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Committee for Medicinal Products for Human Use (CHMP)

# Concept paper on the revision of the note for guidance on quality of modified release oral dosage forms and transdermal dosage forms: Section I (quality)

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The proposed guideline will alter guideline: CPMP/QWP/604/96

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

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| Keywords | **modified release, oral, transdermal, quality, dissolution, in vivo/in vitro correlation, adhesion.** |

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# 1. Introduction

The Note for Guidance on modified release products addresses specific quality requirement for modified release products, particularly the in vitro testing. The NfG focus primarily on oral dosage forms including both prolonged and delayed release formulations. However there is room for further guidance particularly in relation to the choice of the appropriate dissolution test and media, details on the development of in vivo/in vitro correlation and new technologies. The requirements for transdermal dosage forms are only briefly described in the document. As such, a more elaborated chapter on transdermal patches is needed in this guideline with special focus on the interchangeability aspects for generic transdermal patches.

# 2. Problem statement

Oral formulations are still the most common pharmaceutical dosage form, even among the newly introduced drugs, and will probably continue to be in the next few years. Several Modified Release (MR) technologies (e.g., hydrophilic matrix tablets, osmotic systems, and coated multiparticulates) are well established and well understood.

In vitro dissolution test is often used during development and quality control as a predictive tool to indicate changes which may have an effect on the efficacy or safety of the product and can also be used as a surrogate for in vivo testing when *in vitro-in vivo* correlations are developed. However the estimation of the release and dissolution of the drug in the intestinal fluid (and the permeation of the intestinal mucosa) with in vitro techniques that are not biorelevant can be misleading in some cases according to the properties of the drug and the formulation. At the same time, developments in formulation and specific types of excipients have led to more complicated MR dosage forms. On the other hand, new drug substances rarely exhibit good solubility (classified as Class II compounds in BCS) and their development as Modified Release forms can be challenging in terms of achievement of in vivo and/or in vitro release. MR products can also present unique challenges when it comes to establishing therapeutic equivalence between two formulations.

In addition, the new quality paradigm –Quality by Design- and new technologies in this respect (e.g. PAT) can be used to provide *in vitro-in vivo* relationships based on the performance of individual dosage form units, or to set up dissolution specifications.

As a result of the interaction of alcohol with modified release oral dosage forms containing strong opioids which lead to “dose dumping” of opioids for some (generic) products, it has become necessary to review the requirements for in vitro or in vivo data for all modified release products.

Taking into account the above it is deduced that there is a need to provide further guidance and elaborate the specific requirements in relation to these points.

Following recent scientific developments and increased number of transdermal patches applications for marketing authorisation, it has become necessary to further illustrate the specific requirements for this dosage form. Although section four of the current guideline attempts to describe the requirements for transdermal dosage forms, clear guidance on limits, e.g., for patch size and drug load versus total amount released are not specified. In addition, the specific requirements for dissolution methods for transdermal patches should be described in greater detail. Finally, skin adhesion properties are not fully addressed and no mention is made to the in vitro methodologies and in vivo testing to assess and control skin adhesion. Especially the concept of generics and interchangeability of transdermal patch formulations has generated the need for further clarification and guidance. The issue regarding interchangeability should be discussed in a separate subsection of this guideline since the objectives of pharmaceutical development differ for those type of products. A patch formulation using an active

substance for the first time can hardly be evaluated based on certain standard requirements, although the methods applied to establish and describe the patch formulations characteristics should be based in general on standardized procedures. In contrast to this individual case evaluation, generic patch development needs to be focussed on comparability aspects. Certain standard requirements have to be established to facilitate the decision making process when it comes to evaluation of product equivalence between originator and the generic patch formulation. Due to the particularities of the transdermal route and its underlying principles of release from the formulation, interchangeability of transdermal patch products is not solely depending on the proof of bioequivalence as known for oral modified release products. Adhesion as well as skin irritation properties might have a significant impact on the in-vivo release characteristics of a patch formulation.

# 3. Discussion (on the problem statement)

The main topics to be discussed during the revision of the guideline in the context of modified release oral dosage forms are:

1. The functionality of the excipients and their role in drug release mechanism should be considered.
2. The choice of the appropriate dissolution test in terms of media and hydrodynamics according to physicochemical properties of the drug substance and formulation properties (i.e. type of excipients, drug release mechanism). The use of biorelevant media for MR of Class II compounds. Food effect.
3. New technologies (e.g. PAT) can provide in vitro in vivo relationships based on performance of individual dosage form units. Quality by Design for dissolution specifications.
4. More details on the development of in vivo/in vitro correlation. Description of the usual two-stage process (e.g. deconvolution followed by comparison of the fraction absorbed to the fraction dissolved) or other approaches that can be used. Details on the development of linear correlations (usually obtained), but also on non-linear correlation that may also be acceptable. In vitro release variability to be taken into account on IVIVC method.
5. Dissolution specifications for evaluation of generics.
6. Interaction of alcohol with modified release oral dosage forms which may lead to “dose dumping”.
7. Narrow and non-narrow therapeutic range drugs.

The main topics to be discussed during the revision of the guideline in the context of transdermal dosage forms are:

1. Skin adhesion has been recently a major issue for TDDS[1] and should be therefore carefully addressed in the revised guideline (cross reference to the PK part of the Guideline).
2. Patch load vs. drug released particularly when the active substance poses a risk for drug abuse
3. patch size and its implications in skin adhesion
4. dissolution methods and *in vivo/in vitro* correlation (cross reference to the PK part of the Guideline)
5. Validation of the manufacturing process
6. Bridging data to be presented in the Pharmaceutical Development part of the Module 3: In-vitro release/In-vitro permeation/In-vivo release.
7. Additional release and shelf life specification testing parameters for transdermal patches:

Cold flow, crystallisation, peel force, adhesion force.

8. For generic transdermal patches:
   Establishment of a parameter that puts patch size and in-vivo release into relation and indicates the appropriateness of the pharmaceutical development in regard to optimize the release properties of the formalution:
   The area activity (% release/cm²)

## 4. Recommendation

The Quality Working Party recommends the revision of this Note for Guidance, in light of the recent developments in the scientific world. Section II of the guideline is also being revised.

## 5. Proposed timetable

It is anticipated that a new draft CHMP guideline may be available in Q1 2011 and then released for external consultation for 6 months. The guideline could then be finalised within 6 months.

## 6. Resource requirements for preparation

An expert drafting group led by the Rapporteur within QPK will revise the guideline. The experts' drafting group will include experts from the various member states with expertise in the fields of modified release and transdermal drug delivery and experts from academia.

## 7. Impact assessment (anticipated)

Clear guidance will facilitate regulatory approval and help industry during the development of these products.

## 8. Interested parties

Regulators, pharmaceutical industry and academic group representatives and possibly European Scientific focus groups in these specialised subject areas.

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

1. Wokovich, A., Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eur J Pharm Biopharm. 2006 Aug; 64(1):1.
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3. E. Jantratid et al. Application of biorelevant dissolution tests to the prediction of in vivo performance of diclofenac sodium from an oral modified-release pellet dosage form. Eur J Pharm Sciences 37 (2009) 434–441

4. Q. Wang et al. Biorelevant Dissolution: Methodology and Application in Drug Development. Dissolution Technologies, AUGUST 2009