human consumption are not considered prohibited cattle materials, and their use does not render human food or cosmetics adulterated. Sections 189.5(e) and 700.27(e) provide that a country seeking to be designated must send a written request to the Director of the Center for Food Safety and Applied Nutrition. The information the country is required to submit includes information about a country’s BSE case history, risk factors, measures to prevent the introduction and transmission of BSE, and any other information relevant to determining whether SRMs, the small intestine of cattle not otherwise excluded from being a prohibited cattle material, material from nonambulatory disabled cattle, or MS beef from the country seeking designation should be considered prohibited cattle materials. We use the information to determine whether to grant a request for designation and to impose conditions if a request is granted.

Sections 189.5 and 700.27 further state that countries designated under §§ 189.5(e) and 700.27(e) will be subject to future review by FDA to determine whether their designations remain appropriate. As part of this process, we may ask designated countries to confirm that their BSE situation and the information submitted by them, in support of their original application, has remained unchanged. We may revoke a country’s designation if we determine that it is no longer appropriate. Therefore, designated countries may respond to periodic FDA requests by submitting information to confirm their designations remain appropriate. We use the information to ensure their designations remain appropriate.

**Description of Respondents:** Respondents to this information collection include manufacturers, processors, and importers of FDA-regulated human food, including dietary supplements, and cosmetics manufactured from, processed with, or otherwise containing material derived from cattle, as well as, with regard to §§ 189.5(e) and 700.27(e), foreign governments seeking designation under those regulations.

In the Federal Register of August 14, 2020 (85 FR 49657), we published a 60-day notice requesting public comment on the proposed collection of information. Although some comments were received, only one pertained to the information collection. The comment suggested requiring greater than a 2-year retention period for records; however, we believe that additional retention requirements may impose undue burden on respondents to the information collection without providing greater utility to the Agency.

We estimate the burden of this collection of information as follows:

**TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN**

<table>
<thead>
<tr>
<th>21 CFR section; activity</th>
<th>Number of respondents</th>
<th>Number of responses per respondent</th>
<th>Total annual responses</th>
<th>Average burden per response</th>
<th>Total hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>189.5(c)(6) and 700.27(c)(6); affirmation of compliance.</td>
<td>54,825</td>
<td>1</td>
<td>54,825</td>
<td>0.033 (2 minutes) ......</td>
<td>1,809</td>
</tr>
<tr>
<td>189.5(e) and 700.27(e); request for designation .....</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>80 (1 minute) .....</td>
<td>80</td>
</tr>
<tr>
<td>189.5(e) and 700.27(e); response to request for review by FDA.</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>26 (15 minutes) .....</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>..........................................................</td>
<td>..................................</td>
<td>..................................</td>
<td>..................................</td>
<td>1,915</td>
</tr>
</tbody>
</table>

1 There are no capital costs or operating and maintenance costs associated with this collection of information.

**TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN**

<table>
<thead>
<tr>
<th>Type of respondent</th>
<th>Number of recordkeepers</th>
<th>Number of records per recordkeeper</th>
<th>Total annual records</th>
<th>Average burden per recordkeeper</th>
<th>Total hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic facilities</td>
<td>697</td>
<td>52</td>
<td>36,244</td>
<td>0.25 (15 minutes) .....</td>
<td>9,061</td>
</tr>
<tr>
<td>Foreign facilities</td>
<td>916</td>
<td>52</td>
<td>47,632</td>
<td>0.25 (15 minutes) .....</td>
<td>11,908</td>
</tr>
<tr>
<td>Total</td>
<td>..........................................................</td>
<td>..................................</td>
<td>..................................</td>
<td>..................................</td>
<td>20,969</td>
</tr>
</tbody>
</table>

1 There are no capital costs or operating and maintenance costs associated with this collection of information.

Based on a review of the information collection since our last request for OMB approval, we have made no adjustments to our burden estimate.

Dated: November 18, 2020.

Lauren K. Roth,
Acting Principal Associate Commissioner for Policy.

