

April 16, 2021

Submitted electronically to: import@HHS.gov

Secretary Xavier Becerra
Department of Health and Human Services
200 Independence Ave. SW
Washington DC 20201

Dr. Janet Woodcock, Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: GRASE RFI Response

Dear Secretary Becerra and Acting Administrator Woodcock,

Vizient, Inc. appreciates the opportunity to respond to the Department of Health and Human Services (HHS) notice, Termination of the Food and Drug Administration’s Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective.¹ Vizient applauds HHS’s efforts to close loopholes inadvertently created by the Unapproved Drugs Initiative (UDI) that have enabled drug manufacturers to drastically raise prices of medically necessary medicines. While Vizient believes the UDI was created with the rightful intention of protecting patients and upholding the Food and Drug Administration’s (FDA’s) high standards, we believe it is critical that FDA be cognizant of the loopholes in the program that spurred price spikes, and that FDA work with HHS and Congress to consider solutions that both close such loopholes and prioritize patient safety.

Background

Vizient, Inc. provides solutions and services that improve the delivery of high-value care by aligning cost, quality and market performance for more than 50% of the nation’s acute care providers, which includes 95% of the nation’s academic medical centers, and more than 20% of ambulatory providers. Vizient provides expertise, analytics, and advisory services, as well as

¹ 85 FR 75331

a contract portfolio that represents more than \$100 billion in annual purchasing volume, to improve patient outcomes and lower costs. Headquartered in Irving, Texas, Vizient has offices throughout the United States.

Recommendations

Vizient appreciates the need to make policy changes that appropriately address unsustainable drug prices while also protecting patients from unapproved and misbranded products. While Vizient thanks HHS for their efforts to end the UDI, we believe that it is critical FDA continue to implement policies to protect patients. As such, Vizient offers the following recommendations, including those provided in [Attachment 1](#), for HHS's and FDA's consideration as it contemplates the future of these unapproved marketed products.

Lists of drugs marketed prior to June 25, 1938 that are currently available on the market:

Vizient's supply chain and analytics expertise have enabled us to identify and analyze some of the drugs currently available on the market that have had a clinical use predating June 25, 1938. As described in [Vizient's analysis](#), we identified 19 drugs that meet this criteria. However, we recognize that our list may not be exhaustive. For example, a recent Health Affairs article noted it is estimated that "thousands of drug products without the required FDA review and approval for safety and efficacy continued to be illegally marketed". Similarly, [FDA guidance](#) indicates "perhaps as many as several thousand drug products are marketed illegally without required FDA approval." Vizient was unable to obtain the specific report FDA relied upon in making this statement but encourages the agency to provide more information regarding which drugs FDA believes may be marketed without required FDA approval. A 2019 article from the Journal of Health-System Pharmacy also lists an array of unapproved medications that are available on the market.²

Given the wide assortment of products that may potentially be subject to reconsideration, Vizient believes there is an opportunity for FDA to collaborate with industry groups to better understand the market of unapproved drugs. For example, FDA's [NDC directory](#) can be used to determine whether a product has an application to validate its approval status. However, when searching for the drug papaverine, no application is listed demonstrating the product is unapproved. While this search tool does not shed light on current market availability, purchasing data that is accessible to other stakeholders, including Vizient, could be utilized to help answer this question. As such, Vizient encourages FDA to support transparency and provide a list of drugs for which no application number is listed to help stakeholders determine which drugs marketed prior to June 25, 1938 are currently available on the market.

² Carcio, R. L., Emmendorfer, T.R., Aspinall, S.L., Mizah, M.T., & Good, C.B. (2019). Review of purchases of unapproved medication by the Veterans Health Administration, 73(23), 1934-1943, <https://doi.org/10.1093/ajhp/zxz227>

To build upon this transparency effort, Vizient also notes that the FDA’s website, including the NDC directory, does not include information as to which unapproved products have pending applications. While Vizient recognizes the sensitive nature of the approval process, we believe that more clear information as to which products may soon be approved would help stakeholders effectively prepare for changes that may occur as a result of such an approval.

The extent to which drugs marketed prior to June 25, 1938, or drugs that might qualify as generally recognized as safe and effective (GRASE), have regulatory approvals in countries outside the United States:

Vizient encourages FDA to work with foreign governments and industry to determine which drugs have regulatory approvals in countries outside the United States. As FDA learns this information, Vizient encourages FDA to make this information available to stakeholders.

Whether there would be adverse clinical or economic consequences to deeming as GRASE those drugs previously approved by the FDA for which patent and regulatory exclusivity have expired:

Vizient appreciates HHS’s and FDA’s willingness to consider adverse clinical or economic consequences to deeming as GRASE those products previously approved by the FDA for which patent and regulatory exclusivity have expired. As Vizient understands, the GRASE exemption is typically interpreted narrowly by FDA and the courts.³ Vizient encourages FDA to clarify how it envisions oversight of these products and whether FDA’s interpretation has changed. Given the historically narrow approach to GRASE and uncertainty regarding whether this approach will be modified, forecasting the adverse clinical or economic consequences is more challenging.

