TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]—Continued

Type of information	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response (hours)	Total hours
Recommended information to be included when firms choose to disseminate HCEI materials to payors about approved or cleared medical devices.	236	10	2,360	20	47,200
Recommended information to be included when firms choose to disseminate information about unapproved products or unapproved uses of approved or cleared products.	717	2	1,434	.5 (30 minutes)	717
Followup information to payors regarding previously communicated about unapproved products or unapproved uses of approved or cleared products.	359	2	718	2	1,436
Total					137,353

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

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 314.81(b)(3)(i) (Form FDA 2253) have been approved under OMB control number 0910–0001.

FDA is issuing this final guidance subject to OMB approval of the collections of information. Before implementing the information collection provisions of the guidance, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the collections of information, including OMB control number(s) for newly approved collections.

III. Electronic Access

Persons with access to the internet may obtain the guidance at *https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm,* or *https://www.regulations.gov.*

Dated: June 7, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–12632 Filed 6–12–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–2065]

Alternative or Streamlined Mechanisms for Complying With the Current Good Manufacturing Practice Requirements for Combination Products; Proposed List Under the 21st Century Cures Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: As required by the 21st Century Cures Act (Cures Act), the Food and Drug Administration (FDA or Agency) is proposing a list of alternative or streamlined mechanisms for complying with the current good manufacturing practice (CGMP) requirements for combination products. Combination products are products composed of two or more different types of medical products (drug, device, and/or biological product).

DATES: Submit either electronic or written comments on this notice by September 11, 2018 to ensure that the Agency considers your comment on this proposed list before it begins work on the final list.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before September 11, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of September 11, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and

identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2018–N–2065 for ''Alternative or Streamlined Mechanisms for Complying with Current Good Manufacturing Practice (CGMP) Requirements for Combination Products.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Melissa Burns, Office of Combination Products, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5125, Silver Spring, MD 20993, 301–795–5616, *melissa.burns@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

In December 2016, the Cures Act (Pub. L. 114–255) was signed into law. Section 3038(c) of the Cures Act mandated that FDA publish in the **Federal Register** a list identifying types of combination products and manufacturing processes for which ''good manufacturing processes'' may be adopted that vary from the requirements set forth in § 4.4 (21 CFR 4.4) or that FDA proposes can satisfy the requirements in § 4.4 through ''alternative or streamlined mechanisms,'' and to review this list periodically. In accordance with this statutory mandate, FDA is publishing a proposed list in section II of this document, which addresses processes for single-entity and co-packaged combination products that can satisfy requirements in § 4.4 through alternative or streamlined mechanisms (hereafter ''mechanisms'').

On January 22, 2013, FDA issued a final rule on CGMP requirements for combination products (see 78 FR 4307 and part 4 (21 CFR part 4, subpart A)). Prior to issuance of the final rule, although CGMP regulations were in place to establish requirements for drugs, devices, biological products, and human cells, tissues, or cellular or tissue-based products (HCT/Ps), there were no regulations to clarify and explain the application of these CGMP requirements to combination products. The final rule clarified which CGMP requirements apply to combination products. It also established a transparent and streamlined regulatory framework for combination product manufacturers to use when demonstrating compliance with applicable CGMP requirements.

A combination product is a product composed of two or more different types of medical products (*i.e.,* a combination of a drug, device, and/or biological product). The drugs, devices, and biological products included in combination products are referred to as ''constituent parts'' of the combination product. Combination products include ''single-entity'' combination products that are physically, chemically, or otherwise combined or mixed and produced as a single entity (§ 3.2(e)(1) (21 CFR 3.2(e)(1)) (*e.g.,* prefilled syringes and drug-eluting stents) and ''co-packaged'' combination products where two or more separate products are packaged together in a single package or as a unit and composed of drug and device products, device and biological products, or biological and drug products (§ 3.2(e)(2)) (*e.g.,* a surgical or first-aid kit).[1] Section 4.4 outlines how manufacturers of single-entity and co-packaged combination products (hereafter ''CP manufacturers'') can demonstrate compliance with applicable CGMP requirements, including through implementation of a streamlined approach to meet the requirements of both the drug CGMP and the device Quality System (QS) regulation by designing and implementing a CGMP operating system that demonstrates compliance with either of the following:

