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Comments on Draft Guidance on Current Good Manufacturing Practice Requirements for Combination Products

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), a consortium focused on orally inhaled and intranasal drug products, appreciates this opportunity to comment on the FDA Draft Guidance on Current Good Manufacturing Practice Requirements for Combination Products[1] ("cGMP Draft Guidance"), released on January 27, 2015. As IPAC-RS has noted in a previous letter to the FDA, the proposed implementation of the FDA's recent cGMP regulations for combination products risks creating an unintended discrepancy. In particular, we are concerned that the FDA Draft Guidance's approach to currently-marketed inhalation products, such as metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal sprays, diverges from the historical approach to these drugs, and in doing so generates burdensome retroactive requirements unrelated to a product's quality, safety or efficacy. We would like to propose that those legacy inhalation products which were previously granted a marketing authorization on the basis of a CDER (FDA Center for Drug Evaluation and Research) review and inspection continue to be regulated under the drug-product cGMP regulations rather than the combination-product regulation which includes both drug cGMP and device Quality Systems requirements.

Background

In 2013, the FDA promulgated a set of regulations that explain how existing good manufacturing practices for drugs and devices should be applied to combination products, now found at 21 CFR Part 4. When issuing those regulations, the FDA took the position that its guidelines did not represent a change in policy and that combination products had always been subject to both drug and device quality requirements (see *Current Good Manufacturing Practice Requirements for Combination Products,* 78 Fed. Reg. 4307, 4310 (2013)). However, the FDA also noted its intention "to provide further information in related guidance, on how to comply with this rule and the underlying regulations to which it refers, including with respect to coming into compliance with pre-manufacturing design control requirements for products currently being marketed." However, prior to the issuance of the cGMP Draft Guidance, the FDA began

[1] http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

enforcing the 2013 regulations on products which received marketing authorizations before the effective date of the regulations.

The FDA's position, at least with regard to some types of inhalation products, has not always been as consistent as the FDA represented in 2013. For example, in 1998, the FDA issued its draft CMC guidance on MDIs and DPIs. Though the FDA acknowledged the role played by the device components of these products, the MDI/DPI draft guidance consistently referred to them as "drug products." Later, the FDA defined both the "drug product" and the "container and closure system" for MDIs as including "the container, the valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging" (see 1998 Draft MDI/DPI Guidance, pg. 60).[2] For DPIs, the FDA included both "the device" and "all its parts including any protective packaging" in the definitions of "drug product" and "container and closure system"(see 1998 Draft MDI/DPI Guidance, pg. 60). Therefore, since at least 1998 the FDA has held the position that inhalation medicines should be regulated under the manufacturing controls applicable to drugs without reference to the separate control systems applicable specifically to devices.

A similar approach was taken in the guidance for nasal sprays, finalized in 2002.[3] There again, the FDA included "the container, closure, pump, and any protective packaging, if applicable," within the definition of a "container closure system" (see 2002 Nasal Spray Guidance, pg. 22). The FDA acknowledged that the "administered dose of nasal and inhalation spray drug products is directly dependent on the design, reproducibility, and performance characteristics of the container closure system," but nonetheless continued to refer to nasal sprays as "drug products," rather than as "devices" or "combination products." Indeed, the FDA made only one reference to the regulations governing devices in this guidance document: a brief statement that applicants using pumps with "electric components" should "refer to the applicable recommendations outlined in the appropriate guidances from the Center for Devices and Radiological Health" (see 2002 Nasal Spray Guidance, pg. 23).