In addition, as phrased by FDA, the agency indicates it may consider recognizing as GRASE drugs that have been approved by FDA. It is Vizient’s understanding that products recognized as GRASE generally do not receive an FDA approval. Vizient requests FDA clarify this point as it is foreseeable that a drug that has been approved by FDA, and that is later recognized as GRASE, may pose different clinical and economic consequences than a drug that is recognized as GRASE without a prior approval. For example, should FDA recognize such drugs as GRASE, how would this impact exclusivities provided or competition more generally?

Vizient strongly supports FDA’s high standards for approval and the agency’s critical role in oversight and patient safety. While the goals of the UDI to encourage clinical research are commendable, it is now apparent that the incentive of a one-year period of *de facto* exclusivity does not sufficiently encourage the desired research. For example, research has shown that the approval process for unapproved drugs “did not necessarily require new clinical evidence

³ See *Weinberger v. Hynson, Westcott & Dunning Inc.*, 412 U.S. 609 (1973); see also FDA Response, Docket No. 97N-0314 (26 April 2001), available at www.fda.gov/ohrms/dockets/dockets/97n0314/pdn0002.pdf (finding that synthroid—a levothyroxine sodium product—was not GRASE). <https://www.regulations.gov/document?D=FDA-1997-N-0041-0026>; <https://www.regulations.gov/document?D=FDA-1997-N-0041-0031>

to establish safety or efficacy.”⁴ Therefore, Vizient urges FDA to continue its rescission of the policy providing *de facto* exclusivity and encourage the agency to work with stakeholders to identify alternative, more targeted research incentives.

Vizient also notes there are several factors which can impact the potential for adverse clinical or economic consequences to deeming as GRASE certain products. Like FDA’s use of advisory committees, Vizient encourages FDA to convene groups of experts to help in this evaluation on a drug-by-drug basis and to gain public input. For example, FDA could seek and consider real-world evidence in decisions regarding unapproved products and related enforcement plans. To the extent funding or additional authority is needed for FDA to implement this process, Vizient encourages FDA to communicate those needs to stakeholders and Congress. Such committees could also be helpful in identifying post-marketing risk mitigation strategies that would support safety and FDA’s oversight efforts.

Any published literature or clinical studies related to any drugs potentially exempt from the new drug approval requirement:

Vizient appreciates HHS’s request for published literature or clinical studies related to any drugs that may be exempted from the requirement that a new drug receive approval. To build upon this data-gathering effort, Vizient encourages FDA to identify a list of drugs that are of greatest safety concern to FDA to help stakeholders in identifying literature or in potentially supporting future clinical studies. In addition, Vizient is uniquely positioned to work alongside our member hospitals and health systems, and with other organizations focused on best practices, to determine if there are any clinical deficiencies with certain unapproved drugs (e.g., Tralement’s approval in relation to the revised recommendation from the American Society for Parenteral and Enteral Nutrition (ASPEN)). Vizient reiterates our encouragement of a regulatory approach that carefully considers appropriate incentives, safety and efficacy and access to critical medications.

Conclusion

Vizient appreciates the efforts of HHS and FDA to address the rising cost of drugs in the United States. Vizient recognizes that the issue of drug pricing is complex and multi-faceted. The unintended consequences of the UDI represent one aspect of drug pricing dynamics. However, by working effectively through regulatory activity and collaborating with the private sector, notable improvements can be made to improve drug safety while avoiding unnecessary pharmaceutical price increases.

Vizient membership includes a wide variety of hospitals ranging from independent, community-based hospitals to large, integrated health care systems that serve acute and non-acute care

⁴ Gupta, R., Dhruva, S.S., Fox, E.R. & Ross, J.S. (2017). The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States. *Journal of Managed Care Specialty Pharmacy*, 23(10):1066-1076, doi: 10.18553/jmcp.2017.23.10.1066.

needs. Additionally, many are specialized, including academic medical centers and pediatric facilities. Individually, our members are integral partners in their local communities, and many are ranked among the nation's top health care providers. In closing, on behalf of Vizient, I would like to thank the HHS for providing us the opportunity to comment on this important RFI. Please feel free to contact me or Jenna Stern at jenna.stern@vizientinc.com, if you have any questions or if Vizient may provide any assistance as you consider these issues.

Respectfully submitted,



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Future Directions of the Unapproved Drugs Program

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Overview

Vizient® supports the Food and Drug Administration's (FDA's) long-standing role in protecting public health and overseeing a pharmaceutical supply chain that contains safe and efficacious products. In response to the November 2020 notice, "Termination of the Food and Drug Administration's Unapproved Drugs Initiative; Request for Information Regarding Drug Potentially Generally Recognized as Safe and Effective," ("Notice") which requested information and withdrew FDA's Marketed Unapproved Drugs—Compliance Policy Guide, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs, Vizient endeavored to identify solutions to support FDA's review process and oversight of unapproved drugs.

Vizient, Inc. is the nation's largest health care performance improvement company. Vizient provides solutions and services that improve the delivery of high-value care by aligning cost, quality and market performance for more than 50% of the nation's acute care providers, which includes 95% of the nation's academic medical centers, and more than 20% of ambulatory providers. Vizient provides expertise, analytics, and advisory services, as well as a contract portfolio that represents more than \$100 billion in annual purchasing volume, to improve patient outcomes and lower costs. Headquartered in Irving, Texas, Vizient has offices throughout the United States.

