



Corporate Regulatory and Quality Science

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Dockets Management Branch (HFA -305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20852

RE: Medical Devices; Draft Guidance; Medical Devices Made With Polyvinylchloride Using the Plasticizer di - (2-Ethylhexyl) phthalate; Availability [Docket 02D-0325]

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Medical Devices Made With Polyvinylchloride Using the Plasticizer di - (2-Ethylhexyl) phthalate," published in the Federal Register on September 6, 2002 at 67 FR 57026.

Thank you for the opportunity to provide comments on this guidance document. For over twenty years, Abbott has manufactured life-saving medical devices made with PVC using the plasticizer DEHP. We monitor the science regarding PVC containing the plasticizer DEHP and recognize the need to make decisions based on sound, objective scientific evidence. Abbott further recognizes replacing materials or plasticizers used to manufacture medical devices is not a simple task and involves many considerations, including the impact to medical device performance and the biocompatibility of new materials.

Abbott understands that FDA must use the available science to guide its decisions to promote and protect the public health. We also acknowledge the potential health impact of PVC medical devices containing DEHP is a controversial topic. Therefore, we recommend FDA's guidance in this area reflect the known science. Our comments focus on the procedural precedent established by using a guidance document to address this issue, opportunities for further public comment, alternative mechanisms to notify the public, and specific recommendations to the current draft version of the guidance document.

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Procedural Precedent

From a procedural standpoint we are concerned with FDA's use of a guidance document to "encourage" manufacturers to change the materials used to manufacture medical devices, and establish new labeling requirements. We are concerned the Agency is setting a precedent by using a guidance document in this manner. Further, we note FDA relied upon regulation to establish user labeling requirements for devices containing natural rubber¹, latex condoms², and menstrual tampons³ and question why the same approach would not apply here.

Controversial Nature Calls For Further Public Comment

The human impact of DEHP exposure from medical devices containing PVC is a scientific topic that is highly controversial. FDA acknowledges the controversial nature of this topic in its *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices* when FDA states, "the ability of DEHP and other phthalate esters to produce adverse effects in humans has been a topic of active discussion and debate in the scientific and regulatory communities."⁴ More recently, The European Commission Scientific Committee on Medicinal Products and Medical Devices adopted an opinion contrary to FDA's recommendations in its guidance document when it stated, "[i]n view of the lack of a full analysis of all risks associated with potential alternative materials, at this moment no specific recommendations can be made to limit the use of DEHP in any particular patient group."⁵ If the Agency determines procedurally to proceed with a guidance document, we recommend FDA issue and solicit public comment on a second draft version of the guidance document following its review of comments on this first draft, and subsequent revision.

FDA's Good Guidance Practices state, "[a]fter providing an opportunity for comment, FDA may decide that it should issue another draft of the guidance document."⁶ Furthermore, in the preamble to its final rule on Good Guidance Practices, FDA agrees draft guidance on a medical or scientific topic that is highly controversial is an appropriate situation in which to issue a second draft of a guidance document.⁷ For the above reasons, should FDA move forward with this guidance document, we recommend FDA issue a second draft version for public comment.

Proposed "User" Labeling May Not Be the Optimal Solution

Next, we recommend FDA consider alternative approaches to notifying the public of the potential effect of PVC medical devices containing DEHP. We note the potential medical effects of PVC medical devices containing DEHP are confined to certain sensitive

¹ 21 CFR § 810.437.

² 21 CFR § 801.435.

³ 21 CFR § 801.430.

⁴ U.S. Food and Drug Administration, Center for Devices and Radiological Health, *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*, September 2001, 3.

⁵ European Commission, Health & Consumer Protection Directorate-General, *Opinion on Medical Devices Containing DEHP Plasticised PVC; Neonates and Other Groups Possibly at Risk from DEHP Toxicity*, Adopted by The Scientific Committee on Medicinal Products and Medical Devices, September 26, 2002, 26.

⁶ 21 CFR § 10.115(g)(1)(v).