• The drug CGMP regulations in parts 210 and 211 (21 CFR parts 210 and 211) and the following specified provisions from the device QS regulation (§ 4.4(b)(1), ''drug CGMP-based streamlined approach''): (1) § 820.20 (21 CFR 820.20) Management responsibility, (2) § 820.30 (21 CFR 820.30) Design controls, (3) § 820.50 (21 CFR 820.50) Purchasing controls, (4) § 820.100 (21 CFR 820.100) Corrective and preventive action, (5) § 820.170 (21 CFR 820.170) Installation, and (6) § 820.200 (21 CFR 820.200) Servicing; or

• The device QS regulation in part 820 (21 CFR part 820) and the following specified provisions from the drug CGMP regulations (§ 4.4(b)(2), ''device QS regulation-based streamlined approach''): (1) § 211.84 (21 CFR 211.84) Testing and approval or rejection of components, drug product containers, and closures; (2) § 211.103 (21 CFR 211.103) Calculation of yield; (3) § 211.132 (21 CFR 211.132) Tamper-evident packaging requirements for

[1] There are also ''cross-labeled'' combination products (§ 3.2(e)(3) and (4)). With respect to cross-labeled combination products, part 4, subpart A was intended to clarify only that the CGMP requirements applicable to the drugs, devices, or biological products also apply to these types of articles when they are constituent parts of such combination products. Constituent parts of cross-labeled combination products need only comply with the requirements otherwise applicable to that type of product (*e.g.,* 21 CFR parts 210 and 211 for a drug constituent part or 21 CFR part 820 for a device constituent part). The ''streamlined approach'' and related mechanisms described in this notice are generally not relevant or applicable to cross-labeled combination products. However, to the extent that the constituent parts of a cross-labeled combination product are manufactured at the same facility, the manufacturing process would be akin to when the manufacture of the constituent parts of a co-packaged combination product occurs at the same facility. Accordingly, as discussed in the combination product CGMP guidance (Ref. 1), for cross-labeled combination products manufactured at the same facility, the Agency does not intend to object to the use of a streamlined CGMP operating system for the manufacture of the combination product rather than distinct systems for the manufacture of each constituent part that is occurring at that facility.

over-the-counter (OTC) human drug products; (4) § 211.137 (21 CFR 211.137) Expiration dating; (5) § 211.165 (21 CFR 211.165) Testing and release for distribution; (6) § 211.166 (21 CFR 211.166) Stability testing; (7) § 211.167 (21 CFR 211.167) Special testing requirements; and (8) § 211.170 (21 CFR 211.170) Reserve samples.

If the combination product includes a biological product constituent part, the CGMP operating system must also demonstrate compliance with applicable CGMP requirements for biological products in parts 600 through 680 (21 CFR parts 600 through 680), and if the combination product includes an HCT/P, the CGMP operating system must also demonstrate compliance with the applicable current good tissue practice requirements in part 1271 (21 CFR part 1271).

Following publication of the final rule, FDA reviewed data and rationales provided by manufacturers who proposed various means of addressing CGMP considerations for combination products. FDA also considered feedback on its draft guidance on CGMP requirements for combination products, published in January 2015, in which stakeholders requested further guidance on circumstances in which flexible approaches may be available and how to engage with FDA on them. The final ''Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products'' includes discussion of existing mechanisms to comply with the final rule and of circumstances in which FDA did not intend to object to manufacturers applying practices that vary from the requirements set forth in the rule (Ref. 1). The Agency continues to apply a risk-based approach to evaluating methods for ensuring the quality of combination products and to welcome proposals from manufacturers for how to enhance the efficiency of development and manufacturing activities, while ensuring the safety and effectiveness of the combination products produced.

II. Proposed List of Mechanisms for Complying With § 4.4 CGMP Requirements for Combination Products

A. Introduction

The following is a proposed list of mechanisms for demonstrating compliance with relevant combination product CGMP requirements, as described below. Where applicable, reference is made to sections of the ''Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products'' for additional information (Ref. 1). FDA will continue to evaluate this list in light of Agency experience and stakeholder input. Manufacturers are welcome to propose other approaches not described, and FDA continues to encourage dialogue with the Agency on various means of demonstrating CGMP compliance for combination products.

