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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the Guideline on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00)

Agreed by Safety Working Party	8 July 2011
Adoption by CHMP for release for consultation	21 July 2011
End of consultation (deadline for comments)	30 October 2011

The proposed Guideline will replace the Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00).

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

Keywords	*reduction, replacement, refinement, in vivo, in vitro, local tolerance*

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1. Introduction

The existing guideline on local tolerance is dated 1 March 2001 (1). Over the past years, newer routes of administration, *e.g.* transdermal systems, are being used more frequently and a shift has been observed towards the regulatory acceptance of scientifically valid *in vitro* methods as well as formally validated *in vitro* methods as part of an integrated testing strategy. In addition, recently the ICH Guideline M3(R2) - Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (2) – came into force and included a section on local tolerance.

2. Problem statement

The focus on local tolerance testing has broadened over the last few years, with newer methods of drug delivery being developed. *In vitro* methods are becoming an integral part of the non-clinical testing local tolerance testing programme of human medicinal products and approaches aiming at reducing or refining animal studies are routinely implemented in regulatory guidelines, where applicable.

Taking into account the progress in the development of newer drug delivery strategies, a revision of the Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products is warranted. The revision will also aim to harmonise local tolerance testing requirements with those out lined in the ICH Guideline M3(R2) - Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (2).

3. Discussion (on the problem statement)

Local tolerance should be evaluated prior to human exposure of a product in order to ascertain whether the product (both active substance and excipients) is tolerated at contact sites of the body following clinical use. Local tolerance testing should be conducted according to “state of the art” methods.

Although non-clinical studies still heavily rely on animal data, adherence to the 3Rs principles is clearly evident both at the EU and ICH level. Various *in vitro* test systems are currently used for different purposes and at different time-points within the non-clinical development programme. Wherever possible, studies on animals, including studies on local tolerance, should be substituted by validated *in vitro* tests.

The introduction of tailor-made non-clinical testing strategies, involving both *in vivo* and *in vitro* testing, is expected to entail a reduction of animal use.

The full revision of Directive 86/609/EC was recently completed and resulted in the adoption of Directive 2010/63/EU on the protection of animals used for scientific purposes on 3 June 2010 [3]. This Directive will take effect on 1 January 2013. Different articles relate to the application of the 3R’s. As such, article 4 clearly states that:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.

Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.

Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.

Therefore, the Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products (1) should be revised in order to take into account scientific and legislative progress and to also to formulate guidance on when and how 3R alternatives (replacement, reduction and refinement) can be considered for regulatory acceptance.

4. Recommendation

The CHMP recommends revising the Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products (1) in line with current scientific progress and legislative requirements.

5. Proposed timetable

It is anticipated that a draft of the revised guideline may be released for consultation in 2011.

6. Resource requirements for preparation

The preparation of this guideline will involve the Safety Working Party of the CHMP.

7. Impact assessment (anticipated)

The revised guideline is expected to provide clear information on the conditions and strategy for regulatory acceptance of non-clinical local tolerance methods. It is also anticipated that this will facilitate regulatory acceptance of 3R alternatives and thus to reduce animal use in non-clinical testing conducted to support the conduct of clinical trials and marketing authorisation.

8. Interested parties

Animal welfare organisations and relevant research organisations on alternative approaches to animal testing.

9. References to literature, guidelines, etc.

1. Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00)
2. ICH M3 (R2)Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (CPMP/ICH/286/95).
3. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276/33).