Other FDA guidance documents continued to refer to inhalation products as drug products with a container closure system. In 2010, however, the FDA issued a Jurisdictional Update, classifying MDIs as "drug-device combination products."[4] Although this represented a departure from the FDA's earlier characterizations of MDIs as a drug product with a container closure system, the FDA stated that MDIs are regulated by CDER "under the new drug provisions of the Federal Food, Drug and Cosmetic Act." In line with the FDA's previous position, MDI accessories such as spacers or locking clips were described as "devices" to be "regulated under the device provisions of the act by CDRH (FDA Center for Devices and Radiological Health);" and accessories such as replacement-actuators or dose counters were described as "device components of combination products." Notably, FDA reiterated that other types of accessories, such as actuators and spacer-actuators "have been regulated by CDER

[2] http://www.fda.gov/downloads/Drugs/Guidances/ucm070573.pdf
[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf
[4] http://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103179.htm

under the new drug provisions of the act," based on "FDA's determination that the primary mode of action of the combination product is attributable to its drug component." Furthermore, the FDA made no statements suggesting that, even as combination products, MDIs as such would be required to comply with regulations applicable to devices. Rather, the FDA explained that the MDIs' "primary mode of action . . . is attributable to the drug component."

For over ten years, the FDA (CDER) has consistently suggested that MDIs, DPIs, and nasal sprays should be regulated according to the drug-related provisions of the Food, Drug & Cosmetics Act and its implementing regulations. And because legacy MDIs, DPIs, and nasal sprays were not required to comply with the device-specific regulations from 21 CFR part 820 now listed in 21 CFR § 4.4(b)(1), many inhalation products currently being marketed were approved without submissions containing information required to support a medical device marketing authorization or inspection. Instead, these drug products were approved on the basis of, among other requirements, an inspection of manufacturing facilities by CDER to verify compliance with 21 CFR Parts 210 and 211 cGMPs. Imposing the device control requirements on these legacy products retroactively will substantially increase burden on the sponsors for reasons not related to safety or efficacy or quality of these products. Additionally, due to the FDA (CDRH) least burdensome approach, there is limited clarity as to the specific approaches to take regarding these newly determined device components.

Comments

1. Retroactive application of additional requirements is inconsistent with FDA's previous position and guidance documents, is burdensome and unnecessary

We are concerned with the unintended consequences of suggesting that inhalation products were always required to comply with those sections of the device-related cGMPs identified in 21 CFR § 4.4(b)(1). The cGMP Draft Guidance does not clarify how legacy products may be brought into compliance with these new regulations. In particular, we are concerned that requiring currently marketed products to develop the Quality System documents called for by 21 CFR Part 4 will create a significant burdensome requirement to generate retrospective paperwork without benefits to patient safety. Although the Draft Guidance makes a reference to leveraging "existing data in developing a design history file for a combination product that may not have been developed under design controls," it does not explain why the creation of a design history file would be appropriate or necessary for a product already developed and approved by the FDA in full compliance with 21 CFR Parts 210 and 211 cGMPs (Draft Guidance, pg. 19). The Draft Guidance has already concluded that manufacturers may avoid preparing "a development plan" or conducting "design review meetings for the product as currently marketed because the development stages that these activities would support have already occurred" (Draft Guidance, pg. 19). We propose extending this logic to the other aspects of the design history file to permit use of the current drug product specifications as design outputs for all future changes.

The creation of additional paperwork (even when relying on and re-processing existing information) in order to demonstrate compliance with a set of additional regulations which were not considered relevant by either the sponsor or the Agency at the time of the product's approval is unlikely to have a positive effect on patient safety or a product's efficacy and quality, and will only create additional documentation for the sponsor to produce and for the Agency to use valuable resources to assess and review. Further, in addition to the development plan and the design review meetings, there are other 21 CFR Part 4 requirements which do not lend themselves to retroactive compliance. Many of the regulations contemplate Quality System documentation which will be created and used prior to the issuance of a marketing authorization. The documentation for legacy products, although in a different format, was already captured in a pharmaceutical development report and justifies the choices made in preparing a device for submission to the FDA for approval. Since the FDA has already approved legacy MDI, DPI, and nasal spray products in question, the FDA will derive little benefit from the opportunity to review a design history file based on the existing and approved specifications for the product.

