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07 Feb 2022 | **Analysis**

US FDA's Reclassification Of Certain Drugs As Devices May Be 'Seismic Event' For Some

by Brenda Sandburg

Sponsors are receiving information requests and complete response letters as a result of the agency's transition plan, which was made in response to the Genus v. FDA ruling. The decision's aftershocks could reshape the landscape for a number of products, attorney says.

The US Food and Drug Administration's plan to transition certain products regulated as drugs to device status could have significant repercussions for the pharmaceutical industry. While the agency is focusing on whether imaging agents meet the device definition, it is also reexamining other product categories as well. Sponsors have already received complete response letters and notices of deficiencies in their applications as a result of the reclassification.

In August, the agency announced in a Federal Register notice that it would be publishing a list of approved drug products it tentatively determines should transition to device status in accordance with the US Court of Appeals for the District of Columbia Circuit's decision in Genus Medical Technologies LLC v. FDA. (Also see "*Imaging Drugs Make Jump To Devices In New Decision By FDA*" - Pink Sheet, 9 Aug, 2021.)

In its 16 April *ruling*, the appeals court said Congress had not granted the agency sweeping discretion to classify as a "drug" a product that meets the statutory definition of both a "drug" and a "device." It concluded that excepting combination products, devices must be regulated as devices, and drugs – if they do not also satisfy the device definition – must be regulated as drugs. (Also see "*US FDA Stuck With Less Flexibility On Drug Vs. Device Designations After Appeals Court Decision*" - Pink Sheet, 22 Apr, 2021.)

FDA has not yet issued a list of approved products for reclassification. The agency told the *Pink Sheet* that it is currently evaluating feedback it received in response to the Federal Register

notice. The court ruling and the agency's response to it has shaken many sectors of industry.

"It has the potential to be a seismic event," David Fox, a partner at Hogan Lovells, said in an interview. "There will be aftershocks from this decision for years and it could remake the landscape for a number of products."

Lisa Dwyer, a partner at King & Spalding, agreed that the fallout from the case will likely last for years.

"The decision in *Genus* is one of the most *potentially* disruptive cases in the FDA space in years," Dwyer said. "I am placing emphasis on the word 'potentially' because the decision left FDA with significant discretion. Even though the decision in *Genus* made headlines, the actual holding was fairly narrow."

Dwyer, a former senior policy advisory in the FDA Commissioner's Office, said the court did not say, if it's a close call, that a product has to be regulated as a device. Rather, it said that it is important for FDA to bring its expertise to bear on close questions. Moving forward, she said, FDA will simply have to analyze, based on relevant facts, whether certain products or product categories meet the definition of "device."

"Ever since the decision came out, our phone has been ringing off the hook. There is enormous interest," Dwyer added. "Clients in lots of different areas have questions about the potential implications."

Ophthalmic Products At The Forefront

The Association for Accessible Medicines noted that FDA's announcement has had an impact on new drug applications and abbreviated new drug applications.

"AAM's member companies are now receiving information requests, deficiencies, and/or complete response letters as a direct result of the agency's reclassification decisions – indicating that FDA is implementing a new regulatory structure for these products without any process whatsoever," AAM said in its comments to the agency.

"FDA in turn appears likely to miss multiple GDUFA [Generic Drug User Fee Act] goal dates and/or add additional review cycles, including for several significant products."

AAM said its members report that they may need to defer the submission of ANDAs and biosimilars while they scramble to conform their nearly-completed ANDA and 351(k) BLA submissions to the agency's newly imposed regulatory requirements for approval.

Eyenovia, Inc. is one of the companies that has been caught in the fallout from the Genus

decision. The company announced in October that it had received a complete response letter from FDA stating that MydCombi, a combination microdose formulation of tropicamide and phenylephrine for in-office pupil dilation, had been reclassified as a drug-device combination product.

The company said it was preparing additional documentation requested by the FDA and planned to resubmit its NDA in early 2022. (Also see "*Keeping Track: A Lawsuit-Driven Complete Response Letter, A Refuse To File Letter, And Some Good News*" - Pink Sheet, 19 Nov, 2021.)