Vizient identified the following potential solutions, described in more detail below, for the U.S. Department of Health and Human Services (HHS) and FDA to consider as the need to address the safety and efficacy of unapproved products continues:

1. **Enhance transparency** to promote greater understanding of legacy drugs and improve regulatory decision-making
2. **Work collaboratively** with stakeholders to identify the legacy drugs for which additional clinical information would be helpful to ensuring safety and effectiveness
3. **Utilize the rulemaking process** to clarify the agency's approach to unapproved drugs
4. **Clarify criteria** for grandfathered pre-1938 and Generally Recognized as Safe and Effective ("GRASE") drugs to provide greater market certainty and transparency
5. **Actively consider the evolving health care landscape**, including the need for a resilient supply chain and the policy changes stemming from the Coronavirus Disease 2019 ("COVID-19") public health emergency.

Background

In 2006, FDA established the Unapproved Drugs Initiative (UDI) to, in part, begin the review process of drugs that were developed and marketed prior to the establishment of today's FDA safety and efficacy requirements.¹ Given several laws since 1906 have shaped FDA's marketing approval requirements, some drugs, often referred to as legacy drugs, are available in the United States even though they lack required FDA approval for marketing.² Some of these drugs have a long history of use by health care providers and hospitals.

¹ FDA, *Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs*, (June 2006) [hereinafter "2006 CPG"]; 2011 CPG.

² See 2011 CPG, Appendix 1, *stating* "Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below... A. 1938 and 1962 Legislation... B. DESI... C. Prescription Drug Wrap-Up... D. New Unapproved Drug... E. Over-the-Counter (OTC) Drug Review"

Under the UDI, if a previously unapproved drug receives approval status, FDA asks manufacturers of the remaining unapproved versions to exit the market in accordance with guidance FDA released in 2011.³ This creates a sole source supply of the newly approved drug, which excludes competitors depending upon market exclusivity and patent protections that could be granted. The duration of this protected period varies depending on the product and in some cases, can greatly lengthen the duration of exclusivity for the drug.

Previous analysis by Vizient concluded \$19.07 billion in potential savings to U.S. health care spend if market exclusivity were to be ended for five commonly used drugs approved by the FDA through the UDI program termination.⁴ Also, a 2017 study found that 17 out of 19 drugs that obtained approval through the UDI between 2006 and 2015 relied on literature reviews, bioequivalence studies or both, and did not include new clinical trial evidence.⁵ Vizient continues to call attention to the financial hardship of additional market exclusivity and excessive patenting of drugs that have had a long-standing use in hospitals. In addition, the products were approved and received exclusivities without engaging in the research, development and clinical trial activity that is generally required when a new drug is approved.⁶

In November 2020, HHS issued a notice withdrawing FDA guidance that was fundamental to the UDI.⁷ As a result, issues that prompted FDA to establish the UDI in 2006 may reemerge if no action is taken. Additionally, should FDA decide to re-establish UDI in its most recent form, unintended consequences stemming from the program, such as drug spikes and drug shortages, are anticipated to continue. Vizient appreciates that the underpinning goal of the UDI is the need to protect patients. Vizient values the critical role FDA plays in protecting public health by both setting high approval standards for marketed drugs and working tirelessly to provide oversight and enforcement over the market.

Recommended Solutions

1. Enhance transparency to promote greater understanding of legacy drugs and improve regulatory decision-making.

Historically, there has been a lack of clear information regarding available legacy drugs, those legacy drugs about which FDA has particular concern and the status of drug approvals for such categories of drugs. This has detracted from the laudable goal of ensuring the safety and efficacy of all drugs. As of late 2020, the National Drug Code database listed more than 1,500 unapproved prescription drugs, “although it is unclear which of these have approved alternatives, how many are still marketed, and which products sell in meaningful volumes.”⁸ Vizient recommends FDA enhance transparency regarding the status of legacy drugs and enforcement and approval considerations, as outlined below.

³ 2011 CPG.

⁴ https://www.vizientinc.com/-/media/documents/sitecorepublishingdocuments/secured/solutions/pharmacy/UDI_fact_sheet_final.pdf

⁵ 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, 1073 (Oct. 2017), available at <https://www.jmcp.org/doi/full/10.18553/jmcp.2017.23.10.1066>.

⁶ Allan Coukell, *What Will Replace the Unapproved Drugs Initiative*, HealthAffairs.org (January 15, 2021), available at <https://www.healthaffairs.org/doi/10.1377/hblog20210111.326715/full/>.

⁷ 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.govinfo.gov/content/pkg/FR-2020-11-25/pdf/2020-26133.pdf> [hereinafter “Notice”].

⁸ Allan Coukell, *What Will Replace the Unapproved Drugs Initiative*, HealthAffairs.org (January 15, 2021), available at <https://www.healthaffairs.org/doi/10.1377/hblog20210111.326715/full/>.

