1227 25th Street, NW
Washington, D.C. 20037-1156

October 24, 2012

VIA ELECTRONIC SUBMISSION
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on Unique Device Identification System; Proposed Rule; Docket No. FDA-2011-N-0090 / RIN No. 0910-AG31

Dear Sir or Madam:

On behalf of the Combination Products Coalition ("CPC"), we welcome the opportunity to comment on FDA's proposed Unique Device Identification System. The CPC supports the use of Unique Device Identifiers ("UDI"), where appropriate, and recognizes the public health benefits they can provide, many of which are detailed in the proposed rule preamble. Our comments are intended to address how the UDI System should apply to combination products specifically, and in a way that furthers the important public health goals of these regulations in the most efficient manner possible.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination product arena. One of the principal goals of our organization is to work collaboratively with the Agency on issues affecting combination products in order to advance our common missions of providing the best possible health care for patients. Because of our diverse cross-industry membership, we think the CPC brings a broad and unique perspective on the potential impact the Unique Device Identification System could have with respect to marketing and use of combination products.

In the first part of these comments we briefly review background regarding combination products and how the proposed UDI System would apply to these products and their device constituents. After this, we provide suggestions for FDA's consideration and address the combination product questions posed by FDA.

I. Background

A. Combination Products

A combination product is a product that is comprised of two or more differently regulated constituents. Through its definition of "combination product" at 21 CFR 3.2(e), FDA has grouped combination products into three general categories:

1. A product comprised of two or more regulated constituents, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity. 21 CFR 3.2(e)(1). These are often referred to as "single entity" or "integral" combination products.
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products. 21 CFR 3.2(e)(2). These are typically called "co-packaged" combination products.
3. A product in which constituents are not physically together, but due to certain statements made in labeling are linked in such a way that they are considered combination products. 21 CFR 3.2(e)(3) and (4). These are often referred to as "cross-labeled" combination products.

As defined in regulations, combination products can be comprised of two constituents (e.g., drug-device, biological-device) or more, such as three-constituent "triple combination" products. Some examples of triple combination products include the Peg-Intron Pen, a biological-device combination that is cross-labeled for combined use with the drug Rebetol, and surgical kits comprised of two devices and one drug.[1]

Three (or more) constituent combinations also could have combinations within combinations. For example a biological-device product could be a 2-constituent combination product in its own right, and then be co-packaged with a third drug constituent to make a second distinct combination product. Alternatively, a single drug, single device, and single biological product might be brought together to form a single combination product. The potential variations in combinations have real implications in how a given combination product is addressed under FDA's proposed UDI System.

B. The UDI System

As part of Food and Drug Administration Advancement Act of 2007 ("FDAAA"), Congress added section 519(f) to the Food, Drug, and Cosmetic Act ("FDCA") directing that FDA –

> Shall promulgate regulations establishing a unique device identification system for medical devices requiring the label of devices to bear a unique identifier, unless [FDA] requires an alternative placement or provides an exception for a particular

[1] M Gross, The Combination Product Problem, Regulatory Focus (June 2009).

> device or type of device. The unique identifier shall adequately identify the device through distribution and use, and may include information on the lot or serial number."

It is notable that the identification system that Congress called for is one specific to *medical devices*; the provision does not mention combination products, so there is no statutory directive to require UDIs for combination products. This is not to say that FDA could not integrate combination products into an identification system in some way, but as it is not driven by the statute the Agency has full latitude in the kind of System it would choose to adopt for these products.

Proposed 21 CFR 801.3 adopts the definition of "combination product" provided at 21 CFR 3.2(e), i.e., single entity, co-packaged, *and* cross-labeled products. FDA's treatment of combination products is set out in proposed 21 CFR 801.25 –

> (a) *Application to combination products*. The label and each device package of every combination product for which the primary mode of action ["PMOA"] is that of a device shall bear a unique device identifier (UDI) as provided by § 801.20. . .
>
> (b) *Device constituent parts of a combination product*. The label and each device package of each device constituent part of a combination product shall bear its own unique device identifier (UDI), distinct from any UDI assigned to the combination product, and regardless of whether the combination product is required to have a UDI, except that a UDI is not required for a device constituent part that is physically, chemically, or otherwise combined with other constituents of a combination product in such a way that it is not possible for the device constituent part to be used except as part of the use of the combination product.[2]

In short, under these regulations –

1. A UDI is generally required for each *combination product* with a device PMOA, **and**

2. A UDI is generally required for each device *constituent*, regardless of the PMOA, unless the device is combined with other constituents as described in 801.30(a)(11) or is subject to another regulatory exception at 21 CFR 801.30.