[FR Doc. 2020-26059 Filed 11-24-20; 8:45 am]

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**Termination of the Food and Drug Administration’s Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective**

**AGENCY:** Food and Drug Administration (FDA), Department of Health and Human Services (HHS).

**ACTION:** Notice; request for information.

**SUMMARY:** The Department of Health and Human Services is issuing this Notice to withdraw FDA’s Marketed Unapproved Drugs—Compliance Policy Guide, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs, and to request information from the public regarding drugs that may be grandfathered or generally recognized as safe and effective.

**DATES:** Part I of this Notice shall be effective thirty days from the date of publication in the Federal Register. To be considered, responses and comments related to Part II of this Notice must be received electronically at the email
The Department will consider information submitted by the public in response to Part II of this Notice on a rolling basis, and until further notice.

ADDRESSES: Responses to Part II must be submitted electronically, and should be addressed to Import@hhs.gov. In the subject line of the email message, submissions should include “GRASE RFI Response.”

FOR FURTHER INFORMATION CONTACT: Nick Uehlecke, 200 Independence Ave. SW, Washington, DC 20201; or by email at Import@hhs.gov; or by telephone at 1–877–696–6775.

SUPPLEMENTARY INFORMATION: The Trump Administration, through the Department of Health and Human Services (HHS), is continuing its efforts to reduce the price of prescription drugs. This Notice addresses two related but distinct issues: (1) The Food and Drug Administration’s (FDA) Unapproved Drugs Initiative (UDI) and (2) the construction of the statutory exemptions from the definition of “new drugs” subject to FDA approval under the federal Food, Drug, and Cosmetic Act (FD&C Act), namely so-called pre-1938 grandfathered drugs and drugs that are “generally recognized as safe and effective” or “GRASE.”

I. Unapproved Drugs Initiative

In 1938, Congress created the modern scheme for federal regulation of drugs. Before 1938, there was no requirement under federal law for a manufacturer to obtain FDA approval before marketing a drug. Today, as a general rule, under the FD&C Act, a “new drug” must be approved by the FDA for safety and efficacy pursuant to an approved New Drug Application (ANDA) before the drug is introduced into interstate commerce. See FD&C Act 21 U.S.C. 321(p) (defining “new drug” under the Act); FD&C Act 505(a), 21 U.S.C. 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug."). A “person” that introduces a “new drug” into interstate commerce is subject to, among other sanctions, injunctions and/or having the subject product seized in an ex parte proceeding under admiralty rules. See FD&C Act 302, 21 U.S.C. 332 (injunction authority); FD&C Act 304, 21 U.S.C. 334 (seizure authority).

Not all drugs are “new drugs” which require FDA approval. There are two primary carve-outs from the FD&C Act’s definition of “new drug.” First, when Congress enacted the modern FD&C Act in 1938, it exempted from the definition of “new drug” all drugs “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.” FD&C Act 201(p)(1), 21 U.S.C. 321(p)(1). Second, drugs that are generally recognized as safe and effective which have also “been used to a material extent or for a material time” are not “new drugs.” FD&C Act 201(p)(1) and 21 U.S.C. 321(p)(1) and (2). Drugs that meet either of these exceptions may be legally marketed without FDA pre-approval for safety and efficacy, subject to the agency’s other regulatory authorities.

Through a guidance document issued in 2006 and later revised in 2011, and without conducting notice-and-comment rulemaking, FDA launched a program called the Unapproved Drugs Initiative (UDI). The UDI sprang from a laudable objective, namely to reduce the number of unapproved drugs on the market. To achieve this end, FDA provided in its 2011 UDI Guidance that “the first company to obtain an approval [of a previously unapproved drug] will have a period of de facto market exclusivity before other products obtain approval.” The agency “hope[d] that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.” Ultimately, manufacturers of older drugs previously thought to be exempt from the FDA approval requirement obtained market exclusivity for those products after FDA took unapproved versions off the market. An unintended consequence of the “period of de facto market exclusivity” provided by the UDI allowed manufacturers an opportunity to raise prices in an environment largely insulated from market competition.