For each mechanism described below, CP manufacturers should consider what documentation would be sufficient to support that the mechanism, including the specific approach for implementing it, assures appropriate control of the manufacture of the combination product to ensure safety and effectiveness of the product. Appropriate evidence and an explanation of the rationale to support the approach should be accessible at the manufacturing facility for review during facility inspections. For additional discussion on how to interact with FDA regarding the mechanisms described below, see section III.

B. Mechanisms for Complying With Drug CGMP Requirements (Part 211) Specified in § 4.4 [2]

FDA interprets the mechanisms identified in the sections below as a means to demonstrate compliance with the specified part 211 requirements identified in § 4.4:

1. Section 211.165 Testing and Release for Distribution

Use of product samples that are not finished combination products (but that are representative of the finished combination product with respect to the characteristics and attributes being tested) when performing testing required by § 211.165 to determine whether the drug constituent part meets final specifications. To meet the requirements of § 211.165, the CP manufacturer would need to establish, including where appropriate through bridging studies and other quantitative means, that any differences in the manufacturing process for the representative samples as compared to the finished combination product do not affect the drug constituent part. For example, as part of product release testing, drug-eluting lead manufacturers could perform release testing for identity, potency, or other quality attributes on a representative lead tip assembly that contains the drug constituent part, but does not contain the full electronic and mechanical assembly, so long as they can establish that the differences in the manufacturing process do not impact the drug constituent part and the sample is representative of the finished combination product with respect to the quality attributes being tested.

(See also Section IV.B.5 of Reference 1 for additional information on testing and release for combination products.)

2. Section 211.166 Stability Testing

Use of bracketing and matrixing approaches to stability studies for combination products. Principles for bracketing and matrixing approaches to meet the requirements of § 211.166 have already been addressed by the Agency with regard to drug products (Ref. 2), and such principles can also be applied to combination products. For example, when assessing stability for a prefilled syringe that is marketed in various fill volumes, one of the approaches that a CP manufacturer could utilize, if appropriate, is bracketing based on the smallest and the largest fill volume of product configurations. In determining the extremes for a bracketing approach and/or when justifying the use of a matrix design for single-entity combination products, it is important that the drug-device interactions and variations in the manufacturing processes are considered. For co-packaged combination products, such approaches can be applied to the drug constituent part of the product.

Leveraging stability data for an already marketed combination product. Such mechanisms can be considered when the new combination product is a modification of an already marketed product and the modification does not impact the stability of the drug constituent part. For example, when developing new lengths of a drug-coated catheter product for which the catheter materials, drug coating, manufacturing process, and packaging configurations are largely unchanged from existing marketed sizes, the CP manufacturer would generally be able to leverage existing stability data to establish initial product shelf life or to support reduced stability data requirements, so long as characteristics of the product that could impact stability (materials, packaging configuration, etc.) remain the same. However, if the device constituent part of a drug-coated catheter includes a new material that is in contact with the drug coating, for example, new stability studies would generally be needed under § 211.166.

[2] Several drug CGMP mechanisms included in this proposed list depend upon use of a more broadly defined batch. FDA notes that approaches that depend upon broadly defined batches may increase the number of distributed products implicated when corrective actions are necessary to address postmarket issues.

(See also Section IV.B.6 of Reference 1 for additional information on stability requirements for combination products.)

3. Section 211.167 Special Testing Requirements

Defining ''batch'' based on the drug constituent part rather than the finished combination product for purposes of special testing requirements for pyrogens and endotoxins. For example, a manufacturer of a combination product that has a sub-assembly coated with a drug, which is then incorporated into several ''batches'' or ''lots'' of the overall combination product, may be able to define a batch for purposes of pyrogen and endotoxin testing as a batch of that sub-assembly for purposes of meeting the requirements of § 211.167. As with the other mechanisms described in this list, this mechanism would only potentially be available if there would be no impact on the drug constituent part from subsequent manufacturing processes, including when the constituent parts are combined to produce the final combination product. CP manufacturers should consider whether such risks may be introduced later in the production process (after the batch has been defined). This approach will most frequently apply for co-packaged combination products or single-entity combination products for which only a component or sub-assembly of the overall product is in contact with the drug constituent part.

(See also Section IV.B.7 of Reference 1 for additional information on special testing requirements for combination products.)

