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Avoiding Market Disruptions for Legacy Drugs

Background

- We support the Department of Health and Human Services (HHS) and Food and Drug Administration (FDA) in their recent withdrawal of the Unapproved Drugs Initiative (UDI),[1] which inadvertently led to a rise in drug prices and access challenges for many drugs that are widely used. Moreover, the UDI did not end up achieving its objective of increasing the amount of clinical information about legacy drugs, as new applications often did not include new clinical data. Statutory changes are needed to ensure that manufacturers of legacy drugs[2] may obtain approvals without disrupting market prices and supply.

- Under the Food, Drug, and Cosmetic Act (FDCA), not all drugs are "new drugs" that require FDA approval. Congress exempted from the definition of "new drugs" certain longstanding drugs that are "grandfathered" or that are generally recognized as safe and effective (GRASE).[3] FDA has previously recognized that drugs currently on the market might meet these criteria, although when FDA subsequently announced the UDI, the agency implied that no drugs meet these criteria.[4]

- Under the UDI, FDA encouraged entities to obtain drug approvals for these legacy drugs, which afford qualifying sponsors market exclusivity for a specified range of years via the inability of competitors to submit new applications. FDA also went a step further, announcing that after a grace period the agency would clear the market of existing competitors, even though the sponsor usually did not invest in clinical data development or other significant costs that would justify that extraordinary market advantage.[5]

- Such market exclusivity allowed manufacturers to raise drugs prices dramatically, despite their limited investment.[6] A 2017 study found that the average wholesale unit price of 26 out of 34 drugs for which pricing data was available increased by 37%, while the average wholesale unit price of 11 of the drugs surveyed increased by more than 128%.[7]

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[1] HHS; FDA; Termination of the Food and Drug Administration's Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective, 85 Fed. Reg. 75,331, (Nov. 25, 2020), *available at* https://www.federalregister.gov/documents/2020/11/25/2020-26133/termination-of-the-food-and-drug-administrations-unapproved-drugs-initiative-request-for-information.

[2] The term "legacy drugs" refers to drugs that are lawfully on the market because they either qualify for grandfathering or are generally recognized as safe and effective under 21 U.S.C. § 321(p). .

[3] 21 U.S.C. § 321(p).

[4] FDA, *Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs* 12 (June 2006); *Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without NDAs or* ANDAs (Sept. 2011), *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketed-unapproved-drugs-compliance-policy-guide.

[5] *See* 21 U.S.C. § 505(b); 21 C.F.R. § 314.108.

[6] For example, FDA approved a version of vasopressin by "relying on published literature alone to support clinical pharmacology, safety and efficacy" for the proposed indication. FDA, Center for Drug Evaluation and Research, Summary Review, Vasostrict 2 (Mar. 20, 2014), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204485Orig1s000SumR.pdf. Despite adding no new clinical information, following its approval the price of the drug increased by 1644%. Vizient, Inc., Financial Consequences of Good Intentions: The Unanticipated Costs of the Unapproved Drugs Initiative (UDI) 7 (Feb. 2020), *available at* https://newsroom.vizientinc.com/sites/vha.newshq.businesswire.com/files/doc_library/file/UDI_Analysis_US_Market_Spend_FINAL_022420.pdf.

[7] Ravi Gupta et al., *The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States*, 23 J. OF MAN. CARE & SPECIALTY PHARM. 1066, 1071-73 (Oct. 2017), *available at* https://www.jmcp.org/doi/full/10.18553/jmcp.2017.23.10.1066.

- These drug price increases also often lead to increased costs to the health care system, including the Medicare and Medicaid programs. For example, the approval of one drug identified through the UDI led to an estimated increase of $50 million per year to the Medicaid program.[8]

- For many legacy drugs, it is not necessary for manufacturers to develop new clinical trial data to provide an assurance of safety and effectiveness. The majority of the products targeted by the UDI are chemically well-defined and are widely used in health care settings. A 2017 study found that 17 out of 19 drugs that obtained approval through the UDI between 2006 and 2015 relied on "literature reviews and bioequivalence to older drug products."[9]

- Due to these concerns, among others, HHS and FDA withdrew the UDI in 2020. FDA still retains the authority to enforce the requirements of the FDCA, including ensuring that drugs are safe and effective.

- The following proposed statutory language would:[10]

    - (1) ensure that manufacturers only receive market exclusivity for a drug already available as a legacy drug if they complete clinical investigations essential to the approval of the drug;

    - (2) avoid drastic price increases and access challenges by preventing extra-statutory efforts to clear the market of legacy drugs based on one manufacturer obtaining approval;

    - (3) require FDA to provide clarity regarding the criteria for legacy drugs, so that manufacturers and the public understand which drugs are entitled to remain on the market absent approval; and

    - (4) help control costs for the Medicare and Medicaid programs.

Proposed Statutory Language

Section 505 of the Food, Drug, and Cosmetic Act is amended by adding at the end the following:

"(z) AVOIDING MARKET DISRUPTION FOR LEGACY DRUGS.

"(1) In the event that the Secretary grants approval of an application submitted under section 505 of a drug for which a drug of the same active ingredient (including any ester or salt of the active ingredient) is in distribution at the time of approval that qualifies as generally recognized as safe and effective or, if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended:

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[8] FDA approved a version of colchicine, Colcrys, even though the drug had been available on the market for many years and the approval did not alter the guidelines regarding its use previously issued by professional societies. Aaron S. Kesselheim and Daniel H. Solomon, *Incentives for Drug Development – The Curious Case of Colchicine*, N. Eng. J. Med. 362;22, 2046 (June 2010), *available at* https://www.nejm.org/doi/pdf/10.1056/NEJMp1003126?articleTools=true.

[9] *Id.*

[10] The proposed legislation would prevent FDA from removing grandfathered drugs and GRASE drugs from the market solely because a drug with the same active ingredient has been formally approved by FDA. In addition, it would ensure that only manufacturers that have completed clinical investigations essential to approval obtain marketing exclusivity. However, drugs that FDA approved between 1938 and 1962, which FDA only evaluated for safety because an evaluation of efficacy was not required during that time, would not be impacted.

"(A) the periods of exclusivity otherwise available to such drug under sections 505, 505A, or 527 shall only apply if, in addition to satisfying the requirements identified in such sections, the Secretary certifies that the application contained a new clinical investigation conducted by or sponsored by the applicant that is essential to the approval of the drug; and

"(B) the Secretary shall not prioritize enforcement action against other drugs in distribution that share the same active ingredient (including any ester or salt of the active ingredient) as the drug receiving such approval based solely on the granting of such approval.

"(2)

"(A) The Secretary shall promulgate regulations providing criteria for the following exceptions to the term "new drug":

"(i) A drug that is generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; or

"(ii) A drug that any time prior to June 25, 1938, was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use."

"(B) The Secretary shall issue a Notice of Proposed Rulemaking pursuant to subparagraph (A) within one (1) year of enactment of this [Act].

"(C) In promulgating regulations pursuant to subparagraph (A), the Secretary shall:

"(i) include consideration of previous statements by the Food and Drug Administration in the Orange Book, or otherwise, that recognized the existence of marketed drugs meeting the criteria described in subparagraph (A); and

"(ii) provide criteria for determining whether representations made for a currently marketed drug constitute the same representations concerning the conditions of its use."

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