EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Infectious Diseases Working Party (IDWP)

Concept paper on the revision of the guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B

Agreed by Infectious Diseases Working Party (IDWP)	4 October 2023
Adopted by CHMP for release for consultation	14 December 2023
Start of public consultation	26 January 2024
End of consultation (deadline for comments)	30 April 2024

The proposed guideline will replace guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B (CHMP/EWP/6172/03).[1]

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Chronic Hepatitis B (CHB), Hepatitis B virus (HBV), functional cure.

[1] If this supersedes a previous guideline – otherwise delete.

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1. Introduction

This concept paper addresses the need to update the guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B (CHMP/EWP/6172/03)[1]. This guideline was originally adopted by CHMP on the 23 February 2006 and came into effect on the 1st of September 2006. In recent years there have been several applications for scientific advice on new products and treatment strategies aimed at achieving functional cure, including finite and combination treatment regimens. Furthermore, there has been development of new antiviral and immunomodulatory treatment options with mechanisms of action different to those of nucleos(t)ide analogues (NUCs) or peg-interferon alfa-2a (PEG-IFN). Therefore, a revision of the guideline is necessary to reflect these new developments and the implications for clinical development programmes.

2. Problem statement

This concept paper concerns the need to update the current guideline to provide guidance on the clinical evaluation of medicinal products intended for the treatment of hepatitis B. Reasons to update the current text include the following developments:

In recent years, several Hepatitis B virus (HBV) endpoint meetings have taken place with participation of international experts to discuss treatment goals, treatment durations, endpoints, study populations and the definition of functional cure[3,4]. The EMA guideline needs to be revised to take into account the outcome of these international conferences. Also, updated EASL treatment guidelines[2] and methodological guidance documents[3,4] relevant for decision making have been published and should be reflected as appropriate in the guideline.

Since the preparation and adoption of the current guideline text, the treatment goal of functional cure has evolved, which has changed the development landscape of agents intended for the treatment of chronic hepatitis B infection. The current guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B (CHMP/EWP/6172/03)[1] concerns clinical study designs and endpoints that apply to NUCs and interferons. However, novel treatments have already been tested in clinical studies including capsid assembly modulators (CAM), silencing RNAs (siRNA) and antisense oligonucleotides (ASO), nucleic acid polymers (NAP) and immunomodulatory therapies like Toll-like receptor agonists, checkpoint inhibitors and monoclonal antibodies. Thus, the current guidance does not address the development of agents with other mechanisms of action and combination regimens aiming at achieving functional cure of chronic hepatitis B infection.

Moreover, since adoption of the current guideline, undetectable HBV DNA, and a combined endpoint of sustained suppression of HBV DNA and sustained HBsAg loss have been accepted as surrogate markers for efficacy in studies evaluating chronic suppressive and finite therapies, respectively. Therefore, the acceptable and recommended primary endpoints for clinical trials have changed.

Overall, considering the new developments in the field of HBV clinical development there is a need to update the current guideline, especially to reflect the new agents and the aim to develop treatment regimens that achieve functional cure.

3. Discussion (on the problem statement)

The following elements of the current guideline need to be revised or added:

- Clinical trial requirements including trials that aim to demonstrate the efficacy of treatments aiming at achieving functional cure, including finite and combination treatment regimens.

- Update recommendations for primary efficacy endpoints to include endpoints relevant to achieving viral suppression or functional cure.
- Efficacy and safety considerations when stopping suppressive NUC treatments in clinical trials aimed at evaluating regimens intended to achieve functional cure.
- Considerations specific to the development of agents with novel mechanisms of action.
- Statistical analyses in trials that evaluate finite treatment regimens.
- Definitions of HBV cure, diagnostic criteria, and patient characteristics.
- Editorial and structural changes to improve readability.

4. Recommendation

The IDWP recommends revising the existing EMA guideline on the clinical evaluation of medicinal products intended for the treatment of hepatitis B (CHMP/EWP/6172/03), taking into account the issues identified above.

5. Proposed timetable

Timetable for the concept paper is the following:

Discussion at IDWP:	October 2023
Adoption by CHMP	January 2024
Released for public consultation:	February 2024 – April 2024
Adoption and publication of the final version:	May 2024

6. Resource requirements for preparation

The update of the guideline will be carried out by the IDWP, in co-operation with the SAWP and the CHMP. A drafting group of 4-5 members will be constituted. The IDWP will appoint a rapporteur among its members who will lead the drafting group and the discussion at IDWP during the development of the guideline.

CHMP will discuss and adopt the concept paper, the draft guideline before external consultation and the finalised guideline before publication.

7. Impact assessment (anticipated)

The guidance will clarify requirements for regulators and industry with respect to the development of medicinal products aiming at functional cure, with a novel mechanism of action and/or aiming at finite or combination treatment approaches.

Overall, it is anticipated that the revised guidelines will have a positive impact on the development of applications for new treatments of chronic hepatitis B.

8. Interested parties

EMA: PDCO, SAWP, MWP, CTCG, consultation with other working parties or committees will be initiated as appropriate.

External parties: European learned societies and scientific organisations (e.g. European Association for the study of the liver (EASL)), EU/EEA Regulatory authorities, patient representatives and Pharmaceutical Industry.

9. References to literature, guidelines, etc.

1: CHMP guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B (CHMP/EWP/6172/03)

2: EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, J Hepatol, 2017 Aug;67(2):370-398. doi:10.1016/j.jhep.2017.03.021

3: Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference, J Hepatol. 2020 Mar;72(3):539-557., doi: 10.1016/j.jhep.2019.11.003

4: Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference, Hepatology. 2023 Jun 21, doi: 10.1097/HEP.0000000000000431