Based on its ongoing review of FDA regulatory programs, the Department has decided to withdraw the 2006 and 2011 Guidance, effective thirty days after the date of publication of this Notice in the Federal Register. All compliance manuals, website statements, and other informal issuances with respect to the 2006 and 2011 Guidance are also hereby withdrawn. The withdrawal of the 2006 and 2011 Guidance Documents complies with FDA’s current Good Guidance Practices regulation, which allows for “periodic[] review of[] existing guidance documents to determine whether they need to be changed or withdrawn.” 21 CFR 10.115(k)(1). Nothing in this Notice otherwise limits FDA’s authority to take action against manufacturers of unapproved drugs that meet the statutory definition of a “new drug” (such as, for example, an unapproved drug that claims to mitigate, treat, or cure COVID–19) or violate the FD&C Act in other ways. Further, nothing in this Notice limits FDA’s grant of regulatory exclusivities authorized by statute, such as new chemical entity exclusivity, orphan drug exclusivity, or pediatric exclusivity. This Notice does not apply to drugs subject to (1) Investigational New Drug applications (IND) that are in effect as of the effective date of this Notice, (2) any subsequent NDA based on new clinical trial investigations (other than bioavailability studies) derived under such IND, and (3) existing approved NDAs.

The Department is withdrawing the 2006 and 2011 Guidelines for several evidence-based reasons. After the UDI began, reports emerged that Americans were paying significantly more for prescription drugs approved by FDA through the UDI than they had paid previously. One report noted that a drug approved through the UDI “sells for about $4.50 a tablet—nearly 50 times the price of the unapproved version.” Another report asserted that “[t]hanks at least partially to the FDA program, the price of vasopressin . . . has risen 10-fold” and the cost of “a vial of..."
neostigmine ... has gone from less than $5 to $90."16  

In 2017, scholars from the Yale School of Medicine and the University of Utah published a peer-reviewed study corroborating the previous reports.7 The study reviewed 34 drugs subject to the UDI between 2006 and 2015. The scholars found the average wholesale unit price of 26 of the 34 drugs for which pricing data was available increased by a median of 37% (interquartile range of 23%–204%).8  

The average wholesale unit price of 11 of the drugs surveyed in the study increased by more than 128%.9  

The study also linked the UDI to drug shortages, which the authors defined as "a supply issue that affects how a pharmacy prepares or dispenses a drug product that influences patient care when prescribers must use an alternative agent."10 In this regard, the scholars found that 24 of the 34 drugs experienced shortages after FDA took enforcement action after an entity obtained FDA approval of a previously unapproved drug. The median shortage was 217 days.11  

Finally, the authors considered whether the UDI generated new clinical data evidence for older drugs. The authors found that, of the nineteen drugs that obtained FDA approval during the study period, only two were supported by "new clinical trial evidence."12 The other seventeen drugs "were supported by literature reviews and bioequivalence to older drug products."13  

Therefore, the Department has concluded that while the UDI began subject to the UDI between 2006 and 2011 Guidance remaining in effect. In Dep’t of Homeland Sec. v. Regents of the Univ. of California, 140 S. Ct. 1891 (2020), the Supreme Court struck down the Department of Homeland Security’s rescission of the Deferred Action for Childhood Arrivals (DACA) program. The Department believes that rescinding the 2006 and 2011 Guidance will have a positive impact on public health. Moreover, eliminating this program allows FDA’s resources to be directed toward monitoring unapproved "new drugs" that fall squarely within the traditional scope of the definition of that term in the FD&C Act. At the same time, the Notice allows FDA to use its limited review resources on innovative potential therapies, as opposed to older drugs with longstanding use.  

Besides, any reliance interests (if they existed) would be minimal. This Notice does not apply to drugs subject to (1) INDs in effect as of the effective date of this Notice, (2) any subsequent NDA based on new clinical investigations (other than bioavailability studies) derived under such IND, and (3) existing approved NDAs.  

II. Pre-1938 Grandfathered and GRASE Drugs: Request for Information  

As noted above, when Congress enacted the FD&C Act in 1938 and later amended the Act in 1962, it exempted certain drugs from the FDA approval requirement. Section 201(p) of the FD&C Act, 21 U.S.C. 321(p), excludes from the definition of "new drug" certain drugs marketed prior to June 25, 1938 and drugs generally recognized as safe and effective, or GRASE. In the 2011 Guidance, FDA stated that "it is not likely that any currently marketed prescription drug is grandfathered or is otherwise not a new drug," though the
agency stated “that it is at least theoretically possible.”

