strengths, these strengths have also been discontinued. On our own initiative, we have also determined whether these strengths were withdrawn for safety or effectiveness reasons.

After considering the citizen petition and reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that CUBICIN (daptomycin) Powder for Injection, 250 mg/vial and 500 mg/vial, and CUBICIN RF (daptomycin) Powder for Injection, 500 mg/vial, were not withdrawn from sale for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that these drug products were withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of CUBICIN (daptomycin) Powder for Injection, 250 mg/vial and 500 mg/vial, and CUBICIN RF (daptomycin) Powder for Injection, 500 mg/vial, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would indicate that these drug products were withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list CUBICIN (daptomycin) Powder for Injection, 250 mg/vial and 500 mg/vial, and CUBICIN RF (daptomycin) Powder for Injection, 500 mg/vial, in the ''Discontinued Drug Product List'' section of the Orange Book. The ''Discontinued Drug Product List'' delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to these drug products may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for these drug products should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: August 2, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023–16775 Filed 8–4–23; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2020–D–1530]

Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a final guidance for industry entitled ''Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs).'' This guidance provides applicants and manufacturers of drugs, including prescription and over-the-counter (OTC) drug products, with a recommended framework for predicting the mutagenic and carcinogenic potential of NDSRIs that could be present in drug products and recommends acceptable intake (AI) limits for NDSRIs. NDSRIs, which are a subcategory of nitrosamine impurities that share structural similarity to the active pharmaceutical ingredient (API) in drug products, typically lack compound-specific mutagenicity and carcinogenicity data to inform safety assessments. This guidance provides a recommended methodology for AI determination that uses structural features of NDSRIs to generate a predicted carcinogenic potency categorization and corresponding recommended AI limit that manufacturers and applicants can apply, in the absence of other FDA-recommended AI limits, in their evaluation of potential impurities in their drug products.

DATES: The announcement of the guidance is published in the **Federal Register** on August 7, 2023.

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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*.
- 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–2020–D–1530 for ''Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs).'' Received comments 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, 240–402–7500.

- 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.govinfo.gov/content/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, 240–402–7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Bldg., 4th Floor, Silver Spring, MD 20993–0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Jason Bunting, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6366, Silver Spring, MD 20993–0002, 301–796–1292.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled ''Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs).'' FDA is implementing this guidance without prior public comment because we have determined that prior public participation is not feasible or appropriate (§ 10.115(g)(2)). FDA made this determination because of the importance of providing additional timely information to manufacturers and applicants regarding recommended AI limits of NDSRIs, a class of nitrosamine impurities that has been identified in many drug products and also could be present in APIs. This guidance applies to drugs, including prescription and OTC drug products that are the subject of an approved or pending new drug application (NDA) or abbreviated new drug application (ANDA), as well as products [1] not marketed under a drug application, including nonprescription drugs subject to section 505G (21 U.S.C. 355h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (*i.e.,* OTC monograph drugs) or are otherwise subject to current good manufacturing practice. This guidance also applies to prescription and OTC drug products in clinical development. In addition, this guidance applies to certain biological products that contain chemically synthesized fragments or biologic-led combination products that contain a drug constituent part whether such products are in development or the subject of an approved or pending biologics license application (BLA). The recommendations in this guidance apply to both drug product and drug substance manufacturers.

This guidance provides manufacturers and applicants of drugs with a recommended framework for predicting the mutagenic and carcinogenic potential of NDSRIs that could be present in drug products and recommends AI limits for NDSRIs. This approach will assist manufacturers and applicants in taking steps to detect and prevent unacceptable levels of nitrosamine impurities in drug products. Although this guidance document is immediately in effect, it remains subject to comment in accordance with FDA's good guidance practices regulation (§ 10.115(g)(3)(D)).

Nitrosamine compounds have the potential to be potent genotoxic agents in several animal species, and some are classified as probable or possible human carcinogens. Nitrosamines are included in a group of high potency mutagenic carcinogens referred to as ''cohort of concern'' compounds in the International Council for Harmonisation (ICH) guidance for industry entitled ''M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk'' (March 2018). In 2020, FDA published a guidance for industry, ''Control of Nitrosamine Impurities in Human Drugs,'' (85 FR 55017, September 3, 2020) (Nitrosamine Guidance), recommending that manufacturers of APIs and drug products take steps to detect and prevent unacceptable levels of nitrosamine impurities in drug products, or avoid their presence when feasible, and updated the guidance on February 24, 2021.

NDSRIs are a class of nitrosamines sharing structural similarity to the API, and thus, differ in certain respects from small molecule nitrosamine impurities specified in the Nitrosamine Guidance. NDSRIs are unique to each API and are generally formed in a drug product through nitrosation of APIs (or API fragments) that have secondary or tertiary amines when exposed to nitrosating agents such as residual nitrites in excipients used to formulate the drug product. NDSRIs that have been recently identified in a number of drug products generally lack carcinogenicity and mutagenicity data (typically from animal studies) from which an AI can be determined. Based on the chemical structure of certain drugs, there is a risk of NDSRIs forming in a substantial number of drug products; however, it is currently unknown if all or some NDSRIs are in fact high-potency mutagenic carcinogens. It is challenging to establish an AI limit for NDSRIs because of the lack of available mutagenicity data and robust carcinogenicity data from which applicants would otherwise determine AI limits. These challenges have led to some applicants and manufacturers conducting unnecessary studies or, in some cases, discontinuing drug products from the market.

