European Guidance on Modified Release Dosage Forms

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London

PQRI Workshop on Application of IVIVC in Formulation Development
September 5 - 6, 2012
Bethesda, Maryland
Disclaimer

The views expressed during this presentation are those of the speaker and do not necessarily represent the views of the MHRA or the EMA/CHMP.
Outline

European Regulatory System

Status of European Guidance on MR Products

MHRA Experience

Key Messages and Opportunities
European Regulatory System

- CHMP
- EMA
- National MAs, National Scientific Advice
- Assessors in National Agencies
- Working Parties e.g. Scientific Advice/Guidelines

MA: marketing authorisation
European Guidance on MR Products (currently in revision)

NOTE FOR GUIDANCE ON QUALITY OF MODIFIED RELEASE PRODUCTS:
A: ORAL DOSAGE FORMS
B: TRANSDERMAL DOSAGE FORMS
SECTION I (QUALITY)

14 July 2010
EMA/CHMP/QWP/202350/2010
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)

NOTE FOR GUIDANCE ON MODIFIED RELEASE ORAL AND TRANSDERMAL DOSAGE FORMS:
SECTION II (PHARMACOKINETIC AND CLINICAL EVALUATION)

20 May 2010
EMA/CHMP/EWP/1535/2010
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation)
## European Guidance relating to IVIVC (currently in revision)

<table>
<thead>
<tr>
<th>IVIVC Topic Covered</th>
<th>Quality Section</th>
<th>Clinical Section</th>
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<tbody>
<tr>
<td>Levels of IVIVC: definitions</td>
<td>✔</td>
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</tr>
<tr>
<td>Levels of IVIVC: advantages, disadvantages of different levels</td>
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<tr>
<td><strong>Role of IVIVC</strong></td>
<td></td>
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<tr>
<td>• establishing discriminatory power of in vitro dissolution test (Quality)</td>
<td>✔</td>
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</tr>
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<td>• clinical relevance of in vitro dissolution tests and associated dissolution specifications (PK and Clinical)</td>
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## European Guidance relating to IVIVC (currently in revision)

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<td>IVIVC data analysis: acceptable methodology for model development</td>
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<td>IVIVC development and validation: reporting</td>
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<td>Applications: specification setting</td>
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<td>Applications: waiver of BE studies for product variations</td>
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Why do companies develop IVIVCs?

*in vitro* dissolution = surrogate for BE study

save time and money

Why do regulators encourage IVIVCs?

**Approval Process**

- **Benefit**
- **Risk**

- Approval
- Refusal or Withdrawal

**Post-approval**

Reassurance that positive benefit/risk balance is maintained throughout life of product

CHMP Opinion + Annexes (SmPC, Conditions)
Examples of MR Product Variations: Methods

Search of Sentinel database
“granted licenses prolonged release formulations”
385 licenses/69 companies

“Type II variations - pharmaceutical”
63 licenses of interest

Compiled all variations for 63 licenses

3 representative examples + additional points from 4-5 others
MR Product Variations: Example 1

23 variations

5 pharmaceutical variations

Pharmaceutical variations:
- Change chemical identification test
- Remove score line
- Increase pack size
- Change manufacturing site
- Change dissolution specification

MA: 2001
MR Product Variations: Example 2

58 variations

16 pharmaceutical variations

Pharmaceutical variations:
- Change manufacturing site x2
- Change batch size, manufacturing process
- Change product specification (microbiological)
- Change storage site
- Change analytical methods
- Change frequency of IPC
- Change shelf life dissolution specification

MA: 1998

2011: 4.5/year
MR Product Variations: Example 3

54 variations

30 pharmaceutical variations

Pharmaceutical variations:
- Manufacturer, batch release site x 3
- Batch size
- In process control spec
- Add pack size
- Add storage and release site
- Extend shelf life
- Minor change to manufacturing process
- Add packaging site
- Change manufacturer of active
- Change dissolution method, specification

MA: 2004

2011: 9/year
Supporting evidence:
- Quality Overall Summary
- Batch data
- Stability data
- IVIVC (Level A)

Purpose of Variation:
To update the dissolution test method in line with the USP monograph and to change the specification time points and limits.

Var 17: 2007
MA: 2004

2011: 9/year
Dissolution Profiles

Proposed Low and High

IVIVC

Predicted C(t)

Upper limit (UL)

Lower limit (LL)

Target (Pivotal Batch)

% Released in vitro

Time (h)

0 4 8 12 24

% Released in vitro

% Released in vivo

0 20 40 60 80 100

PK Parameter

UL/LL

UL/Target

LL/Target

Cmax 116 113 97.1

AUC 112 106 94.9

Relative Bioavailability

MR Product Variations: Example 3 (cont’d)
MR Product Variations: Example 3 (cont’d)

Dissolution Profiles

Upper limit (UL)
Target (Pivotal Batch)
Lower limit (LL)

% Released in vitro
Time (h)