Status of Legacy Drugs

The Notice specifically sought comments regarding the existence of remaining unapproved drugs that may have been available prior to 1938 and may be eligible for grandfathering. Similarly, the Notice requested feedback regarding drugs that may be GRASE. Vizient is aware of the need for more, consistent information regarding the universe of unapproved drugs. **We urge HHS and FDA to share publicly the results of this request for information, and to continue to work with stakeholders to make available a clear and reliable resource to determine the status of legacy drug formulations.**

As part of this effort, FDA could develop and maintain a public database that clarifies the legacy drug types for which approved drugs exist, and highlight drug types about which the agency has identified particular concerns or is otherwise seeking additional clinical information. Stakeholders could share valuable information, including clinical, stability, bioequivalency and shelf-life data, which would be resource-efficient for FDA if it were to develop a database. Such a database would better enable FDA to identify those drugs for which critical unanswered clinical questions exist and focus resources appropriately. It would also assist purchasers and providers in making better informed decisions in the best interest of patients.

In addition, it would be helpful if FDA shared information, to the maximum extent possible, regarding whether a manufacturer has submitted an application for an unapproved drug that has been marketed for decades, including the proposed indication for use. Awareness of when an application has been submitted supports transparency and could help stakeholders plan proactively for supply channel changes that would impact inventory management, clinical use, and budget forecast if a product is approved and pre-existing competition is removed. While it is understood that FDA does not disclose the existence of a specific applicant's New Drug Application ("NDA") or Abbreviated NDA ("ANDA"),⁹ it is unclear whether FDA could disclose that an application has been submitted for a historically unapproved drug in general, without specifying the manufacturer or any proprietary or commercial information. The Freedom of Information Act ("FOIA") permits FDA to disclose records in the possession or control of the agency when requested in writing by any person, unless exempted.¹⁰ Depending on the context, disclosure of the existence of an application for a particular drug type, without naming the applicant, may or may not implicate the disclosure of commercial confidential or trade secret information. To the extent that FDA determines that information is potentially proprietary and protected from disclosure, the agency could redact non-public information, or still disclose such information if the applicant has voluntarily disclosed it or has agreed to its disclosure. Towards that end, for legacy drugs, FDA could ask the applicant for permission to disclose the existence of the application.

Other regulatory bodies have taken similar steps to promote transparency. For example, the European Medicines Agency ("EMA") publishes a list of new medicines, including generics, that are being evaluated for centralized marketing authorization by EMA's Committee for Medicinal Products for Human Use on a monthly basis.¹¹ The list includes the international non-proprietary name for each medicine, and includes the active moiety for generic medicines. Likewise, Health Canada ("HC") publishes a Submissions Under Review List for New Drug Submissions that contains new active substances accepted for review and new and supplemental drug submissions for new uses under review.¹² HC updates the list monthly and includes

⁹ 21 C.F.R. § 314.430.

¹⁰ 5 U.S.C. § 552.

¹¹ *Medicines Under Evaluation*, EMA.Europe.eu, <https://www.ema.europa.eu/en/medicines/medicines-under-evaluation#2019-section> (last visited on Feb. 20, 2021).

¹² *Drug and Health Product Submissions Under Review (SUR)*, Canada.ca, <https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/submissions-under-review.html> (last visited on Feb. 20, 2021).

the drug, the month and year HC accepted the submission, the therapeutic area, and, for submissions accepted for review on or after October 1, 2018, the company name and class of submission.¹³

FDA's Enforcement and Approval Considerations

Currently, stakeholders have limited timely insight regarding when or why FDA acts to address risks posted by unapproved drugs. **We recommend FDA share more information than it might otherwise have withheld so the public understands the agency's concerns or uncertainties about certain legacy drugs.** For example, under FDA's prior risk-based approach to enforcement of unapproved products the agency gives higher priority to enforcement action against unapproved drugs in certain categories (e.g., drugs with potential safety risks, drugs that lack evidence of effectiveness, and drugs that violate current good manufacturing practices), yet it is unclear which products have been reviewed for priority or what information gaps exist. Granting access to more information regarding FDA's enforcement and approval considerations could prompt stakeholders to address common challenges, share useful information, and target resources appropriately to help resolve FDA's questions. This transparency may further engender public confidence in these decisions and benefit public health.

Given FDA's commitment to "increasing transparency related to the scientific basis for drug approval decisions,"¹⁴ there is an opportunity for the agency to apply that view to unapproved drugs. A transparent approach to legacy drugs would advance research and development by limiting unnecessary duplication, reducing unnecessary risks for participants in clinical trials, and improving the public's understanding of and trust in FDA's regulatory decisions and priorities.

2. Work collaboratively with stakeholders to identify the legacy drugs for which additional clinical information would be helpful to ensuring safety and effectiveness.

