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Congress of the United States

House of Representatives

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December 10, 2015

The Honorable Gene L. Dodaro
Comptroller General of the United States
U.S Government Accountability Office
441 G St, N.W.
Washington, DC 20548

Dear Comptroller General Dodaro,

We are writing to request that the Government Accountability Office (GAO) conduct a study to assess the Food and Drug Administration's (FDA) regulatory pathway for reviewing generic versions of nonbiologic complex drugs (NBCDs).

The FDA has begun approving generic versions of NBCDs. NBCDs are drugs of non-biological origin with an active ingredient that has molecular diversity. Examples include sodium ferric gluconate (which treats iron deficiency anemia in kidney dialysis patients) and liposomal doxorubicin hydrochloride (which treats several types of cancer). With these new types of generic drugs comes discussion about the proper method of regulation and approval. The current regulatory pathway used for generic approval of small molecule drugs is being used for the evaluation of NBCDs. Given the complex natures of these large molecule drugs, we seek GAO's input on whether the current statutory pathway for generic NBCDs is adequate to guarantee patient safety.

Therefore, the goal of the requested GAO study is to evaluate whether generic versions of NBCDs that are not fully characterized present unique challenges in meeting generic-drug approval standards that are different from those presented by small-molecule generic drugs. For purposes of this study, an NBCD is not considered fully characterized if: (1) the active ingredient has molecular diversity; (2) scientific analytic methodologies are unable to fully identify the molecular structures and physiochemical properties of the active ingredient; and (3) the nature of the active ingredient is not understood sufficiently to identify all the molecular components that produce the therapeutic effect of the drug, and the mechanisms of action that produce such effect.

Regarding generic drug applications, if the study concludes that meeting approval standards does present unique challenges, GAO should consult with appropriate public and private entities in analyzing the following questions:

- FDA has previously approved a generic version of a reference product on the basis of the product being "adequately characterized."[12] What degree of characterization of the proposed generic version and the reference product should be required in order to determine the safety and effectiveness of the generic version?

- What degree of similarity should be required to deem that the active ingredient of the proposed generic version is the same as the active ingredient of the reference product?

- What types of evidence should be required to demonstrate that the proposed generic version is bioequivalent to the reference product?

- What requirements should be established with respect to the comparability of the manufacturing process for the proposed generic version and the manufacturing process for the reference product?

- Whether and to what extent clinical evidence is needed to demonstrate that there is no difference in immunogenicity between the proposed generic version and the reference product?

- Whether and to what extent other clinical evidence is needed to demonstrate that the proposed generic version is as safe and effective for patients as the reference product?

Once these questions are answered, the study should assess whether the current statutory abbreviated-approval pathways can address the use of reference products. The study also should recommend whether and when FDA should develop a public policy document offering comprehensive, general principles on the evidence necessary to obtain the FDA's approval of generic drug applications that use such reference products.

The study described above is based on H.R. 1576, the Generic Complex Drugs Safety and Effectiveness Act, which is attached for your review. It is important to note that H.R. 1576 includes additional questions, and we request that the study conducted pursuant to this letter address all questions presented in H.R. 1576.

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[1] *Sanofi-Aventis U.S. LLC v. Food and Drug Administration,* 10-01255, (D.C. Cir. 2012)
[2] Letter from Food and Drug Administration to Chespeake Regulatory Group, Frommer Lawrence & Haug, and Covington and Burling (March 31, 2011).

Please contact Alan Slobodin of the majority committee staff at (202) 225-2927 and Una Lee of the minority committee staff at (202) 225-3641 should you have any questions. Thank you in advance for your assistance on this matter.

Sincerely,

Fred Upton
Chairman

Frank Pallone Jr.
Ranking Member

Tim Murphy
Chairman
Subcommittee on Oversight
and Investigations

Diana DeGette
Ranking Member
Subcommittee on Oversight
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Joe Pitts
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Gene Green
Ranking Member
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