanie Del Paine: Well, it is. For example, in the device world, stability testing means one thing, but in the drug world, stability testing means something else, and there’s no substantial overlap. For a device, stability testing means determining if the device will fatigue over the lifetime of the product. Stability in the drug world, on the other hand, was developed to assess shelf-life viability for the active pharmaceutical formulation. For example, does the formulation maintain potency, do degradants form over time, etc. With the FDA’s final rule, a primary issue for a device manufacturing now is, “How do I look at this drug component, in addition to the stability work I’ve already done?” That’s a whole new ball of wax for device manufacturers.

Nolan Baird: That’s a really good example and a very good point. The cultures of the drug and device worlds are very different cultures that develop products in unique ways. You’ve highlighted one of the biggest challenges between these two cultures—there are common terms across both cultures that can have different meanings and create challenges. Stability is a great example. We’ve also struggled with terms like “target product profile” and “process validation.” There are a number of terms that appear to be common, but, in fact, have different meanings.

Steven Binion: Quality system regulations have existed for a while now for devices, likewise on the drug side. The FDA’s thinking was to provide an option for combination product manufacturers to perform operations under a “streamlined” CGMP approach. In this approach, manufacturers can elect to follow either the drug GMPs or the device QSRs, adding in elements from the other GMPs that aren’t inherently included. With the FDA’s final rule, the drug and device GMP requirements remain the same, but the approach to operating under a streamlined process certainly is a different situation, because manufacturers are now applying both device and drug CGMPs.
**Stephanie Del Paine:** Absolutely right, Steve—it’s important to acknowledge the differences in culture between the drug and device worlds, as Nolan brought up. Take the stability example I described earlier; it’s important for a combination product manufacturer to be more savvy about how the drug stability testing guidelines apply to a device combined with a drug. You need to determine how you can do multiple tests on one device, for example, rather than having a device set aside for each indicated test. You have to be knowledgeable about relevant tests, and how they may apply, and be aware of those tests that are not relevant or helpful in gaining market clearance for your combination product.

**Jena Passut:** We mentioned earlier the topic of terminology, in which certain aspects regarding drugs were called one thing, but with devices, termed something else. Is there any impetus in combination products to align drug and device terminology, or is that an issue at all?

**Stephanie Del Paine:** Not that I know of. However, the FDA’s final rule and its draft guidance on implementing the final rule, as well as the TIR, provide clarity on how terms are used. I don’t think there’s a goal to have terms interchangeable in the device and drug world. But there are things that can happen in the future that perhaps should be re-evaluated. For example, given the amount of work that goes into stability testing, is it possible to improve how we design stability studies so the testing encompasses the requirements from both worlds in one study? That’s not possible in many cases now, largely because of the current conventions for devices and drugs in, for example, the timeframe covered during testing and what specifically is monitored. It would be fantastic if somehow in the future, device and drug worlds met with regard to stability testing conventions. That would be great.

**Jena Passut:** We’ve discussed several challenges. What are some tips you can offer to deal with some of the challenges, first of all, complying with the FDA rule?

**Rosemary Gonzales:** As companies develop combination products, they are faced with

the challenges of competition and regulatory expectations. Companies are searching for innovative ways to address user needs and ensure they are providing value by having a product that is safe and effective. In addition, regulatory expectations are increasing. The TIR provides guidance to companies that are in this arena and ultimately serves the patient and user needs.

**Stephanie Del Paine:** I agree completely, Rosemary. You need to determine what you don’t know, and one way to do that is to have an expert come in who’s experienced, or who can at least identify potential gaps in complying with the rule.

**Nolan Baird:** Steve mentioned the streamlined approach earlier. I would recommend folks take a look at the streamlined approach as a template of a gap assessment. As you compare regulations between device and drugs, a lot of what the final rule has attempted to do is identify gaps and eliminate redundancies. Focusing on the streamlined approach would be a great first step for a drug or device company identifying their own internal gaps.

**Steven Binion:** I don’t think I can stress this enough to either a start-up or an established company. Especially for novel combination products, consideration of the final rule as early as possible in the development stage is critical. An important step every manufacturer should consider is to take advantage of the mission of OCP and reach out early and often.

**Stephanie Del Paine:** I agree completely. The more communication, the better. An request for designation is determined by OCP, and assigns the lead review center. Devices are classified according to risk, and there are different levels of risk. There are specific guidelines and requirements based on the risk level. Adding a drug to even a Class I device (lowest risk) may elevate the combination product to a higher risk level, including up to Class III (highest risk). For Class III products, there are general and specific control requirements, and potentially case-by-case review requirements that can prolong the review period.