Regarding unapproved drugs, FDA indicates, "Without FDA review, there is no way to know if these drugs are safe and effective for their intended use, whether they are manufactured in a way that ensures consistent drug quality or whether their label is complete and accurate."¹⁵ Vizient appreciates and supports FDA's efforts to ensure that all drugs on the market are safe and effective for use. Vizient is committed to supporting our members in providing safe and effective patient care. For example, we operate a patient safety organization, through which members share patient safety information and opportunities for improvement. Vizient also maintains a clinical database to which our members contribute information to further support safe and effective utilization of medications. **Through more active collaboration with stakeholders, we believe that FDA could obtain and disseminate significant clinical information about legacy drugs. In turn, the agency could concentrate its efforts on particular drug types for which clinical information was truly lacking, and sponsors of new drug applications for these products would be able to more effectively decide whether to perform a clinical trial.**

As Vizient understands, the rationale for the UDI was that incentivizing drug applications through extended market exclusivity would yield additional clinical data. As it turned out, the application process itself did not necessarily translate to an increase in data about a drug. For many legacy drugs, however, it also appears

¹³ "The submission 'class' includes whether the submission is for a new active substance or a biosimilar, if it is being reviewed as per a formal expedited process, if review is taking place as part of an aligned process with a health technology assessment organization, and more." *Id.*

¹⁴ *FDA Continues to Support Transparency and Collaboration in Drug Approval Process as the Clinical Data Summary Pilot Concludes*, FDA.gov, March 26, 2020, <https://www.fda.gov/news-events/press-announcements/fda-continues-support-transparency-and-collaboration-drug-approval-process-clinical-data-summary> (last visited Feb. 20, 2021).

¹⁵ Food and Drug Administration (Feb. 2021). Unapproved Drugs, available at: <https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs>, last accessed: March 18, 2021.

that it was, in fact, 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, not new clinical trial evidence.”¹⁶

The cost and time-consuming nature of clinical trials are significant impediments for manufacturers to seek approvals of drug products. Alternatively, manufacturers may use the fact that they spent time and money on clinical trials, or even in the submission of clinical data derived from published literature, as justification for significant price increases after approval. Nevertheless, in many instances, the market exclusivity that follows such approval may be disproportionate to the level of investment required to demonstrate safety and efficacy, as there are often considerable data already available. The UDI was particularly vulnerable to the scenario where a manufacturer’s financial incentives to gain approval is uniquely disproportionate with their investment in obtaining approval, especially since clinical trials were not routinely performed and other data sources readily available. Image 1, provides several examples of products where little to no new clinical information was provided in the NDA, yet various exclusivities were provided and significant price increases.

Image 1. Minimal Safety and Efficacy Investment for Market Exclusivity

FDA approval of Colcris® (colchicine)

- Developed as an effective second-line treatment for gout
- Manufacturer’s brief clinical trial confirmed the drug’s safety and efficacy, and dosing adjustments recommended by one of the major rheumatology professional societies
- Three years market exclusivity
- Plus, seven years of market exclusivity for the use of the drug for another indication, based mostly on previously collected data and limited safety information from the new trial

Outcome: Despite the manufacturer adding no “meaningful improvement to the public health,” the manufacturer raised the price of the drug by a factor of more than 50, from \$0.09 per tablet to \$4.85 per tablet

FDA approval of Vasopressin® (vasopressin)

- Developed in 1928; granted FDA approval in 2014
- No new clinical information, “relying on published literature alone to support clinical pharmacology, safety and efficacy” for the proposed indication
- Patent approved as innovation through 2035

Outcome: WAC increase 1,644% (\$283.25 to \$4,939)

FDA approval of Dehydrated Alcohol 98% to Dehydrated Alcohol 99%

- Developed in 1993 for relief of intractable chronic nerve pain
- Received 7-year orphan indication
- Used to treat severe heart disease

Outcome: WAC increase 688%* on package of 10 (\$1,295 to \$9,950)

*Increase based on 5 years following the market exit of competition in 2020

FDA approval of Selenium 40 mcg/mL to Selenious Acid 60 mcg/mL

- Parenteral selenium developed in the 1980s; received FDA approval as injection in 2019
- No new clinical data required^A; received 5-year New Chemical Entity (NCE) exclusivity through April, 2024
- Used to treat nutritional deficiency

Outcome: WAC increase 1190%*¹⁶ on package of 25 (\$443.25 to \$8,575)

*Calculated to account for concentration change

A – See Food and Drug Administration, CDER applications number 209379Orig1s0000, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209379Orig1s000MultiDisciplineR.pdf

¹⁶ 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, 1073 (Oct. 2017).

Instead of re-creating a dynamic in which manufacturers are able to raise drug prices despite providing little or no additional clinical information about the drug, FDA should work with stakeholders to identify which legacy drugs need clinical trial data to determine a drug’s safety and efficacy. Further, taking such a targeted approach to identifying particular drugs of concern and the reasons for which expanded safety and efficacy information are required is consistent with the risk-based approach FDA outlined in the 2011 CPG.¹⁷ If there are existing clinical and/or formulation deficiencies with presently marketed prescription pharmaceuticals, prescribers should have access to that information to inform treatment decisions. FDA should then collaborate with a wide range of stakeholders, including manufacturers, providers, group purchasing organizations, and professional societies, to determine existing specialty guidelines for the appropriate use of these drugs, sources of data and areas of safety concern. Stakeholders may be able to identify additional scientific literature or real world data, or potentially work collaboratively to take on the costs of additional data generation through registries or other approaches that would ultimately provide sufficient evidentiary support for a particular drug or drug class. In many cases, these options may be superior to undertaking costly new clinical trials with human subjects that may ultimately be unnecessary, except as a pretense for a company to obtain market exclusivity or market dominance.