⁷ 65 FR 56470.

patient populations, and not the public at large⁸. FDA specifically identifies male neonates, pregnant women who are carrying male fetuses, and peripubertal males as sensitive patient populations.⁹ Yet, global labeling of the medical devices identified in the guidance document would reach a much broader audience. Global labeling may unnecessarily alarm the general public as to the safety of medical products manufactured with PVC containing DEHP. Such concern is unwarranted, since "[t]he risk of not doing a needed procedure is far greater than the risk associated with exposure to DEHP."¹⁰ Furthermore, the message could lose its value, if it is located on many different device types and alternative devices are not widely available.

We recommend FDA consider whether there are more effective and direct mechanisms to reach the practitioners who serve the sensitive patient populations. Medical professionals should be educated about the potential risk of DEHP and weigh this risk against the benefits of using the particular medical device. Professional organizations, such as the American Academy of Pediatrics, American College of Cardiology, The American Society for Clinical Nutrition, and the American Society for Parenteral and Enteral Nutrition, which have been established to serve practitioners could provide effective notification and education to practitioners regarding the concerns related to DEHP, aggregate exposure, and the identified medical procedures. Additionally, FDA's own resources, such as its web site and *FDA Consumer* magazine, are effective means of educating both practitioners and patients.

Specific Recommendations

In addition to the above general recommendations, we have the following specific recommendations to the draft guidance document. It would be useful to clarify at the beginning of the document that the suggestions to reformulate, coat, or label PVC medical devices containing DEHP are intended to apply only to devices intended for use with sensitive patient populations, and not device categories as a whole. In publishing this guidance document, FDA states:

FDA recognizes that many devices with PVC containing DEHP are not used in ways that result in significant human exposure to the chemical [DEHP]. Therefore, this draft guidance focuses on the small subset of medical devices where PVC containing DEHP may come in contact with the tissue of a sensitive patient population in a manner and for a period of time that may raise concerns about the aggregate exposure to DEHP.¹¹

Despite FDA's intent to focus on the small subset of medical devices used with sensitive patient populations, we are concerned the guidance document will be interpreted and applied much more broadly than intended. Much of this concern stems from the broad language used to identify the types of PVC medical devices containing DEHP. The section "**What types of CDRH-regulated devices typically may be of concern?**" contains broad device categories. Furthermore, although this section is intended to identify medical devices, it also contains medical procedures, which further complicates

⁸ See 67 FR 57026.

⁹ U.S. Food and Drug Administration, *Public Health Notification: PVC Devices Containing the Plasticizer DEHP*, David Feigal, Jr., MD, MPH, July 12, 2002.

¹⁰ *Ibid.*

¹¹ 67 FR 57026.

the information. To address these concerns we recommend FDA clearly define sensitive patient populations and present the examples of medical devices as follows:

“The following types of PVC medical devices containing the chemical DEHP when intended for use with sensitive patient populations may be of concern:

Intravascular (IV) tubing and catheters/cannulae used for the delivery of lipids¹²
Hemodialysis circuits
Extracorporeal membrane oxygenation membranes and by-pass circuits
Cardio-pulmonary by-pass circuits
Bags used to store and transport blood
Bags used to store and transport lipid-containing enteral or total parenteral nutrition formulae
Tubing used in enteral or parenteral nutrition sets to transfer lipophilic substances.”

Moving to the section, **“What does FDA recommend that you do if your device is made with PVC containing DEHP?”** we are concerned with the recommendation to consider “‘minimizing patient exposure to DEHP’ as a design requirement in...design control procedures,” and recommend FDA delete this item. Despite the non-binding status of the guidance document, we are concerned that a failure to consider DEHP exposure during design control procedures will impact the submission review process. Reliance on the guidance document could lead to questions about design control procedures, specifically the design requirement to consider DEHP exposure, which if not addressed would hold up review. This could occur with a new product submission or when a change to an existing device requires a new submission. Similarly, during a pre-approval inspection a failure to consider the design requirement could result in inspectional observations on Form FDA 483. Although FDA may not cite failure to follow a guidance document on Form FDA 483,¹³ will the underlying design control regulations support an inspectional observation of failure to consider DEHP exposure as a design requirement?¹⁴ We recommend FDA clarify this item in its response to public comment.

