



4164-01-P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2013-D-1170]

### Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment; Guidance for Industry; 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 a guidance for industry entitled "Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment." The purpose of this guidance is to assist sponsors in all phases of development of direct-acting antiviral (DAA) drugs for the treatment of chronic hepatitis C. This guidance finalizes the draft guidance of the same name issued on May 4, 2016.

**DATES:** The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

**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-2013-D-1170 for "Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment; Guidance for Industry; Availability." 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.

- 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.

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

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 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:** Jeffrey Murray, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6360, Silver Spring, MD 20993-0002, 301-796-1500.

**SUPPLEMENTARY INFORMATION:**

I. Background

FDA is announcing the availability of a guidance for industry entitled "Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment." This guidance addresses nonclinical development, early phases of clinical development, and phase 3 protocol designs. Important issues addressed in this guidance include: trial design options, choice of noninferiority margins for active-controlled phase 3 trials in the evaluation of interferon (IFN)-free regimens, and trial design options and safety evaluations for specific populations including patients with decompensated cirrhosis, patients either pre- or post-liver transplant, and patients with chronic kidney disease and clinical virology considerations. This guidance finalizes the draft guidance of the same name issued on May 4, 2016 (81 FR 26805). Changes made to the guidance took into consideration comments received. In addition to editorial changes primarily for clarification, the major changes are as follows:

- Modification of several sections to focus on IFN-free DAA regimens.

- Additional clarification on trial designs for combinations of investigational DAAs with or without ribavirin.
- Additional clarification on the recommended trial population to include patients with clinical or laboratory evidence of chronic hepatitis C disease, such as the presence of fibrosis by biopsy or noninvasive tests.
- Additional details on DAA drug development in patients with decompensated cirrhosis, including recommendations for a review by an independent adjudication committee for all serious hepatic events, deaths, liver transplantations, and changes in prespecified alanine transaminase, aspartate transaminase, and bilirubin parameters and a recommendation for long-term followup to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation.
- Additional clarification on efficacy endpoints, specifically additional post-treatment followup (e.g., 1 year or longer) may be needed if one or more drugs in the regimen has a long plasma or intracellular half-life or prolonged antiviral activity.

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 "Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment." 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. This guidance is not subject to Executive Order 12866.

## II. The Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that 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). The collections of information in 21 CFR parts 312 and 314 have been approved under OMB control numbers 0910-0014 and 0910-0001, respectively.

## III. Electronic Access

Persons with access to the internet may obtain the guidance at either <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <https://www.regulations.gov>.

Dated: November 2, 2017.

**Anna K. Abram,**

*Deputy Commissioner for Policy, Planning, Legislation, and Analysis.*

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