"Companies are searching for innovative ways to address user needs and ensure they are providing value by having a product that is safe and effective. In addition, regulatory expectations are increasing.”

— Rosemary Gonzales
Jon Cammack: In addition to all the practical advice already given, I would reiterate the importance of direct dialogue with the OCP; they are very willing to engage with stakeholders on complying with the new regulation. We also believe TIR48 is a practical document that complements what the FDA has written in the final rule and the accompanying draft guidance.

Jena Passut: We talked a little bit about tips you could offer for complying with the FDA rule on combination products, but what advice can you offer for the actual review of the products?

Nolan Baird: There needs to be a strong effort toward communicating upfront, not just with the OCP, but with Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health. The earlier you can get feedback, the better off a submission is going to be down the road, and I would definitely discourage industry from filing a combination product blindly with FDA—you risk being surprised by the feedback. The FDA is learning through this process as well, and I would like to see other agencies becoming more open to having these dialogues early, like OCP does, so everyone's interests can be served as expeditiously as possible.

Rosemary Gonzales: One relevant example that has generated a lot of specific guidance from the agency is incorporating human factors into design controls. It is important to ensure you work with the agency as soon as possible to obtain feedback regarding human factors strategy. Otherwise, programs could potentially be pushed back by years.

Nolan Baird: Human factors is a great example of where you can submit a protocol to the lead agency and then during the review process, the secondary agency may see the protocol totally differently and come back with a variety of questions. Having those cross-agency discussions as early as possible is in everyone's best interest.

Steve Binion: For combination products, you need to be aware that in the review process, it will be different because there'll be a consult either from CDRH to CDER or CBER or vice-versa. So, be aware of all of the elements that are involved in keeping your submission on track while still trying to take advantage of OCP as a potential facilitator, even mediator, when issues arise during review.

Jena Passut: OK. So we have the FDA rule and TIR48 for the U.S. Can you tell me what's happening internationally or what needs to happen internationally?

Stephanie Del Paine: I've been working with ISO on a draft international standard (DIS). The DIS, ISO 12417-1, is titled, Cardiovascular implants and extracorporeal systems—Vascular device-drug combination products—Part 1: General requirements. We plan to finalize the DIS in September, and then it will be released. The DIS, and ultimately the ISO standard, provides guidance that is applicable internationally. For example, in drafting the standard, we've considered compendial drug requirements for a combination product, and considered the United States Pharmacopeia (USP), as well as the European, British, and Japanese Pharmacopeias. We've also referenced several ICH (International Conference on Harmonization) guidelines that address international recommendations for quality, purity, and manufacture of drug substances/products. In an upcoming ISO meeting in September, we'll be working on Part 2 of ISO 12417. Part 2 addresses local guidance and identifies specific requirements by regulatory agencies in various countries according to the types of changes made to a combination product.

Rosemary Gonzales: Originally, when the committee proposed TIR48, we intended it to be a global guidance. We started with the U.S., and now there are several ISO initiatives, e.g., for auto injectors, there's ISO 11608. There are definitely several ISO standards that are available for combination products. Barr, maybe you know more of what we're going to be doing from a global perspective.

John Barlow Weiner: I haven't heard anything from AAMI on that yet. I think we'd be interested in the idea. CGMP is an area where there's opportunity for working...
together internationally, so it’s worth thinking about from that perspective, too.

**Jon Cammack:** An ISO document on CGMP considerations for combination products would be very useful for industry. Right now, there aren’t harmonized criteria in the rapidly growing area of combination products, and so companies do their best to comply with local, national, and individual international guidance and regulation. A harmonized, international guidance would simplify development and commercialization operations, and we could start with TIR48 as a “straw man” for drafting purposes.

**Jena Passut:** I guess we should just stay tuned?

**Nolan Baird:** I believe it’s correct that the European Union is continuing to evolve their thinking on combination products and how they’re regulated. I know some drug filings are starting to ask for device elements, but they don’t necessarily have classifications across Europe for combination products like exists in the U.S. At a minimum, there are differences between how combination products are regulated in Europe and the U.S.—that presents a challenge for global filings, for sure.

**John Barlow Weiner:** When we prepared TIR48, there was an effort to keep at least some latitude for it to be potentially used by those outside the U.S. Do others think that TIR48 has value to manufacturers for activities that aren’t necessarily focused on the U.S. market?

**Rosemary Gonzales:** In general, even if it’s U.S. or outside, TIR48 is good guidance for any company developing combination products.