Under these rules, a 2-constituent combination with a device might result in 0, 1 or 2 UDIs as described in Table 1, below.

[2] This exception is repeated at 801.30(a)(11).

Table 1		
	Combined per 801.30(a)(11)	Combined Another Way
PMOA = Device	1 UDI for the combination	2 UDIs (1 for the combination and one for the device constituent)
PMOA = Drug/Biological	No UDI	1 UDI for the device constituent

In the case of a three-constituent system, the number of UDIs could range from 0 to 4. For example if two device constituents and one drug/biological constituent are brought together individually, they could have anywhere from 0 to 3 UDIs as described Table 2, below. If two of the constituents are pre-configured in a way that creates a combination product to which a third constituent is added (i.e., a combination product within a combination product), and the primary mode of action is that of a device, there could be a UDI for each combination and a UDI for each constituent resulting in up to **four** UDIs.

Table 2: Device1+Device2+Drug Combination		
	Combined per 801.30(a)(11)	Combined Another Way
PMOA = Device	1 UDI (Combination)	3 UDI (Device 1, Device 2, Combination)
PMOA = Drug/Biological	0 UDI	2 UDI (Device 1, Device 2)

II. General Recommendations

A. The UDI System Should Not Apply to Cross-Labeled Combination Products

As noted above, under the proposed UDI regulations all combination products would be subject to the UDI requirement including those created by cross-labeling. The proposed rule would require that the label and packaging for the combination product with a device PMOA have its own unique UDI. If the constituents are separated and just cross-labeled there would seem to be no reason to identify them with a combination product UDI; the device constituent would be identified by a UDI, the drug constituent would almost certainly be identified by an NDC code, and all the goals of the proposed rule would be achieved. In addition, what constitutes the "label" for a combination product in this case is unclear. Given that drug and biological constituents would be part of the combination product, the regulation might be read as requiring UDIs on the labels of constituents – something that would make little sense for products that are separated from devices and most likely carry an NDC number.

Therefore, the CPC recommends that the proposed UDI regulations be revised to make clear that UDIs for combination products will not be required for cross-labeled products, i.e., those combination products defined by 21 CFR 3.2(e)(3) and (4).

B. FDA Should Not Require UDIs for Combination Products Unless There are No UDI or NDC Numbers Associated with Product Constituents

Proposed 21 CFR 801.25(a) would require a UDI for a combination product with a device PMOA, plus a separate UDI for each device constituent unless that constituent was subject to an exception at 21 CFR 801.30. Identification of a device being used with the combination, which is the focus of the proposed rule and the intent of its authorizing legislation, would generally be provided by a UDI for the constituent (if one was required) or an NDC code (if the device constituent fell within the exception proposed at 21 CFR 801.30(11)). Further, having multiple identifying numbers on labels and packaging could lead to confusion. Therefore, we believe that the proposed requirement for a combination product UDI is unnecessary except in the instance that there would be no UDI or NDC assigned through a constituent.

Further, the CPC believes the rule should provide manufacturers with the flexibility to decide what information will be reflected in the global UDI database ("GUDID"), and specifically whether it indicates the product is a device, combination product, or both. FDA could issue product-specific recommendations for how certain combinations should be labeled and what information should be reflected in the GUDID to help ensure consistency in the information captured.

Therefore, the CPC recommends that FDA revise the current proposed regulation at 21 CFR 801.25(a) to state that a combination product UDI would only be required in those instances where no constituent UDI or NDC code would be required, and to allow flexibility in the information that is captured in the GUDID as described above.

The CPC believes that this approach would mitigate the potential for confusion among patients, physicians, and manufacturers, would satisfy the requirements of FDCA 519(f), and would further the public health objectives of UDI System.

C. The Exception at 21 CFR 801.30(11) to the UDI Requirement Should Be Clarified

Under the proposed regulations a "UDI is not required for a device constituent part that is physically, chemically, or otherwise combined with other constituents of a combination product in such a way that *it is not possible* for the device constituent part to be used except as part of the use of the combination product." The CPC believes it would be useful for the Agency to clarify precisely what it means by "is not possible." For example it might be *possible* to intentionally misuse a combination product in a way that allows for independent use of the constituent, such as draining the drug from a pre-filled syringe, or chemically removing with a drug coating from a device. We believe such an interpretation would go too far, but as written the regulations might be read that way.

