The European Agency for the Evaluation of Medicinal Products
*Human Medicines Evaluation Unit*

London, 29 July 1999
CPMP/QWP/604/96

# COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

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

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| **DISCUSSION IN THE QUALITY WORKING PARTY (QWP)** | July 1996, January 1997<br>October 1997, January 1998 |
| **TRANSMISSION TO THE CPMP** | April 1998 |
| **RELEASE FOR CONSULTATION** | April 1998 |
| **DEADLINE FOR COMMENTS** | October 1998 |
| **ADOPTION BY CPMP** | July 1999 |
| **DATE FOR COMING INTO OPERATION** | January 2000 |

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# QUALITY OF MODIFIED RELEASE PRODUCTS:
# A: ORAL DOSAGE FORMS
# B: TRANSDERMAL DOSAGE FORMS
## *SECTION I (QUALITY)*

# 1. INTRODUCTION

## 1.1 Preamble

Pharmaceutical dosage forms may be developed in which the rate or place of release of active substance(s) has in some way been modified compared with conventional release formulations. Such modifications may have a number of objectives, but the intention of this NfG is to cover those formulations in which the release of active substance is modified in order to maintain therapeutic activity for an extended time, to reduce toxic effects or for some other therapeutic purpose.

This section II document will cover the various parts of the application for Marketing Authorization related to the quality and should be read in conjunction with section I of this NfG relating to clinical aspects. Furthermore, it is clear that this NfG will cross-refer to other quality guidelines and to official compendia.

For clear definitions on the terminology used to describe different types of release models and other definitions, reference is made to the Annex 1.

## 1.2 Scope

This NfG concerns quality aspects, especially *in vitro* testing, of dosage forms in which release of active substance is modified. Many principles discussed under paragraph 2 on prolonged release oral products will be relevant to other prolonged or delayed action dosage forms intended for administration via other routes; see paragraphs 3 and 4.

# 2. PROLONGED RELEASE ORAL DOSAGE FORMS

## 2.1 Development pharmaceutics

### 2.1.1 General remarks

The quality of a prolonged release dosage form is continuously improved during the different development phases of a new drug product. The choice of the composition is normally made early in the development based on small-scale batches taking into account physicochemical properties of the drug substance, stability and drug absorption. As soon as the constituents are chosen, gradual upscaling of the manufacturing process will start. During this period it is reasonable to expect that necessary adjustments will be made to reach full-scale production. These adjustments might be changes in composition, manufacturing processes, equipment or manufacturing site.

In some cases these adjustments may have an effect on the properties of the drug product. It is therefore recommended that an *in vitro* dissolution test is developed which is able to indicate predict changes which may have an effect on the efficacy or safety of the product.

The formulation chosen in early development should be tested under different dissolution conditions to determine its sensitivity to the expected physiological environment after administration. The discriminatory power of the test conditions chosen for routine control may be determined by comparison of the *in vitro* dissolution data and the bioavailability data of the different formulations. If an *in vivo-in vitro* correlation (IVIVC) is established, the dissolution test -after proper validation- can be used as a qualifying control method with *in vivo* relevance, while in the case of the absence of an IVIVC the dissolution test can be used only as quality control method.

After completed scale-up and without an established IVIVC, it is reasonable to compare the laboratory/pilot scale batches with the full production scale batches in a bioavailability study if

the scale-up factor exceeds 10 in order to verify the dissolution test conditions chosen for the release of clinical materials, upscaling and manufacture (see also 2.1.4).

It is bad practice to subdivide prolonged release dosage forms but it may be justified in exceptional cases.

### 2.1.2 Therapeutic objectives and principle of the release system

The therapeutic objectives and rationale of the prolonged release product should be provided. Pharmacokinetic (e.g. AUC, $C_{max}$, $T_{max}$, $t_{1/2}$) and physico-chemical characteristics of the active substance (e.g. solubility at different pH, partition coefficient, particle size, polymorphism) relevant to the development of the product should be given. Detailed information on the release controlling excipient(s) should be given. Reference is made to the NfG "Development Pharmaceutics".

The prolonged release system should be described:

- the manner in which prolonged release is intended to be achieved (membrane type, matrix, etc.)
- release mechanism and kinetics if known (diffusion, erosion, osmosis, etc. or a combination of these)
- single non-disintegrating unit or disintegrating tablet/capsule containing multiple-units of pellets, etc.