FDA should also explore working with the National Institutes of Health to provide funding for clinical trials to address particular risk areas regarding these drugs.¹⁸ By establishing “open source” clinical data, FDA and stakeholders would gain valuable information about a class of drugs, rather than relying on individual companies to conduct separate, costly trials. This would serve as an efficient approach for FDA’s efforts over the long term. More importantly, this approach would allow FDA to ensure that the drugs that present the greatest uncertainties or pose the most acute risks to public health are safe and effective for use, without unnecessarily limiting access to drugs that are widely accepted and present minimal concern.

3. Utilize the rulemaking process to clarify the agency’s approach to unapproved drugs

The Notice included two steps HHS took to change the UDI – the withdrawal of guidance and a request for information.¹⁹ In addition, HHS independently issued, “Frequently Asked Questions Regarding the Department of Health and Human Services’ Announcement on the Unapproved Drugs Initiative” (“FAQ”), which provided additional information regarding the implications of the Notice.²⁰ For example, the FAQ answers, “Will manufacturers of drugs subject to the program still be able to obtain regulatory exclusivity?” and “How does this announcement impact parties that have relied on the UDI program?”. However, FDA has not yet addressed these actions by HHS. Rather, FDA has made minor modifications to its “Unapproved Drugs” website and continues to reference the Marketed Unapproved Drugs – Compliance Policy Guide (Sec. 440.1000) that was withdrawn in the Notice.²¹ These different sources of information create confusion among stakeholders regarding unapproved drugs and the broader provider and patient community. More fundamentally, the Notice acknowledged that many elements of the UDI should be initiated through regulation, rather than non-binding guidance. **Given FDA’s role in protecting public health and**

¹⁷ 2011 CPG

¹⁸ See Kesselheim & Solomon, *supra*, at 2,046.

¹⁹ 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.govinfo.gov/content/pkg/FR-2020-11-25/pdf/2020-26133.pdf> [hereinafter “Notice”].

²⁰ HHS; Frequently Asked Questions Regarding the Department of Health and Human Services’ Announcement on the Unapproved Drugs Initiative, *available at* <https://www.hhs.gov/sites/default/files/covid-19-unapproved-drugs-initiative.pdf>.

²¹ See FDA, Unapproved Drugs (last updated 2/17/2021), *available at* <https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs>

regulating drugs, Vizient recommends formal action by FDA, via rulemaking, to alleviate confusion created by various sub-regulatory guidances over a period of years by FDA and HHS. The current unique circumstances present an opportunity for FDA to initiate a notice and comment rulemaking process to gain stakeholder feedback and improve the agency’s approach to unapproved drugs.

4. Clarify criteria for grandfathered pre-1938 and Generally Recognized as Safe and Effective (“GRASE”) drugs to provide greater market certainty and transparency.

The Notice acknowledges that the UDI created confusion as to whether there are currently marketed prescription drugs that qualify as grandfathered or otherwise as not “new drugs,”²² such as drugs that qualify as GRASE. As indicated in the Notice, in the 1980 version of the Orange Book, FDA stated that “[t]he law also permits drugs to be legally marketed without such fully approved applications under certain circumstances,” including “drugs marketed prior to 1938 that are not subject to the pre-market clearance procedures of the law” and “drug products marketed between 1938 and 1962 that were approved for safety but not effectiveness.”²³ In the Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (“2011 CPG”), FDA acknowledged that “a product would not be considered a new drug if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time.”²⁴ However, FDA stated in the same 2011 CPG that “it is not likely that any currently marketed prescription drug is grandfathered or is otherwise not a new drug,” although FDA acknowledged “that is at least theoretically possible.”²⁵

Vizient’s ongoing review suggests that certain currently marketed drugs potentially qualify for grandfathering because they meet the statutory criteria: (1) the type of drug was marketed between January 1, 1907 and June 25, 1938; and (2) they are the same drug product as the one marketed between that time frame and the labeling describes the same conditions of use.²⁶ In addition, our ongoing review suggests that certain currently marketed drugs may qualify as GRASE because their uses have been established in peer-reviewed medical journals and documented to a material extent by professional medical societies for a significant period of time. Despite acknowledging that it “is at least theoretically possible” for drugs on the market to meet these criteria, FDA disregarded this possibility with the issuance of the 2006 and 2011 CPG policies.²⁷

As noted above, based on Vizient’s own analysis, there may be a dozen injectable drugs that could be eligible for grandfathered marketing and/or could qualify as GRASE, including indigo carmine, papaverine, phenobarbital, hyoscyamine sulfate, and physostigmine salicylate. The 2011 CPG policy announced a risk-based enforcement approach to unapproved drugs marketed prior to September 19, 2011, and provided that drugs introduced to the market after September 19, 2011 would be subject to immediate enforcement action, with no mention of an analysis of whether the drug could qualify for an exemption.²⁸ The FDCA affords qualifying sponsors that obtain approvals market exclusivity for a specified range of years via the inability of competitors to submit their own applications; but FDA went a step further and cleared the market of existing

²² 85 Fed. Reg. 75,331, 75,333 (Nov. 25, 2020), available at <https://www.govinfo.gov/content/pkg/FR-2020-11-25/pdf/2020-26133.pdf>

²³ FDA, *Approved Prescription Drug Products with Therapeutic Equivalence Evaluations* at I-3 (1st ed. 1980) [hereinafter “Orange Book”].