2. Language in the Draft Guidance Could Create Confusion over Container Closure System Definition

In addition, the Draft Guidance risks creating confusion over the FDA's stance on "container closure systems." The cGMP Draft Guidance describes a container closure system as an article that "merely holds the drug," contrasting such a system with an article "that does not merely hold or contain the drug, but also delivers it" (Draft Guidance, pg. 10-11). The Draft Guidance suggests that articles falling into the second category "may also be subject to the QS regulation" (cGMP Draft Guidance, pg. 11). However, this distinction has not been drawn in previous FDA guidance documents on container closure systems. For example, in the 1999 Container Closure System Guidance[5] (the "CCS Guidance"), the FDA observed that "a container closure system is often called upon to do more than simply contain the dosage form" (CCS Guidance, pg. 11). Instead, the FDA determined that two key components of container system performance were "container closure system functionality and drug delivery" (CCS Guidance at pg. 11). The Guidance specifically provided examples of "packaging system[s] for which drug delivery aspects are relevant," including "a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler" (CCS Guidance at pg. 11). In addition to the CCS Guidance, the FDA made similar observations about the role container closure systems played in drug delivery in the 1998 Draft MDI/DPI Guidance and in the 2002 Nasal Spray Guidance.

Additional confusion could stem from the language on page 22 of the cGMP Draft Guidance:

> Drug product components, containers, and closures must be tested in accordance with 21 CFR 211.84. A drug component is

[5] http://www.fda.gov/downloads/Drugs/Guidances/ucm070551.pdf

> any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the drug product. As explained in section III.C.3, a container closure system is the sum of packaging components that together contain and protect the drug product. Combination product manufacturers would not need to demonstrate compliance with this provision for device constituent parts or materials used in the manufacture of a device constituent part, except if the device constituent part or component thereof is also a drug component or constitutes the drug container or closure or a part thereof. For CGMP operating systems established in accordance with 21 CFR 4.4(b)(2) (QS regulation-based streamlining approach), if materials are used solely for manufacture of a device constituent part that is not part of the drug container or closure (e.g., a co-packaged device), the manufacturer need only demonstrate compliance with applicable provisions of 21 CFR part 820 to show appropriate control of such materials for that device constituent part (including 21 CFR 820.30, 820.50, 820.80, and 820.86).

This language appears to contemplate that there may exist a class of drug containers or closures that are also devices. This contrasts with the position taken on page 11 of the cGMP Draft Guidance, which suggests that articles with delivery functionality are devices and not container closure systems.

3. Examples would be helpful

We would also like to request that the FDA include in a revised cGMP Guidance an example related to a metered dose inhaler, dry powder inhaler, or nasal spray, e.g. in Section V of the cGMP Draft Guidance. In particular, such an example would be most helpful if it described the process the FDA contemplates for addressing the application of the regulations to a currently marketed product which had been previously approved by the FDA as a drug product with a container closure system.

4. Definitions need to be clear and consistent

As is apparent from Comment 2 above, lack of clarity, or inconsistency in the use of definitions have far-ranging consequences and may lead to unnecessary workload increases for all parties. We therefore commend the FDA for its discussion on page 10 of the cGMP Draft Guidance regarding the difference between a “constituent part” and a “component.” We would like to request, however, a further clarification with illustrations. For example, if a company produces a component which, without the addition of a drug product, would not meet the definition of a “device,” would that component be deemed a “constituent part” under 21 CFR part 4? An example of such a component might be the plastic housing that surrounds a

container holding a drug product. The plastic housing itself would not be considered a "device" under the Food and Drug Act and would not have a "device mode of action" as that term is used in 21 CFR part 3.

Conclusion

IPAC-RS appreciates the opportunity to comment on the Draft Guidance, and to provide the FDA with feedback on the proposed text. We hope to have further opportunities to engage with the FDA on this issue. If you have any questions about these comments, please feel free to contact us through Reed Abrahamson at the IPAC-RS Secretariat, at 1500 K Street NW, Washington, DC 20005, or by email at reed.abrahamson@dbr.com.

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The International Pharmaceutical Aerosol Consortium on Regulation and Science (*IPAC-RS) is an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDP) by collecting and analyzing data, and conducting joint research and development projects. Our members include innovator and generic companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of a variety of debilitating diseases such as asthma, chronic obstructive pulmonary disease and diabetes. We aim to build consensus and contribute to effective regulations and standards by sharing the results of our research through conferences, technical journals, and discussions with regulatory bodies. Learn more about IPAC-RS on our website: http://ipacrs.org/.*

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