Fox, former FDA associate chief counsel for drugs, said the most immediate impact of FDA's reclassification has been in the ophthalmic area. FDA is taking the position that the current regulation that considers ophthalmic components, including eye droppers and dispensers, to be drug components will no longer apply.

As a result, he said FDA is asserting that these products will become combination products and be subject to new requirements. While a drug is subject to good manufacturing practice requirements, a combination product that includes a medical device is also subject to the device quality system regulation (QSR). Manufacturers of these products will now have to become steeped in device culture and norms, Fox noted.

Bausch Health US LLC said in its comments that in recent months companies have received FDA deficiency letters for NDAs under review that cite the Genus decision.

Bausch quotes one letter which states that in implementing the Genus decision, "FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the 'device' definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser)."

In comments submitted on behalf of its clients, Foley & Lardner noted that FDA has been issuing CRLs to manufacturers of eye drops if they have not submitted data to support compliance with QSR. The firm said that requiring companies to comply with QSR in pending NDAs will delay approval of products. It also said FDA should not require holders of approved NDAs to reexamine their standard eye-drop container closure systems for compliance with QSR requirements.

Classifying Imaging Agents By Mode Of Action

The agency is specifically looking to reclassify certain types of contrast agents as devices. Fox said which get designated as devices will depend on whether they achieve their primary intended purposes through chemical action or depend on physical effects (under the definition of a

device).

"This is going to carry over to a fairly pitched battle over what it means to have chemical versus physical action," he said. "More litigation is likely over the line between chemical and physical action."

The agency received numerous comments asking the agency to continue to regulate imaging agents as drugs.

GE Healthcare, one of the largest manufacturers of medical imaging equipment, said the DC Circuit did not say that all (or even any) contrast agents must be regulated as devices now or in the future. It noted that the Genus decision expressed some doubt as to whether contrast agents could truly be classified as a device under the existing statutory definition.

In a footnote, the court said that "it is not immediately obvious to us how a contrast agent satisfies the device definition's requirement that the regulated product be 'an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory.'"

GE said FDA should issue a Federal Register notice with two proposed lists:

1. A proposed list of categories of FDA-approved drugs that may be potentially reclassified based on the *Genus* decision, and

2. A proposed list of categories of FDA-approved drugs that cannot be reclassified, despite the *Genus* decision.

Once the agency has finalized these lists, GE said it should issue a draft guidance proposing that FDA will call for Requests for Designation for each category of product on the first list in a sequenced manner, and propose the sequence.

In its notice on implementing the Genus decision, FDA said it would take time for an applicant to transition a product with regard to labeling, bringing manufacturing facilities into compliance with QSR, and preparing for a device inspection, among other things. GE said it believes applicants will need at least 18 months to come into compliance with QSR and ensure their facilities are ready for inspection.

Bracco Diagnostics Inc., a developer of medical imaging agents, submitted a 59-page document urging FDA to continue regulating medical imaging agents as drugs or biological products rather than as devices. It said medical imaging agents do not fall within the instrument clause of the statutory definition of device.

On Target Laboratories LLC, which is developing products for targeted fluorescent imaging, said that imaging agents that rely on targeted or selective receptor binding to identify specific cells, lesions, or tissues of interest should continue to be regulated as drugs based on their demonstrable reliance on chemical and metabolic processes to achieve their primary intended purposes.

Arnold & Porter also advocated that imaging agents that meet the definition of a drug, but not a device, continue to be regulated as drugs. The firm said an example of such an imaging agent would be one that must be taken up and metabolized by cells for detection of body structures or lesions.

Hyman, Phelps & McNamara told FDA that all catheter lock solutions meet the statutory definition of a device even when they contain an antimicrobial agent.

PhRMA Proposes Three-Step Approach

AAM asserted that FDA's interpretation of Genus as holding that various components of a combination product must be separately classified and separately regulated is legally untenable. It said the decision did not invalidate FDA's longstanding regulation that eye cups, eye droppers, and other dispensers intended for ophthalmic use be regulated as drugs "if packaged with the drugs with which they are to be used."