**Stephanie Del Paine:** There are different regulations internationally. One good example is different medical product sterilization requirements for Japan and the U.S.

“A harmonized, international guidance would simplify development and commercialization operations, and we could start with TIR48 as a ‘straw man’ for drafting purposes.”

— John Cammack
In general, the requirements are more stringent for Japan. I think it’s safe to assume that some international regulatory differences will remain.

**Nolan Baird:** There are elements of TIR48 that offer insight on a global scale as far as managing suppliers, and third party manufacturers. Again, it’s a good start on how to manage combination products.

**Steven Binion:** I agree with that. There was a real effort on the part of the team that worked to draft TIR48 to bring in international references and/or considerations.

**Nolan Baird:** Although the title of TIR48 seems very FDA specific, hopefully it will be useful beyond that.

**Jena Passut:** What’s missing or needed in the world of combination products?

**John Barlow Weiner:** An important aspect discussed earlier is alignment between and among global markets. Currently, there are international efforts on specific drug and biologic regulations in terms of conversions and coordination, but there’s still more to be done. Those efforts will make it easier to address combination products on the international stage. For now, realistic first steps are focusing on higher level principles of collaboration and learning about best practices, and steering away from unnecessary forced conversions as we develop workable and efficient systems. The U.S. is now in a relatively favorable position because we have a defined program for combination products. Other countries are starting to look to the U.S. approach as a reference that could be useful. That’s not to indicate that we can’t do more in the U.S.; for example, there is no actual independent regulatory program for combination products. It’s not clear that would necessarily be helpful, but what we’re doing now is simultaneously leveraging drug and biologic and device regulations and approaches for combination products in a

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way that ensures safe and effective products, and that doesn't create unnecessary burden for industry. At FDA, we attempt to actively engage industry for input on hot topics or particular challenges that need attention from us. We also look inside FDA (e.g., with staff) in terms of what they're seeing as challenges. For example, an area that received a lot of interest in the last year or so is human factors as discussed earlier, and we're working on (draft) guidance to hopefully introduce in 2015. Another area we're hearing more about is adverse event reporting and market safety reporting.

Our approach has been to work on the highest priority areas first, and we recognize there's more that needs to be done.

**Stephanie Del Paine:** There's also the issue of sustainability of the TIR. It is possible that in the near future, technologies may change and requirements and regulations may change. We would need to address those changes in a revised TIR if and when they occur. One change in particular I see coming from the international field is an ICH guidance on elemental impurities where there are specific requirements and target allowable amounts for various types of elemental impurities. We'll need to be vigilant and look to the horizon to ensure the TIR remains current and relevant.

**Jena Passut:** Anybody have any final thoughts about what's missing or needed in combination products?

**Nolan Baird:** I think we need to prepare for the future. One of the things we are having active discussions about internally in my company is planting the seeds for a cultural change in the way we operate. Whether a company has labeled themselves as a drug company, or whether they label themselves as a device company, to continue to operate in that traditional mindset, in the future world of combination products, I think they will be facing an uphill battle. I think this is the starting point of an evolution in the industry, and companies and cultures are going to have to evolve to adapt and to be successful. And until they do that, I think they're going to continue to struggle.

**Stephanie Del Paine:** That's an excellent example. Before the rule, the drug and the device regulatory worlds were kind of courting or dating, but now there's a clear marriage with FDA's final rule on combination products. This rule may need to evolve, too; there may be future drug-specific or device-specific regulations that are relevant and applicable to combination products and should be incorporated.

**Nolan Baird:** Agreed. New and evolving modern technologies like the cellphone, and Bluetooth, and other types of unique communication and connectivity technologies are becoming available. This will likely significantly impact future healthcare, including combination products. The impact may be very specific for unique products, but more broad, too, enabling complementary technologies that provide total patient care and total patient solutions.

**Jena Passut:** Is there anything that you'd like to add to this discussion?

**John Barlow Weiner:** I like the concept of a changing mindset, and really support the view that success in the combination products area, like other areas, is clearly advanced by stakeholders working towards shared goals and working together. So whether it’s with devices and drugs or regulators and companies coming together to work things out and identify successful ways forward, we can work more quickly and efficiently when we collaborate. I’m very hopeful that will be a theme of the future in this area.

**Jon Cammack:** I completely agree with Barr. The more stakeholders can collaborate, similar to our efforts on TIR48, the better. I think we learned a lot from each other in the process, and it bodes well for future efforts and introduction of innovative products that truly meet unmet patient needs.
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