4. Section 211.170 Reserve Samples

Keeping reserve samples that are representative of the finished combination product. CP manufacturers may use validated surrogates as representative samples to meet the requirements of § 211.170, provided the surrogate is appropriate, both in terms of the manufacturing process and the characteristics of the container closure. For example, maintaining only a sub-assembly of a coated single-entity combination product or only the drug constituent part of a co-packaged combination product as a reserve sample would generally be permissible under the regulation when: (1) All manufacturing process steps after the coating step or the fill for the drug constituent part are shown not to affect the drug constituent part, (2) the immediate container closure has essentially the same characteristics as that for the drug constituent part as packaged in the combination product for distribution, and (3) the representative samples are suitable for all required testing of the drug constituent part for which the reserve samples are being kept.

Using samples from representative lots of a larger batch for retention of reserve samples. To meet the requirements of § 211.170, CP manufacturers may be able to use bracketing and matrixing approaches to retain reserve samples from certain lots to adequately represent the broadly defined batch of the combination product. For example, CP manufacturers might be able to retain reserve samples of appropriately varied sizes of a drug-coated combination product from within a broadly defined batch that includes multiple lots of different sizes.

(See also Section IV.B.8 of Reference 1 for additional information on reserve sample requirements for combination products.)

C. Mechanisms for Complying With Device Quality System Requirements (Part 820) Specified in § 4.4

FDA interprets the mechanisms identified in the sections below as a means to demonstrate compliance with the specified part 820 requirements identified in § 4.4:

1. Section 820.30 Design Controls

Using existing pharmaceutical development practices and documentation that align with the design control principles and requirements of § 820.30. Robust pharmaceutical development practices would address many design control requirements to assure compliance with § 820.30, where applicable. CP manufacturers need to demonstrate how development processes and terminology align with design control principles and requirements in § 820.30, when required, including, where necessary, developing additional design control elements. When evaluating the adequacy of existing pharmaceutical development processes, particular attention should be given to postmarket management of design changes to the combination product and the alignment of change control practices with the principles and requirements of § 820.30, as applicable.

2. Exemption of Combination Products From Device QS Regulation

Exemption of the combination product from all or certain provisions of the device QS regulation (part 820) if the device constituent part of the combination product is itself exempt from such requirements and use of the device constituent part falls within the scope of the relevant exemption, including with respect to the device constituent part's intended use. Some devices are exempt from all or certain provisions of the device QS regulation (see, for example, liquid medication dispensers such as cups and droppers that fall within the scope of § 880.6430 (21 CFR 880.6430), provided the use of the device is not a new intended use or does not otherwise raise different safety and effectiveness questions (see, for example, limitations to the exemption under 21 CFR 880.9). Consistent with this, for the combination product to be exempt from the associated provisions of the device QS regulation, we interpret this exemption to mean that the use of the device in the combination product must not be a new intended use or otherwise raise different safety and effectiveness questions for the device. This circumstance will most frequently apply to co-packaged combination products. For example, an oral dosing syringe (a liquid medication dispenser under § 880.6430) that is co-packaged with a drug may be exempt from certain provisions of the device QS regulation (and hence the combination product may also be exempt from such provisions); however, incorporation of such a dispenser into a primary container closure system or co-packaging of such a dispenser with an emergency-use product, for example, may constitute a new intended use for the dispenser or raise different safety and effectiveness questions for the dispenser, such that the relevant exemption would not apply.

(See also Section III.C.3 of Reference 1 for additional information on the exemption from provisions of the device QS regulation for combination products.)

III. Interacting With FDA on Mechanisms for Complying With CGMP for Combination Products

1. Process for Interacting With FDA

In some cases, CP manufacturers may interact with FDA to gain approval or otherwise notify FDA of a manufacturing change. In other cases, although a submission or notification is not required, CP manufacturers may want to discuss potential use of CGMP mechanisms with FDA. CP manufacturers are encouraged to interact early with FDA on contemplated CGMP mechanisms.