The Pharmaceutical Research and Manufacturers of America suggested that FDA engage in a stepwise, three-part approach to determine whether or how to transition any products requiring transition under Genus.

First, it said the agency should explain the principles it intends to apply in interpreting the Food, Drug, and Cosmetic Act's definitions of "drug" and "device" in light of Genus. In addition, it said the agency should announce the process it intends to follow, including timelines, for transition, and detail the regulatory requirements it proposes applying to transitional products.

Second, the agency should then identify categories of products that may be appropriate for transition.

And third, it "should engage in a confidential, product-by-product assessment of whether a particular medical product may transition through discussions with each relevant sponsor."

PhRMA said these assessments "should include evaluation of whether or not a product satisfies the provisions of the device definition that the Genus court referred to as the 'mode-of-action clauses,' i.e., whether the product does not 'achieve its primary intended purposes through chemical action within or on the body of man or other animals' and is not 'dependent upon being metabolized for the achievement of its primary intended purposes.'"

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The association said that in cases where there is ambiguity as to whether a particular product meets the device definition, FDA should provide flexibility and defer to manufacturers who have complied with applicable regulations and acted in reliance on FDA approval of a product.

Nine Appeals Of FDA Designations

Sara Koblitz, a partner at Hyman, Phelps & McNamara who represented Genus, said the device classification comes into play when there is an overlap between a product's statutory definition as a drug and device. While the ruling most often applies to imaging or contrast agents, she said that based on FDA's interpretation many products could be impacted and much depends on the way the product works.

Koblitz said the ruling is a win for industry because it limits FDA's authority to regulate every device as a drug with no bright lines. And it is a big win for device companies to know that their products will be regulated as devices, which is significantly less costly.

Genus manufactures the Vanilla SilQ product line of contrast agents, whose key ingredient is barium sulfate, for use in radiographic procedures. The company sought FDA clearance to distribute the products as either devices or grandfathered drugs, which do not need pre-market approval. Following an inspection of Genus's distribution facility, the agency issued a warning letter notifying Genus that its products were drugs.

Genus responded that FDA could not regulate the products as drugs because they do not achieve their primary intended purposes through chemical action within or on the body or through metabolization. FDA replied that the products meet the definition of drug as well as the definition of device since they are intended for use in the diagnosis of disease.

Genus then submitted a Request for Designation (RFD) with FDA's Office of Combination Products (OCP), requesting that the products be classified as devices. The office concluded that the products appeared to meet the definitions for both a device and a drug and that it was appropriate to regulate all contrast agents uniformly as drugs.

In its most recent annual performance report to Congress, FDA said that in fiscal year 2020, OCP received 58 RFDs and reviewed three additional submissions carried over from the previous fiscal year. Of the 61 submissions reviewed, nine had a decision issued, 46 submissions were found to have insufficient information for filing, and four submissions were pending at the end of FY 2020.

FDA said that in the last decade, nine sponsors have sought to appeal an RFD designation. OCP was established under the Medical Device User Fee and Modernization Act of 2002.

The agency has had previous experience transitioning products to a different designation. In

March 2020, insulins, human growth hormone and other protein products originally approved as new drug applications and regulated as drugs were switched to being regulated as biologics. More than 100 products made the transition. (Also see "*Transition Day In The US: 96 Drugs Make The Move To Biologics Regulation*" - Pink Sheet, 23 Mar, 2020.)

The move led to one lawsuit when *Teva Pharmaceuticals USA Inc.* objected to FDA's exclusion of Copaxone (glatiramer acetate injection) from the list. A district court dismissed Teva's complaint, finding FDA's interpretation of "protein" is reasonable and the agency was owed deference. (Also see "*Copaxone Legal Fight May Finally Be Over As Court Finds The MS Treatment Is Not A Biologic*" - Pink Sheet, 5 Jan, 2021.)

Fox noted that drugs and biologics systems may be closer to each other and are regulated by the same FDA staff. "To move from drugs to devices is a much larger shift," he said.