The section **“Do I need to submit a new 510(k) if I replace or modify the PVC in my device?”** is useful. To further the usefulness of this section, it would be helpful, if FDA clarified its expectations, under FDA guidance document “Deciding When to Submit a 510(k) for a Change to an Existing Device,” in regard to material changes, such as the replacement of PVC. It appears that material changes evaluated against ISO 10993-1 require a new 510(k) when the manufacturer generates satisfactory results from the testing indicated by ISO 10993-1, but not when the material supplier provides the manufacturer with satisfactory results from the testing indicated by ISO 10993-1.¹⁵

¹² Clarifying IV administration sets to those used to deliver lipids is supported by FDA’s conclusion in its safety assessment, which states, “based on the results of the safety assessment, CDRH concludes that there is little to no risk posed by patient exposure to the amount of DEHP released from PVC IV bags following infusion of crystalloid fluids...[and]...there is little risk posed by exposure to the amount of DEHP released from PVC bags used to store and administer drugs that require a pharmaceutical vehicle for solubilization when label instructions are followed.” (U.S. Food and Drug Administration, Center for Devices and Radiological Health, *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*, September 2001, 5).

¹³ 65 FR 56471.

¹⁴ See generally, 65 FR 56471.

¹⁵ U.S. Food and Drug Administration, Center for Devices and Radiological Health, *Deciding When to Submit a Change to an Existing Device*, Director, Office of Device Evaluation, January 10, 1997, 15.



Following this logic scheme, the submission of a new 510(k) is determined not by the test results, but rather by the entity, manufacturer or supplier, conducting the testing. By clarifying this point, FDA could avoid the receipt and review of unnecessary 510(k) submissions, thereby conserving valuable reviewer resources. This could also reduce inquiries to the Agency due to concerns about submitting new 510(k) submissions and incurring user fees.

In the section **“What if I choose not to change the material in my device? Should I revise the labeling to state the device contains DEHP?”** we recommend FDA clarify when it would be appropriate to label PVC medical devices containing DEHP by revising the first sentence to read, “Yes, we recommend that you clearly indicate through user labeling that your device contains DEHP, when the DEHP containing device can be reasonably expected to cause significant DEHP exposure in a sensitive patient population.” In addition, we recommend FDA address, in this section, the need for medical device labeling, if other labeling describing the potential risk exists. For example, many lipophilic drugs “caution against the use of PVC containers and administration sets for delivery of the drugs.”¹⁶ In such situations, the drug labeling obviates the need for device labeling. Such an approach is supported by FDA’s conclusion, “there is little risk posed by exposure to the amount of DEHP released from PVC bags used to store and administer drugs that require a pharmaceutical vehicle for solubilization, *when label instructions are followed*” (emphasis added).¹⁷ Therefore, we recommend FDA clarify that it is not necessary to revise medical device labeling, if other labeling describing the potential DEHP risk exists.

It would also be appropriate to clarify, in this section, labeling expectations in regards to coated DEHP-containing devices. As stated early in the guidance document, FDA suggests manufacturers consider “using coatings that may minimize patient exposure to DEHP.” When a manufacturer follows FDA’s suggestion and applies a co-extruded inner lining that does not contain DEHP to a DEHP-containing device it should not be necessary for the manufacturer to identify the device with DEHP labeling, as any fluid transferred via such a device would not have direct contact with DEHP.

Should you have any questions, please contact April Veoukas at (847) 937-8197 or by facsimile at (847) 938-3106.

Sincerely,

A handwritten signature in black ink that reads 'Doug Sporn / jms'.

Douglas L. Sporn
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Corporate Regulatory Affairs, Abbott Laboratories

¹⁶ U.S. Food and Drug Administration, Center for Devices and Radiological Health, *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*, September 2001, 12.

¹⁷ *Ibid.*, 44.