FDA is recommending a predicted carcinogenic potency categorization method that assigns a recommended AI limit to an NDSRI based on the NDSRI's activating and deactivating structural features. Predicted carcinogenic potency categories enable manufacturers to determine recommended AI limits for NDSRIs in APIs and drug products and to facilitate development of methods for confirmatory testing. Potency categorization offers a scientifically based predictive solution to recommending AI limits for data-poor NDSRIs, for which suitable surrogates with robust carcinogenicity data are not available.

The recommendations in this guidance provide a risk-based safety assessment of NDSRIs and can be used by applicants and manufacturers to identify AI limits for NDSRIs in their drug products and APIs in conjunction with the recommendations in the Nitrosamine Guidance. If FDA communicates another FDA-recommended AI limit for a specific NDSRI, manufacturers and applicants should apply that recommended AI

[1] For the purposes of this guidance, we use the term ''drug'' or ''drug product'' to refer to human drug and biological products, including drug-led and biologic-led combination products, regulated by the Center for Drug Evaluation and Research, unless otherwise specified.

limit rather than the AI limit recommended in this guidance based on predicted carcinogenic potency. In general, FDA would expect manufacturers and applicants to control impurities within the recommended AI limit. Additionally, manufacturers and applicants should continue to pursue mitigation efforts to reduce or remove NDSRIs in their drug products.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on ''Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs).'' It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The collections of information in 21 CFR parts 210 and 211 pertaining to current good manufacturing practice have been approved under OMB control number 0910–0139. The collections of information in 21 CFR part 312 pertaining to investigational new drug applications have been approved under OMB control number 0910–0014. The collections of information in 21 CFR part 314 pertaining to NDAs and ANDAs have been approved under OMB control number 0910–0001. The collections of information in 21 CFR part 601 pertaining to BLAs have been approved under OMB control number 0910–0338. The collections of information in 21 CFR part 201 pertaining to OTC monograph drug products have been approved under OMB control number 0910–0340.

III. Electronic Access

Persons with access to the internet may obtain the document at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents,* or *https://www.regulations.gov*.

Dated: August 2, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023–16814 Filed 8–4–23; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Indian Health Service

Notice of Purchased/Referred Care Delivery Area Redesignation for the Confederated Tribes of Grand Ronde in the State of Oregon

AGENCY: Indian Health Service, HHS.

ACTION: Notice.

SUMMARY: This Notice advises the public that the Indian Health Service (IHS) proposes to expand the geographic boundaries of the Purchased/Referred Care Delivery Area (PRCDA) for the Confederated Tribes of Grand Ronde (CTGR) in the State of Oregon to include the county of Clackamas in the State of Oregon. The current PRCDA for the CTGR includes the Oregon counties of Washington, Polk, Yamhill, Marion, Multnomah, and Tillamook. The CTGR members residing outside of the PRCDA are eligible for direct care services, however, they are not eligible for Purchased/Referred Care (PRC) services. The sole purpose of this expansion would be to authorize additional CTGR members and beneficiaries to receive PRC services.

DATES: Comments must be submitted September 6, 2023.

ADDRESSES: Because of staff and resource limitations, we cannot accept comments by facsimile (FAX) transmission. You may submit comments in one of four ways (please choose only one of the ways listed):

1. *Electronically.* You may submit electronic comments on this regulation to *http://www.regulations.gov.* Follow the ''Submit a Comment'' instructions.

2. *By regular mail.* You may mail written comments to the following address ONLY: Carl Mitchell, Director, Division of Regulatory and Policy Coordination, Indian Health Service, 5600 Fishers Lane, Mail Stop: 09E70, Rockville, Maryland 20857.

Please allow sufficient time for mailed comments to be received before the close of the comment period.

3. *By express or overnight mail.* You may send written comments to the above address.

4. *By hand or courier.* If you prefer, you may deliver (by hand or courier) your written comments before the close of the comment period to the address above.

If you intend to deliver your comments to the Rockville address, please call telephone number (301) 443–1116 in advance to schedule your arrival with a staff member.

FOR FURTHER INFORMATION CONTACT: CAPT John Rael, Director, Office of Resource Access and Partnerships, Indian Health Service, 5600 Fishers Lane, Mail Stop: 10E85C, Rockville, Maryland 20857. Telephone (301) 443–0969 (This is not a toll-free number).

SUPPLEMENTARY INFORMATION:

Inspection of Public Comments: All comments received before the close of the comment period are available for viewing by the public, including any personally identifiable or confidential business information that is included in a comment.

Background: The IHS provides services under regulations in effect as of September 15, 1987, and republished at 42 CFR part 136, subparts A–C. Subpart C defines a Contract Health Service Delivery Area (CHSDA), now referred to as a PRCDA, as the geographic area within which PRC will be made available by the IHS to members of an identified Indian community who reside in the PRCDA. Residence within a PRCDA by a person who is within the scope of the Indian health program, as set forth in 42 CFR 136.12, creates no legal entitlement to PRC, but only potential eligibility for services. Services needed, but not available at an IHS/Tribal facility, are provided under the PRC program depending on the availability of funds, the person's relative medical priority, and the actual availability and accessibility of alternate resources in accordance with the regulations.

The regulations at 42 CFR part 136, subpart C provide that, unless otherwise designated, a PRCDA shall consist of a county which includes all or part of a reservation and any county or counties which have a common boundary with the reservation, 42 CFR 136.22(a)(6). The regulations also provide that after consultation with the Tribal governing body or bodies on those reservations included within the PRCDA, the Secretary may from time to time, redesignate areas within the United States for inclusion in or exclusion from a PRCDA, 42 CFR 136.22(b). The regulations require that certain criteria must be considered before any redesignation is made. The criteria are as follows:

(1) The number of Indians residing in the area proposed to be so included or excluded;