- *Pre-Submissions and Meeting Requests.* CP manufacturers who want to obtain FDA feedback prior to submitting a premarket application or a postmarket supplement or who otherwise want to obtain feedback on

their approach may interact with FDA via the existing established process applicable to the lead Center [3] for the combination product. For combination products reviewed under a new drug application (NDA) or a biologics license application (BLA), such interactions will generally be through Type C meetings (Ref. 3).[4] For combination products reviewed under an abbreviated new drug application (ANDA), these interactions will generally be through pre-ANDA meetings (Ref. 4).[5] For combination products reviewed under a device premarket submission (*e.g.,* a premarket approval application (PMA), de novo classification, or premarket notification (510(k)), these interactions will generally be via the pre-submission process (Ref. 5).

Regardless of the type of submission, such interactions should be focused on a general discussion of the mechanism and CGMP approach the CP manufacturer wishes to pursue and associated justification to support the approach. Only representative data is typically appropriate in these interactions; complete data should be included in the subsequent premarket submission or postmarket supplement, if required, and/or be maintained at the manufacturing facility, as appropriate.[6]

• *Premarket Review.* CP manufacturers should include in their original submission for NDAs, BLAs, ANDAs, and PMAs information on any mechanisms for complying with CGMP requirements. For PMAs, this information should be included in the manufacturing section of the PMA. For information regarding where to place information in NDAs, BLAs, or ANDAs, refer to ''eCTD Technical Conformance Guide'' (Ref. 6).

• *Postmarket Supplements or Notifications to FDA.* Postmarket changes to implement a combination product CGMP mechanism for NDAs, ANDAs, BLAs, and PMAs, may require submission of a supplement or notification to FDA.[7] CP manufacturers should consult related guidances relevant to the type of constituent part of the combination product (Refs. 7 to 9).[8] If a CP manufacturer has questions on the appropriate submission type or the need for a submission, they can contact the lead Center for assistance.

2. Content Suggestions

When submitting information on a CGMP mechanism, along with any submission requirements applicable to the submission type, the following content should be included:

• *Applicable CGMP regulation.* Identify the CGMP regulation applicable to the described mechanism. For example, if a submission includes a mechanism related to stability testing, indicate that § 211.166 is the applicable CGMP requirement.

• *Applicable Products.* If the mechanism is to be applied to multiple products and/or product configurations, list all related sizes, strengths, etc., as well as all related application numbers.

• *Related Interactions with FDA.* If the CP manufacturer has had previous interactions with FDA relevant to the proposed mechanism, either for the product addressed in the submission or for related products, the CP manufacturer should provide reference to those interactions. Where applicable, the CP manufacturer may cross-reference previously submitted information.

• *Justification and Scientific Data.* Include a rationale to support that the proposed mechanism assures adequate manufacturing control to ensure product safety and effectiveness. When describing a CGMP mechanism in a premarket or postmarket submission, the description should be accompanied by data necessary to support the approach. When proposing a change from a CGMP approach that was reviewed previously by FDA, such justification should include analysis of how the proposed approach compares to the previously reviewed approach as an effective manufacturing control, including representative data, as appropriate, to substantiate the analysis.

3. FDA Engagement

CP manufacturers are encouraged to discuss combination product CGMP mechanisms with FDA. Any questions on how to engage FDA in such discussions should be directed to the lead Center for the product or the Office of Combination Products, as needed.

4. FDA Review

FDA may review information from a CP manufacturer related to a mechanism for complying with CGMP requirements for combination products in premarket applications, postmarket supplements or notifications, pre-submissions and meetings, and during facility inspections. FDA may determine that the data and rationale presented by a CP manufacturer for a particular mechanism are insufficient to demonstrate that the mechanism, as proposed or implemented, meets the applicable CGMP requirement. FDA generally will notify the CP manufacturer and/or applicant in writing of any such determination.

IV. Other Issues for Consideration

We have developed this proposed list of mechanisms based on information submitted to FDA by CP manufacturers as well as FDA experience with manufacturing processes and CGMP compliance approaches that have been shown through appropriate data and rationales to support the manufacture of safe and effective products. FDA requests comment from stakeholders who believe there are additional types of combination products and/or manufacturing processes where different approaches may be appropriate. When providing such feedback, the suggested approach should be:

• Applicable to a type or range of combination products (*e.g.,* not just a single CP manufacturer's product). Commenters should indicate to which types of combination products or manufacturing processes they believe the suggested approach should apply.

• Supported by adequate data and rationales to demonstrate that such an approach would continue to support manufacturing of safe and effective combination products. Commenters should summarize the data and rationale that support the suggested approach.