²⁴ FDA, *Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs* 12 (Sept. 19, 2011) [hereinafter “2011 CPG”]; see 21 U.S.C. § 321(p)(1) and (2).

²⁵ 2011 CPG at 12.

²⁶ FDCA § 201(p); 21 U.S.C. § 321(p).

²⁷ FDA, *Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs* 12 (June 2006) [hereinafter “2006 CPG”]; 2011 CPG.

²⁸ 2011 CPG.

competitors, even though the sponsor usually did not invest in data development or other significant costs that would justify that extraordinary market advantage.²⁹

Such a significant shift in policy, and one that purported to serve as the basis for enforcement action, should have been subject to notice-and-comment rulemaking.³⁰ The 2006 and 2011 CPGs were issued without providing an opportunity for comment that is provided for any significant guidance document under FDA's good guidance practices. The good guidance practices require that FDA invite public comment on a draft guidance document if it sets forth initial interpretations of statutory or regulatory requirements, initial interpretations or policy that are of more than a minor nature, includes complex scientific issue, or addresses highly controversial issues.³¹ The creation of the UDI certainly qualifies as a guidance document that would require public comment. However, FDA did not allow for public comments, reasoning that "prior public participation [was] not feasible or appropriate," but it is unclear why FDA believed that to be the case.³² In hindsight, the establishment of the UDI would likely have benefited from greater public input, both to assess the real-world implications of the proposed approach and also to evaluate a wider range of options for generating the additional clinical information about these drugs.

Unfortunately, the implementation of the UDI, and particularly, the granting of various durations of exclusivity to the first approved versions of molecules — both statutory and enforcement-driven — has led to inflated pricing and access challenges. Drugs that were previously multi-source have been transformed to sole source, even though it is possible that some legacy drugs may have had a legal basis to remain under the grandfathering criteria (or, to newly enter) or qualify as GRASE. Under the statutory criteria, a drug's eligibility for grandfathering or GRASE requires a fact-based and context-specific inquiry, but FDA's guidance implied categorical ineligibility. Even after rescission of the UDI, the ongoing uncertainty may create a chilling effect for potential market entrants, and it is far from clear how quickly a competitive, multi-source market could be re-established.

To help resolve these issues, **FDA should issue criteria to determine whether a drug product is sufficiently similar to a pre-1938 product to qualify for the grandfathering exemption, provide the criteria and process to determine whether a drug product is GRASE, and work with stakeholders to identify drugs that are not "new drugs" subject to FDA approval.** These different criteria could provide latitude that is consistent with FDA's approach to approved drugs, which recognizes that not every single change renders the product a "new drug" or requires a new application.

With respect to the grandfathering exemption, the criteria should take into account the difficulties with obtaining documentation of clinical studies that predate 1938, and permit manufacturers to document or otherwise demonstrate the relationship between products currently available on the market, their predecessors, and consensus guidelines regarding their use. **We encourage FDA to outline the degree to which the formulation, dosage form, potency, route of administration, indication, or intended patient population may differ, if at all, from historic uses for classes of drugs.** Just as certain changes to an approved drug do not require prior FDA approval, a reasonable approach would presumably recognize that certain variations would not render a legacy drug a "new drug" under the FDCA. Moreover, to make sure there is an opportunity for sufficient input from stakeholders, it is advisable that FDA issue these policies on the grandfathering exemption and GRASE through notice and comment rulemaking that fully

²⁹ See 21 U.S.C. § 505(b); 21 C.F.R. § 314.108.

³⁰ See 5 U.S.C. § 553.

³¹ 21 C.F.R. § 10.115 (version in effect in 2006 and 2011).

³² 76 Fed. Reg. 58,398 (Sept. 21, 2011).

explain FDA's interpretation in light of previous interpretations issued through sub-regulatory guidance. This approach would also allow FDA to create binding criteria and provide a justification for any application of exclusivity not already recognized in the statute, unlike issuing policy via guidance.

5. Actively consider the evolving health care landscape, including the need for a resilient supply chain and the policy changes stemming from the Coronavirus Disease 2019 ("COVID-19") public health emergency.

As HHS and FDA evaluate new approaches to legacy drugs, it is important to consider the broader public health imperative to avoid and mitigate drug shortages, and the national importance of developing a reliable supply chain for our most important medications. As stated in the Notice, an unintended consequence of the UDI is that drugs subject to the program have been subject to drug shortages. A 2017 study found that 24 of 34 drugs evaluated experienced drug shortages after FDA took enforcement action following an entity obtaining FDA approval of a previously unapproved drug.³³ The study found that the median shortage was 217 days.³⁴ Vizient recognizes that FDA is committed to preventing and mitigating drug shortages to the greatest extent possible, and has actively worked with FDA to provide input on numerous drug shortages. **Vizient urges HHS and FDA to consider how legacy drugs fit within broader efforts to ensure a reliable supply of essential drugs, in keeping with the government's far-reaching policy goal of ensuring access to a supply of critical drugs.**