That was not always the case. For many years, FDA acknowledged that at least some drugs are not “new drugs” subject to FDA approval prior to marketing. In a 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.” In the same publication, the agency went on to identify specific products, noting “commonly used large volume intravenous products are not included on the List of [FDA-approved drugs] (e.g., dextrose 5% with water, dextrose 10% with water, sodium chloride 0.9% injection).” since “all of these drug products came on the market in glass containers before 1938 and have not been required to obtain an approved new drug application as a condition of marketing.”

In the 2000 edition of the Orange Book, FDA cited to the barbiturate “Phenobarbital Tablets” as an example of “pre-1938 drugs.”

The 2011 Guidance, issued absent notice-and-comment rulemaking and without prior public comment, contains no acknowledgement of these prior positions.

This evolution in the agency’s thinking has had consequences. Under the UDI, FDA required the manufacturer of an epinephrine brand which originally came onto the market in 1901 to submit an NDA. The drug colchicine, a product FDA acknowledged “was available in oral dosage form during the 19th century,” was also approved through the UDI. The interpretation of the definition of “new drug” espoused in the 2011 Guidance essentially foreclosed the possibility that these two century-old drugs were pre-1938 grandfathered drugs exempt from the approval process. The 2017 study discussed above found that the average wholesale unit price of epinephrine and colchicine increased by 58.3% and 3,323.5%, respectively, costs absorbed by American patients and taxpayers.

The regulatory history of the prescription drug Daraprim raises similar issues. FDA originally approved Daraprim (pyrimethamine) for safety in 1953, and later deemed the drug effective through the Drug Efficacy Study Implementation, or DESI review process. The drug is listed on the World Health Organization’s List of Essential Medications, “a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions.” In 2015, the company Turing Pharmaceuticals “raised the price [of the drug] to $750 a tablet from $13.50, bringing the annual cost of treatment for some patients to hundreds of thousands of dollars.”

Turing came by this windfall, at least in part, because of FDA’s interpretation of the definition of “new drug” in the FD&C Act as articulated in the 2006 and 2011 Guidance, a view that foreclosed the possibility that Daraprim, a drug more than sixty years old, could ever qualify as GRASE. That position effectively prevented other manufacturers of generic versions of this product from entering the market without an approved abbreviated new drug application, allowing Turing to enjoy a single-source position in the marketplace while potential competitors went through the regulatory process. In February 2016, Congress held a hearing on this widely-publicized issue. Ultimately, FDA approved a generic competitor for this single-source drug in February 2020.

The Department wishes to engage with the public on the contours of the exceptions to the definition of “new drug.” In this regard, HHS is reviewing whether certain drugs, including the drug subject to Congressional scrutiny in 2016, might qualify as exempt from the FDA approval requirement. To aid that effort, HHS asks for input from patients, health care providers, industry, and other stakeholders to provide information responsive to any of the topics below:

1. Lists of drugs marketed prior to June 25, 1938 that are currently available on the market.
2. The extent to which drugs marketed prior to June 25, 1938, or drugs that might qualify as GRASE, have regulatory approvals in countries outside the United States.
3. 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.
4. Any published literature reviews or clinical studies related to any drugs potentially exempt from the new drug approval requirement.


Alex M. Azar II,
Secretary, Department of Health and Human Services.

[FR Doc. 2020–26133 Filed 11–24–20; 8:45 am]

BILLING CODE 4150–26–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–D–0529]

Qualification Process for Drug Development Tools; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration’s (FDA or Agency) Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) are announcing the availability of a final guidance for industry and FDA staff entitled “Qualification Process for Drug Development Tools.” Under the 21st Century Cures Act (Cures Act), enacted on December 13, 2016, a new section was added to the Federal Food, Drug, and Cosmetic Act (FD&C Act), which defined a three-stage qualification process for drug development tools (DDTs). This guidance meets the Cures