EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on the revision of the guideline on the development of new medicinal products for the treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 1)

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| Agreed by Gastroenterology Drafting Group | September 2012 |
| Adopted by CHMP for release for consultation | 18 October 2012 |
| Start of public consultation | 14 November 2012 |
| End of consultation (deadline for comments) | 15 February 2013 |

The proposed guideline will replace the guideline on the development of new medicinal products for the treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 1).

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

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| Keywords | Crohn's disease, PCDAI, mucosal healing, patient reported outcome (PRO), health related Quality of Life (HrQoL) |

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# 1. Introduction

Crohn's disease is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (43-60%), followed by disease in the ileum only (19-35%), and in the colon only (20-25%), upper gastro intestinal tract (17-33 %) is variable involved and usually not included in studies for follow up. Symptoms are abdominal pain, diarrhoea, blood in stools, perianal disease and extraintestinal manifestations. The pathophysiological basis of the disorder is still incompletely understood, but inflammatory changes, selected immunological deficiencies, and genetic polymorphisms are involved.

# 2. Problem statement

The "Guideline on the development of medicinal products for the treatment of Crohn's disease (CHMP/EWP/2284/99) currently includes only more general comments for the conduct of clinical studies in children. In 2010, an expert meeting of European experts in paediatric gastroenterology and rheumatology published a statement, which is partly more decisive as regards the needs of and the mode of conduct of paediatric studies in Crohn's disease than the guideline document, leading to obvious discrepancies, with a subsequent need of reconciliation.

The aim of the planned revision is therefore restricted to the chapter 4.3. "Studies in special populations" and its paragraph on "children and adolescents". Besides the a.m. reconsideration of the obvious discrepancies of two public statements, it should also deal with a necessary update according to scientific progress and ongoing discussions in the scientific and regulatory community, and with the evaluation of the experiences with the data that have been generated during the last 5 years with a few products.

Moreover, the FDA and EMA have started with other international authorities to harmonise guidance for conduct of studies in children with IBD. This initiative followed the observation of some disharmony in regulatory requirements for studies in the field with consequently the apparent difficulties for global development programmes. An evaluation on opportunities to harmonise requirements appears to be warranted.

# 3. Discussion (on the problem statement)

Extrapolation:

Currently, the Guideline only generally states that "studies in children are encouraged". The main problem behind, namely the question whether and to what extent extrapolation from adults is possible, remains largely unexplored. Contrary to this, the above mentioned Expert Statement clearly states that "extrapolation from adult studies is limited" and that in most cases separate studies in children are needed. It is therefore intended to evaluate whether more clear statements should be included into the guideline, as to what extent extrapolation of adult data is possible, and whether criteria for extrapolation can be defined. Emerging scientific data on similarities and discrepancies between adult and paediatric disease have to be evaluated including differential drug effects as regards efficacy and safety.

Endpoints in clinical trials for children:

The most obvious discrepancy between the a.m. Expert Statement and the current guideline refers to the recommendation of the guideline to use the PCDAI as primary endpoint in clinical trials, whereas the Expert Statement recommends the use of endoscopy, because it refers to the importance of mucosal healing being predictive for the further overall course of the disease. The PCDAI has been challenged for flaws due to the inclusion of height, abdominal examination, haematocrit, and validation is obviously incomplete as already stated in the current Guideline. A thorough evaluation of the available data on validity and feasibility of these divergent proposals has therefore to be made. The need for the inclusion of additional secondary endpoints, such as PROs and Quality of Life scales, or biomarkers, also has to be evaluated.

Design of the studies in children:

Currently, the Crohn's disease guideline does not include a separate statement on the need or preference for placebo- or actively controlled studies in children. Contrary to this, the a.m. Expert Statement clearly prefers the conduct of actively controlled studies whenever feasible. It has therefore to be evaluated whether this question needs to be dealt with in a different way in children, as compared to adults. In the same context alternative study designs, such as withdrawal-,, mono-therapy-, and add-on-studies need to be evaluated for their suitability in paediatric drug development.

Evaluation of previous dossiers demonstrated a need for re-assessment of PK/PD models due to unexplained discrepancies in outcome between children and adults. The number of patients included was insufficient to support any firm conclusions regarding doses and dosing intervals in children, although available data did suggest a need for higher doses and shorter dosing intervals. A separate paragraph on the need to explore PK and PK-PD relationship according to age and different pathophysiology might be necessary.

# 4. Recommendation

The Gastroenterology Drafting group recommends the revision of the Guideline for conduct of studies for Crohn's Disease, Points to Consider on the evaluation of medicinal products for the treatment of Crohn's Disease.

Points to be addressed and evaluated concern the following fields:

1.) The examination and potential revision of the recommendations for the primary and secondary endpoints and for the principal design of the trials (including the comparator to be used).

2.) The need for more clear guidance as regards the possibility for extrapolation from adults, or the need to generate separate data in children.

3.) The need for inclusion of recommendations regarding exploration of PK/PD relationship in paediatric drug development, including the need for adaptation of the PK/PD model concerning dose finding both in terms of induction and maintenance therapy.

# 5. Proposed timetable

It is anticipated that a new draft CHMP Guideline may be available 9 months after adoption of the concept paper. The draft CHMP guideline will then be released for 6 months for external consultation and following receipt of comments it will be finalised in approximately 3 months. Finalisation will therefore be awaited for the first half of 2014.

## 6. Resource requirements for preparation

The preparation of the revision of the guideline will primarily involve the Gastroenterology Drafting Group

## 7. Impact assessment (anticipated)

The revised guideline will provide updated guidance to both industry and Regulatory Authorities regarding the clinical development and assessment of medicinal products for the treatment of Crohn's Disease in the paediatric population. This is expected to contribute to higher consistency in the development of new products in the field.

## 8. Interested parties

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

European Crohn and Colitis Organisation (ECCO)

United European Gastroenterology Federation (UEGF)

FDA

PRINTO

## 9. References to literature, guidelines, etc.

EMA paediatric gastroenterology and rheumatology expert meeting London, 28-06 2010 EMA/416878/2010

Guideline on the development of new medicinal products for the treatment of Crohn's disease (Ref. CPMP/EWP/2284/99)