Maintaining a sufficient domestic supply of critical drugs is a related government priority. As HHS and FDA are aware, President Biden signed an executive order emphasizing the need to develop a more resilient supply chain for pharmaceuticals and other critical areas, in order to avoid shortages and address future public health emergencies. The order calls for a 100-day review of near term steps, and an in-depth one-year review of a broader set of U.S. supply chains.³⁵ President Biden has also expressed support for on-shoring of essential medicines and the use of advanced manufacturing techniques,³⁶ which FDA has stated could enable U.S.-based pharmaceutical manufacturing to help ensure a stable supply of key drugs.³⁷ FDA recently announced a memorandum of understanding with the National Institute of Standards and Technology to accelerate the adoption of advanced manufacturing technologies, signaling that senior leadership has prioritized the importance of this policy.³⁸

Other efforts initiated last year also seek to ensure sufficient and reliable, long-term domestic production of essential medicines, and to minimize potential shortages by reducing U.S. dependence on foreign manufacturers of these products.³⁹ As part of that initiative, FDA published a list of essential medicines,

³³ 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, 1073 (Oct. 2017), available at <https://www.jmcp.org/doi/full/10.18553/jmcp.2017.23.10.1066>.

³⁴ *Id.*

³⁵ Executive Order on America's Supply Chains (Feb 24, 2021), <https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/executive-order-on-americas-supply-chains/>.

³⁶ The Biden Plan To Rebuild U.S. Supply Chains And Ensure The U.S. Does Not Face Future Shortages Of Critical Equipment, <https://joebiden.com/supplychains/> (last visited Feb. 22, 2021).

³⁷ FDA, *Advanced Manufacturing*, <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing> (last visited Feb. 22, 2021).

³⁸ FDA, *Accelerating the Adoption of Advanced Manufacturing Technologies to Strengthen Our Public Health Infrastructure* (Jan. 15, 2021), available at <https://www.fda.gov/news-events/fda-voices/accelerating-adoption-advanced-manufacturing-technologies-strengthen-our-public-health>; FDA, *Advanced Manufacturing*, <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing> (last visited Feb. 22, 2021).

³⁹ FDA, Executive Order 13944 List of Essential Medicines, Medical Countermeasures, and Critical Inputs, <https://www.fda.gov/about-fda/reports/executive-order-13944-list-essential-medicines-medical-countermeasures-and-critical-inputs> (last visited Feb. 21 2021).

including a number of legacy drugs and a drug category titled “Unapproved Drugs Initiative”.⁴⁰ One of these is vasopressin, which was originally developed in 1928, and formally approved via the UDI in 2014 to treat critically low blood pressure. As mentioned above, following its approval, the price of the drug increased by 1644%.⁴¹ The annual U.S. health care spend on this drug increased from \$30.8 million to \$510 million.⁴² Spend on vasopressin by Vizient’s members increased 107% during the initial onset of the COVID-19 outbreak (March to April 2020) as compared to those two months in 2019. Vasopressin is just one example of the unintended consequences of the UDI and serves as a reminder that future policy decisions regarding these drugs must be consistent with the government’s broader goal of ensuring access to essential medicines.

The COVID-19 pandemic has highlighted the weaknesses in our nation’s response to sudden increases in drug demand. It has also revealed the need to consider the broader drug supply chain. We encourage FDA to consider implementing policies that will allow us to better meet the drug supply demands during this emergency, the next emergency, and in times of non-emergency. FDA has an opportunity now to ensure that its policy on older, widely available drugs is consistent with the goal of ensuring a resilient supply of essential medicines and preventing drug shortages. As FDA considers specific approaches to legacy drugs to serve as a successor to the UDI, Vizient recommends that the agency do so in the broader context of considering the need for a robust supply chain for essential medicines, which includes multiple, diversified manufacturing sources (including raw materials and/or API) and the ability to expand capacity quickly. In contrast, the UDI’s heavy focus on incentivizing approvals for legacy drugs, in hindsight, seemingly contributed to access issues. Because many legacy drugs are also critical to patient care, particularly during public health emergencies, the maintenance of a robust market for legacy drugs is inextricably linked to the broader development of a robust pharmaceutical supply chain. **Before adopting new approaches to legacy drugs or reconsidering aspects of the UDI, we recommend that FDA explicitly evaluate how such approaches would support, or hinder, the overarching objective of a robust drug supply chain pursuant to the President’s Executive Order.**

Summary

Recent actions by HHS have prompted stakeholders to revisit the UDI and FDA’s approval and enforcement actions related to unapproved drugs. Currently, there is a unique opportunity to identify and potentially implement solutions that would help address the unintended consequences of the UDI while also ensuring patient safety and public health. Vizient identified five potential solutions and principles for HHS and FDA to consider as policy is developed to address the safety and efficacy of unapproved products. Vizient and our members are committed to utilizing safe and effective products that prioritize patient safety. We look to be a resource and partner to HHS and FDA as additional actions regarding unapproved drugs are being contemplated.

⁴⁰ FDA, Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order 13944 (Oct. 30, 2020), available at <https://www.fda.gov/media/143406/download>.

⁴¹ 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.

⁴² *Id.*



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