### 2.1.3 Development and validation of dissolution methods

The release rate should be tested *in vitro* by a dissolution test method. This *in vitro* dissolution test must be capable of:

- discriminating between batches with respect to critical manufacturing variables which may have an impact on the desired bioavailability
- showing batch to batch consistency of pivotal clinical, bioavailability and routine production batches
- determining stability of the relevant release characteristics of the product

The prolonged release formulation should therefore be tested *in vitro* under various conditions (media, pH (normally pH range 1-6.8; in cases where it is considered necessary 1-8), apparatus, agitation, etc.). Testing conditions providing the most suitable discrimination should be chosen. For additional details with respect to the choice of apparatus, testing conditions, validation/qualification and acceptance criteria, reference is made to the Ph.Eur. "Dissolution test for solid dosage forms". The volume of medium should preferably ensure sink conditions.

Special attention should be paid to the importance of any variation in the active substance (e.g. particle size, polymorphism), release controlling excipient(s) (e.g. particle size, gelling properties) or manufacturing process.

The assay method of the active ingredient in dissolution samples should be validated according to the relevant ICH guidelines "Validation of analytical procedures" and "Validation of analytical procedures: Methodology", with special attention to the stability of the active ingredient dissolved in the medium and effects from the excipients.

Identical or, if not possible, comparable test conditions should be used for different strengths of the same product. Normally in development, at each time point individual dosage unit results ($n \geq 6$), the mean value and a measure of variability should be presented, other statistical approaches have to be justified. Dissolution profiles should be determined for all strengths and,

if relevant, for any changes in the composition and/or manufacturing process of the product during development.

### 2.1.4 Bioavailability study

A summary of the bioavailability studies should be given. The data should include information on pharmacokinetics (AUC, $C_{max}$, $T_{max}$, $t_{1/2}$, etc.), batch numbers, formulations and dissolution results of the batches used.

Bioavailability studies should be performed with batches of at least 10% of full production scale, unless pivotal clinical studies have been performed with batches of this size. In this case bioavailability studies performed with batches of a smaller scale may be sufficient if these batches have been produced in a manner representative of the full scale manufacturing process. So, if phase II trials (including PK/BA-studies) are conducted at a scale of 15 kg, the pivotal clinical trials (no BA data available) at a scale of 60 kg and full production scale is intended to be 600 kg, no additional BA-studies at a scale of 60 kg are required.

### 2.1.5 Comparison of dissolution profiles

On several occasions dissolution profiles have to be compared for similarity, e.g. after scale-up or changes in composition and/or manufacturing process. The similarity of the profiles may be compared by model-independent or model-dependent methods e.g. linear regression of the percentage dissolved at specified time points, by statistical comparison of the parameters of the Weibull function or by calculating a similarity factor. An example for this last method is given in annex 2.

### 2.1.6 *In vitro-in vivo* comparison

*In vitro* dissolution testing is not only important as a necessary quality assurance for batch-to-batch consistency but in many cases it also indicates that each individual dosage unit will have the desired *in vivo* performance. By establishing a meaningful correlation between *in vitro* release characteristics and *in vivo* bioavailability parameters, the *in vitro* dissolution test can serve as a surrogate marker for *in vivo* behaviour and thereby confirm consistent therapeutic performance of batches from routine production.

Furthermore, an established *in vitro-in vivo* correlation (IVIVC) may reduce the number of bioequivalence studies during product development, be helpful in setting specifications and be used to facilitate certain regulatory decisions (e.g. scale-up and post-approval variations).

Therefore, an attempt to develop such an IVIVC should be considered by the applicant.

However, such a correlation is not intended to serve as a basis for claiming bioequivalence between different products from different MA applicants, based on *in vitro* data only.

For additional details reference is made to annex 1.

## 2.2 Setting specifications

In general, a minimum of three points should be included in the specification on *in vitro* dissolution of an oral prolonged release product: an early time point to exclude dose dumping (typically 20 to 30% dissolved), at least one point to ensure compliance with the shape of the dissolution profile (around 50% dissolved) and one to ensure that the majority of the active substance has been released (generally more than 80% dissolved).

