EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/BMWP/693108/2015
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the reflection paper on non-clinical and clinical development of similar biological medicinal products containing recombinant interferon alpha or pegylated recombinant interferon alpha (EMEA/CHMP/BMWP/102046/2006)

Agreed by Biosimilar Medicinal Products Working Party (BMWP)	October 2015
Adoption by CHMP for release for consultation	17 December 2015
Start of public consultation	04 January 2016
End of consultation (deadline for comments)	31 March 2016

The proposed guideline will replace the Reflection paper: Non-Clinical and Clinical development of similar medicinal products containing recombinant Interferon Alpha, EMEA/CHMP/BMWP/102046/2006.

Comments should be provided using this template. The completed comments form should be sent to bmwp.secretariat@ema.europa.eu

Keywords	*Recombinant interferon alpha, similar biological medicinal products, biosimilar, non-clinical studies, clinical studies*

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Introduction

The current Reflection paper on *similar medicinal products containing recombinant interferon alpha* provides recommendations for the non-clinical and clinical development of recombinant interferon alpha claimed to be similar to a reference product already authorised in the EU. This Reflection paper was published in April 2009. Since then, no products containing biosimilar interferon alpha have been licensed in the EU. It is proposed to update the guidance based on the experience gained with marketing authorisation applications of reference products and scientific advice on biosimilar interferon alpha.

2. Problem statement

Different medicinal products containing recombinant interferon alpha are currently approved in the EU; they differ with respect to their molecular structure, recommended posology, and indications. No biosimilar interferon alpha products have been licensed.

Human interferon alpha 2a or 2b are well-known and characterized proteins consisting of 165 amino acids. The non-glycosylated protein has a molecular weight of approximately 19,240 D. It contains two disulfide bonds, one between the cysteine residues 1 and 98, and the other between the cysteine residues 29 and 138. The sequence contains potential O-glycosylation sites. Physico-chemical and biological methods are available for characterisation of the proteins. Recombinant interferon alpha 2a or 2b is approved in a wide variety of conditions such as viral hepatitis B and C, leukaemia, lymphoma, renal cell carcinoma and multiple myeloma. The sub-types interferons alpha 2a and 2b have different clinical uses. Interferon alpha is used alone or in combination. Interferon alpha may have several pharmacodynamic effects. The relative importance of these effects in the different therapeutic indications is unknown. In general, interferon alpha 2a or 2b use in oncology indications has reduced considerably and been superseded by other treatments.

Peginterferon (PEG-IFN) alpha is synthesized by the covalent attachment of a branched methoxypolyethylene glycol (PEG) polymer, with a molecular mass of about 44,000 D, to interferon (IFN) alpha. Pegylation of IFN alpha was developed to improve the pharmacokinetics properties of the active moiety and to reduce number of weekly injections compared to unpegylated IFN. PEG-IFN alpha 2a and 2b are approved in several indications such as hepatitis B and hepatitis C in combination with other medicinal products.

The dose and treatment regimen required to achieve the desired response vary considerably between different therapeutic indications. PEG-INF alpha and IFN alpha are used subcutaneously although IFN alpha can also be used through intramuscular or intravenous route.

The current guideline includes recommendations for the development of biosimilar IFN alpha. It is also proposed to address pegylated recombinant IFN alpha.

The current guideline requests at least one repeat dose toxicity study in a relevant species. However, a risk-based approach for *in vivo* animal studies has been implemented in the revised general Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and other recently developed or revised biosimilarity guidelines.

The current guideline puts much emphasis on confirmatory clinical trials to compare efficacy and safety of the biosimilar and reference recombinant IFN alpha. However, the revised “overarching” Guideline

on similar biological medicinal products (CHMP/437/04 Rev. 1) states the possibility that, in specific circumstances, a confirmatory clinical trial may not be necessary.

3. Discussion (on the problem statement)

The following aspects will need to be discussed and covered as appropriate by the revised guideline:

1. Considerations whether specific aspects with regard to the development of biosimilar pegylated interferon alpha need to be included in the guideline.

2. The focus of the non-clinical comparability exercise is on in *vitro studies,* which are usually more specific and sensitive to detect differences between the biosimilar and the reference product than *in vivo* studies. For this reason and to avoid unnecessary animal studies, a risk-based approach is now generally accepted. It is suggested to adapt the reflection paper on biosimilar interferon alpha containing products along these lines of thinking.

3. The revised "overarching" Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1) states prerequisites for waiving clinical trials. These conditions may be accomplishable for biosimilar interferon alpha since structure, physicochemical characteristics and biological activity of interferon alpha are well characterisable by state-of-the art methods and PD parameters of clinical relevance are available. Regulatory expectations to support a biosimilar recombinant interferon alpha development without a confirmatory clinical trial will need to be further discussed and included in the guideline.

4. Recommendation

The Working Party recommends revising the *Reflection paper on similar medicinal products containing recombinant interferon alpha* (EMEA/CHMP/BMWP/102046/2006). It is proposed to discuss an update of the non-clinical part of the guideline to include a risk-based approach for *in vivo* animal studies and for the clinical part to discuss the prerequisites for waiving a confirmatory clinical trial including clinical safety/immunogenicity. If considered appropriate, specific guidance for the development of pegylated interferon alpha containing biosimilars will be given.

5. Proposed timetable

It is anticipated that the draft revised guideline will be released for consultation in Q2 2016.

6. Resource requirements for preparation

The BMWP experts will develop the guideline.

7. Impact assessment (anticipated)

Anticipated benefit for industry (revised and potentially reduced requirements) and assessors of biosimilar interferon alpha-containing products.

8. Interested parties

- Pharmaceutical industry and competent authorities of the Member States.
- CHMP and its working parties.

9. References to literature, guidelines, etc.

- Part II of the Annex I of Directive 2001/83/EC, as amended.
- Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1).
- Reflection Paper on non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha (EMEA/CHMP/BMWP/102046/2006).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/24771/2012).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).
- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006).
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96).