In making these clarifications, the CPC recommends using the definition of a combination product from 21 CFR 3.2(e)(1) – which seems similar to the definition FDA has proposed, but which also has years of Agency interpretation behind it elucidate its meaning. Also, to the extent that FDA intends to deviate from this definition it should clearly describe the deviation in regulations.

D. FDA Should Clarify that Exceptions to the UDI Rule Apply to a Device Whether it is a Stand Alone Product or a Constituent of a Combination Product

Proposed regulation 21 CFR 801.30 provides various exceptions to general UDI requirements. FDA should clarify in the regulation that these same exceptions would apply to devices whether they are marketed as stand-alone devices or device components of combination products. For example, as stated in the proposed rule, an insulin syringe would be a device that falls under the exception at proposed 21 CFR 801.30(a)(1) so a UDI would not be required. 77 Fed. Reg. at 40749. Therefore, a manufacturer pre-filling the syringe with insulin should not result in different treatment of the syringe; no UDI should be required because pre-filling has not resulted in any meaningful change to the device that should bring it outside the scope of the exception.

E. FDA Should Add an Exception Clarifying that UDI Requirements Do Not Apply to Device Constituents Being Shipped for Further Processing as Part of a Combination Product

Proposed 21 CFR 801.20(a) requires the label of every medical device and every device package to have a UDI, and proposed 21 CFR 801.25(a) and (b) applies requirements to combination product and device constituent and labels and packaging. However, the proposed regulation does not specifically address devices shipped from manufacturer to manufacturer for incorporation into combination products. For example, if individual device constituents are being shipped to a pharmaceutical manufacturer as part of a fill operation are these constituents subject to UDI requirements? Based on the text of the proposed regulation they might be. However, the CPC believes that these requirements should not apply to devices that are being transferred for further processing into a combination product, and that FDA should add an exception to 21 CFR 801.30 to this effect.

The reason these products should fall within an exception is that UDIs would have negligible value in this situation. Once device constituents have left the control of the original manufacturer they will be subject to further processing to create a combination product. The processing of individual units of devices may take place at different times and under different conditions that have the potential to impact the device constituent, making assignment of the UDI after this further processing more sensible in these cases.

Also, in the event that a device constituent manufacturer detects a problem with a shipment of devices after their sale to another company, the receiving company's quality system, including supplier controls, should be adequate to track the travel of problematic constituents from receipt to sale of a finished combination product. In short, supplier controls in this situation would fulfill the functions of a UDI. Thus, a UDI would provide negligible added value.

Therefore manufacturers should have the flexibility to apply a UDI to labels and packaging <u>after</u> this processing has occurred and a final finished combination product has been produced. Of course if manufacturers decide to apply the UDI to a device constituent before shipping a product for further processing that should be permissible, just not required.

F. Further Guidance Will Be Needed on Application of the UDI Regulations

The CPC strongly recommends that FDA publish guidance before or at the time of the final rule's publication which provides a practical guide to those articles for which UDI number(s) are required and those for which they are not. We believe this guidance should include several examples of how various combination products will be treated under the final rule. In particular, we recommend that the guidance consider various drug-delivery combination products – including but not limited to a prefilled syringe, free standing or supplied within a single-use autoinjector, a refillable multiple-use autoinjector, and a reusable or disposable pen injector – addressing whether they would or would not require a UDI. Having this guidance with the rule is essential to its implementation.

G. Harmonization

To the extent possible, the CPC supports global harmonization regarding combination product regulation, including the UDI regulation.

III. Responses to FDA Questions

A. If a combination product's primary mode of action is not that of a device, is it appropriate to require each device constituent part of the combination product to bear its own UDI?

See Section II.B, above.

B. Should FDA require a UDI on the label and package of every combination product that has a device constituent part, regardless of its primary mode of action, except when the primary mode of action is not that of a device, and the combination product is labeled with an NDC?

FDA should not require a distinct "combination product" UDI on combinations. As discussed in Section II.B, above, requiring UDIs above and beyond CPC's proposed framework adds to the potential for confusion from multiple identifiers and unnecessarily burdens manufacturers.

C. If a combination product's primary mode of action is that of a device, is it appropriate to require each device constituent part of the combination product to bear its own UDI?

See Section II.B, above.

* * *

We hope that our comments are helpful to the Agency as it finalizes the UDI regulations. If the CPC can help in any way please do not hesitate to contact us.

Respectfully submitted,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

bthompson@ebglaw.com
Phone: 202-861-1817