The acceptable variation allowed around each time-point (upper and lower limits*)*, can be determined in different ways:

**a. No IVIVC:**

The tolerance limits may be derived from the spread of *in vitro* dissolution data of batches with demonstrated acceptable *in vivo* performance (biobatch(es)), or by demonstrating bioequivalence between batches at the proposed upper and lower limit of the dissolution range (the so-called "side-batch" concept).

Normally, the permitted variability in release at any given time point should not exceed a total numerical difference of ±10% of the labelled content of active substance (i.e. a total variability of 20%: a requirement of 50±10% thus means an acceptable range from 40-60%), unless a wider range is supported by a bioequivalence study.

**b. Established IVIVC:**

Level A: The specification is based on a 1:1 correlation between the dissolution profile *in vivo* and *in vitro*. The *in vivo* profile can be derived from the plasma concentration time profile using deconvolution (or other appropriate methods). The *in vitro* dissolution profile can be described by certain mathematical models (Weibull function or Hill equation) or just based on release at different time points. Tolerance limits are based on a maximal difference of 20% in the predicted AUC and, if relevant $C_{max}$. Limits based on a difference greater than 20% should be justified.

Level B/C: The tolerance limits are based on one point estimations of three or more compositions and defined by a maximal difference of 20% in the predicted AUC and, if relevant $C_{max}$ . Limits based on a difference greater than 20% should be justified. Limits for other time points should be based on the dissolution profile(s) of the biobatch(es) as under 2.2.a.

Multi-level C: At each time point, the tolerance limit is defined by a maximal difference of 20% in the predicted AUC and, if relevant $C_{max}$. Limits based on a difference greater than 20% should be justified. If there is a correlation between two or more pharmacokinetic parameters, then the specification should be set with the parameter that results in the narrowest dissolution limits, unless otherwise justified

The defined dissolution specification is also applied during the shelf-life of the product. If stability studies with the finished product indicate that the release rate changes, the tolerance limits at release should be narrowed or the shelf-life reduced in order to guarantee that the product at the expiry date complies with the tolerance limits derived from batches which have been shown to have an acceptable *in vivo* performance.

## 2.3 Control tests

### 2.3.1 In process (if necessary)

A dissolution specification which may be applied to intermediate products (e.g. cores, pellets) may be the same or different from that to be applied to the finished product. If different, a justification for the limits chosen should be provided.

### 2.3.2. Finished product

The finished product specification must contain validated acceptance limits for dissolution. All dosage units tested should comply with these finished product specifications, however, in addition acceptance criteria for continued testing if one of the dosage units fails to comply, may be set. The selected acceptance criteria adopted for continued testing must be justified (e.g. by using the conditions of the correlation established or based on the Ph.Eur.).

Routine testing of the finished product is always necessary unless it can be demonstrated that this is not possible or justified. In these cases, routine testing of intermediates (e.g. cores, pellets) may be acceptable.

Preferably, results of batch analysis should be provided for production scale batches; a justification for using pilot scale batches should be given. Dissolution results of individual dosage units, the mean value and a measure of variability should be presented.

If results of production batches are not available, they should be supplied as soon as possible after the Marketing Authorisation has been granted.

### 2.4 Variations to products

EEC Regulation no. 541/95 and 542/95 set out provisions relating to variations to Marketing Authorisations, categorise them into Type I and Type II and defines the changes which can be processed as Type I provided the necessary conditions are met. Additional changes to the product which are not defined as Type I and which do not require new Marketing Authorisations (see Annex II of Regulation 541/95) will be processed as Type II variations.

The supporting data requirements for Type II variations will depend upon the significance of the change, whether or not an IVIVC exists and whether or not the dissolution method/limits is to be changed. If bioavailability/bioequivalence data have not been submitted their absence should always be justified.

When a Level A correlation has been established and the release specification is not changed, Type II variations (for example major changes in non release-controlling excipients, insignificant changes in release controlling excipients or major changes in method of manufacturing) may be accepted on the basis of *in vitro* data, the therapeutic index of the drug substance and predictability of the IVIVC.

In general, bioavailability/bioequivalence data are needed for products with an established Level B or C correlation or no IVIVC, unless justification is provided for absence of such data.