% Released in vivo
% Released in vitro

Predicted C(t)

IVIVC

Relative Bioavailability

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UL/LL
UL/Target
LL/Target
MR Product Variations: Example 3 (cont’d)

Dissolution Profiles

**Upper limit (UL)**

**Target (Pivotal Batch)**

**Lower limit (LL)**

**IVIVC**

**Predicted C(t)**

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Relative Bioavailability
MR Product Variations: Example 3 (cont’d)

1. All batches within specification bioequivalent to each other
2. Proposed limits considered appropriately supported

### PK Parameter

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### Dissolution Profiles

- **Upper limit (UL)**
- **Target (Pivotal Batch)**
- **Lower limit (LL)**

### IVIVC

- **Upper limit**
- **Target**
- **Lower limit**

### Predicted C(t)

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MR Product Variations: Example 3 (cont’d)

1. All batches within specification bioequivalent to each other
2. Proposed limits considered appropriately supported

Dissolution Profiles

IVIVC

Predicted C(t)

Conclusion: Proposed change will not have a detrimental effect on quality, safety or efficacy of the product.
MR Product Variations: Example 3 (cont’d)

1. All batches within specification bioequivalent to each other
2. Proposed limits considered appropriately supported

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Dissolution Profiles

1. Anchor to clinical batches.
2. Relationship to BE limits.

Proposed Low and High

IVIVC

Predicted C(t)

Interpolate

Extrapolate
Dissolution Limits in Product Specifications: Relationship to BE Limits

IVIVC → in vitro = surrogate for in vivo (BE) study

Dissolution Profiles
Dissolution Limits in Product Specifications: Relationship to BE Limits

“...limits are based on a maximal difference of 20% in the predicted AUC and, if relevant C_{max}.”  

NfG CPMP/QWP/604/96

All batches within dissolution specification limits should be bioequivalent to each other.  

All batches should be bioequivalent to target (pivotal batch).
Dissolution Limits in Product Specifications: Relationship to BE Limits

“...limits are based on a maximal difference of 20% in the predicted AUC and, if relevant $C_{\text{max}}$."

NfG CPMP/QWP/604/96

All batches within dissolution specification limits should be bioequivalent to each other.

Dissolution Profiles

Test/Ref (%) 80% 125%

UL/LL

UL/target

LL/target

% Released in vitro

Time (h)

Proposed Low and High Time (h)

% Released in vitro

Proposed Low and High Time (h)
Dissolution Limits in Product Specifications: Relationship to BE Limits

All batches should be bioequivalent to target (pivotal batch).

“...limits are based on a maximal difference of 20% in the predicted AUC and, if relevant $C_{\text{max}}$.”

NfG CPMP/QWP/604/96
Dissolution Limits in Product Specifications: Relationship to BE Limits

“...limits are based on a maximal difference of 20% in the predicted AUC and, if relevant $C_{\text{max}}$."

All batches within dissolution specification limits should be bioequivalent to each other.

All batches should be bioequivalent to target (pivotal batch).

NfG CPMP/QWP/604/96
Impact of IVIVC Validation Range on Justification of Dissolution Limits

Choice of formulations: widest possible range of dissolution behaviour, balancing need to keep release mechanism the same. … consider extending IVIVC range.
Implications for MR Development Program

<table>
<thead>
<tr>
<th>Stage</th>
<th>Target Specification</th>
<th>Prototype Selection</th>
<th>Formulation Optimisation</th>
<th>Scale-up Post-approval Changes</th>
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<tbody>
<tr>
<td>Question</td>
<td>What in vitro</td>
<td>Which prototypes</td>
<td>How must we alter</td>
<td>What is a significant</td>
</tr>
<tr>
<td></td>
<td>characteristics will</td>
<td>should be tested</td>
<td>in vitro release to</td>
<td>change in the in</td>
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<tr>
<td></td>
<td>achieve in vivo</td>
<td>in vivo?</td>
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<td>vitro profile?</td>
</tr>
<tr>
<td></td>
<td>target?</td>
<td></td>
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</tr>
<tr>
<td>Information</td>
<td>• Drug PK</td>
<td>• In vitro dissolution</td>
<td>• Conc-time data (+IVIVC)</td>
<td>• Many batches</td>
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<tr>
<td></td>
<td></td>
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… where extending range of IVIVC, showing applies to pivotal batches - need to consider in design of these studies and include a reference formulation – requires prospective approach.
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<td>sometimes need to extend range of IVIVC, sometimes need to show applies to pivotal batches; need to consider in design of these studies and include a reference formulation</td>
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<td>Applications: specification setting</td>
<td>alignment to average BE criteria</td>
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Key Messages and Opportunities

- Discriminatory Power of Dissolution Tests
- Anchor to Clinical Batches
- Use IVIVC to interpolate within a validated range of dissolution
- Align dissolution specification to average BE limits

Opportunities to contribute:
- Breakout session H
- Upon publication of draft guidance (ema.europa.eu)