Any confidential information submitted to FDA via the docket should be appropriately identified (see *Instructions* above, in **ADDRESSES**).

V. Paperwork Reduction Act

This notice refers to previously approved collections of information

[3] A combination product is assigned to an Agency center (Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, or Center for Devices and Radiological Health) that will have primary jurisdiction (*i.e.,* the ''lead Center'') for that combination product's review and regulation. Assignment of a combination product to a lead Center is based on a determination of which constituent part provides the primary mode of action of the combination product (21 U.S.C. 353(g)).

[4] When final, this guidance will represent the FDA's current thinking on this topic.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

[6] Note that when discussing a mechanism for complying with CGMP requirements for which the CP manufacturer is leveraging information in master file(s), the master file holder must submit a letter of authorization to permit FDA to review such information (see 21 CFR 314.420(d) and 21 CFR 814.20(c)). The specific information within the master file that is being leveraged should be clearly identified to FDA.

[7] Requirements for postmarket supplements are contained, for example, in 21 CFR 314.70 (NDAs), 21 CFR 601.12 (BLAs), and 21 CFR 814.39 (PMAs). Any questions on whether FDA review is required for a postmarket CGMP mechanism should be directed to the lead Center.

[8] With reference to Ref. 8, when final, this guidance will represent the FDA's current thinking on this topic.

found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). We note that the information collected under the underlying CGMP regulations for drugs, devices, and biological products, including current good tissue practices for HCT/Ps, found in parts 211, 820, 600 through 680, and 1271, have already been approved and are in effect. The provisions of part 211 are approved under the OMB control number 0910–0139. The provisions of part 820 are approved under OMB control number 0910–0073. The provisions of parts 606 and 640 are approved under OMB control number 0910–0116. The provisions of part 610 are approved under OMB control number 0910–0116 and OMB control number 0910–0338 (also for part 680). The provisions of part 1271, subparts C and D, are approved under OMB control number 0910–0543.

We note that the information collected under the related submission types have already been approved and are in effect. The collections of information regarding formal meetings with sponsors and applicants have been approved under OMB control number 0910–0429. The collections of information regarding new drug approvals (NDA) and abbreviated new drug applications (ANDA) have been approved under OMB control number 0910–0001. The collections of information regarding pre-ANDAs have been approved under OMB control number 0910–0797. The collections of information regarding pre-submissions have been approved under OMB control number 0910–0756. The collections of information regarding PMAs have been approved under OMB control number 0910–0231. The collections of information for premarket notification (510(k)) have been approved under OMB control number 0910–0120. The collections of information for the de novo classification process have been approved under OMB control number 0910–0844. The collections of information regarding biologics license applications have been approved under OMB control number 0910–0338.

VI. References

The following references are on display in the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. ''Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products,'' January 2017. *https://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.*
2. ''Guidance for Industry: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products,'' January 2003. *https://www.fda.gov/downloads/Drugs/Guidances/ucm073379.pdf.*
3. ''Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,'' December 2017. *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf.*
4. ''Draft Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA,'' October 2017. *https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf.*
5. ''Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff,'' September 2017. *https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.*
6. ''eCTD Technical Conformance Guide,'' November 2017. *https://www.fda.gov/downloads/Drugs/UCM465411.pdf.*
7. ''Guidance for Industry: Changes to an Approved NDA or ANDA,'' April 2004. *https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf.*
8. ''Draft Guidance for Industry: Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products,'' December 2017. *https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM590118.pdf.*
9. ''Guidance for Industry and FDA Staff: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes,'' April 2011. *https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf.*

Dated: June 7, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–12634 Filed 6–12–18; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2014–D–0223]

Humanitarian Device Exemption Program; Draft Guidance for Industry and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of the draft guidance entitled ''Humanitarian Device Exemption (HDE) Program.'' This draft guidance concerns the HDE program as a whole and, among other topics, it explains the criteria FDA considers to determine if ''probable benefit'' has been demonstrated as part of the Agency's decision-making process regarding marketing authorization for a humanitarian use device (HUD). The draft guidance also incorporates recent amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act) that affect the HDE program and answers other common questions that we receive about the program. This draft guidance is not final nor is it in effect at this time.

DATES: Submit either electronic or written comments on the draft guidance by August 13, 2018 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*