## 3. DELAYED RELEASE DOSAGE FORMS

NOTE: Many principles discussed under paragraph 2 are also relevant to delayed release dosage forms; some additional points will be given below.

Several delayed release dosage forms have been identified by the Ph.Eur.: gastro-resistant capsules, tablets and granules.

### 3.1 Development pharmaceutics

A full summary of the bioavailability studies (including batch numbers, formulations, etc.) should be provided.

The rationale for the delayed release should be given, e.g. the protection of the gastric mucosa, the protection of the active substance against the influence of acidic gastric medium or intended release of the active substance in a predefined segment of the gastro-intestinal tract for locale treatment, etc.

The choice of the excipient(s) responsible for the gastroresistance (and intentional release at a certain pH) should be discussed.

In principle two different types of formulations can be distinguished for delayed release products with respect to the behaviour in the stomach:

- single unit non-disintegrating dosage forms

- disintegrating dosage forms with multiple units of pellets

The development of single unit non-disintegrating dosage forms is discouraged since their residence time in the stomach is unpredictable and in general longer than disintegrating dosage forms with multiple units of pellets. Therefore, such single unit non-disintegrating dosage forms are liable to a higher risk of dose-dumping. If a single unit non-disintegrating is developed for special targeting purposes, e.g. colon tablets, release of the active substance via uncontrolled diffusion processes during gastro-resistance testing should be investigated.

If the SmPC does not exclude the co-administration with food, gastro-resistance should also be tested at a higher pH (e.g. in the range 2-5) both for single unit non-disintegrating and disintegrating dosage forms with multiple units.

### 3.2 Control tests

Single unit non-disintegrating dosage forms should comply with the Ph.Eur. test on gastro-resistance. Dissolution should preferably be tested routinely both at a low pH (e.g. pH 2) to identify possible damage to the gastro-resistant coating or diffusion of the active substance through the coating and at a pH simulating the intestinal segment for release (e.g. pH 6.8). Appropriate limits, based on batches used in the clinical trials including biostudies which show acceptable *in vivo* performance, should be set.

The Ph.Eur. test on gastro-resistance is not suitable for disintegrating dosage forms with multiple units of pellets. Such products should be tested for gastro-resistance and dissolution preferably in one test system. After exposure for at least 1 hour to an acidic medium, the medium should be changed (e.g. to pH 6.8) and the release of the active substance should be tested. Reference is made to the Ph.Eur. "Dissolution test for solid dosage forms".

The specification for dissolution of disintegrating dosage forms with multiple units of pellets should be derived from batches which show acceptable *in vivo* performance. The specification should require two points: one after 1 hours of gastric simulation (e.g. NMT 10% of the active substance released) and one for complete dissolution after changing to a medium of higher pH. Individual dosage unit results ($n \geq 6$), the mean value and a measure of variability should be presented. With regard to acceptance criteria for continued testing, reference is made to the Ph.Eur. "Dissolution test for solid dosage forms".

### 3.3 Variations to products

Type I variations are applicable to delayed release products provided the necessary information is submitted to support the change.

Since the *in vitro* test on gastro-resistance for delayed release dosage forms is considered relevant to the *in vivo* situation, variations in the excipients responsible for delayed release in such products can be supported by *in vitro* data only, where justified. Profiles of release after gastro-resistance testing should of course be unchanged.

## 4. TRANSDERMAL PATCHES

NOTE: Many principles discussed under paragraph 2 are also relevant to transdermal products; some additional points will be given below.

A Transdermal Drug Delivery System (TDDS) or transdermal patch is defined as a flexible pharmaceutical preparation of varying size containing one or more active substances to be applied on the intact skin for systemic absorption, reference is made to the Ph.Eur.

Such TDDS are designed to provide a slow delivery of the active substance(s) through the intact skin resulting in a constant systemic absorption rate. In a TDDS normally the rate-

limiting step for systemic absorption of the active substance(s) is the absorption through the skin.

### 4.1 Development pharmaceutics

A full summary of the bioavailability studies (including batch numbers, formulations, etc.) should be provided.

A rationale for the TDDS should be given taking into account the therapeutic benefit, pharmacokinetic properties of the drug substance (e.g. pharmacodynamy, $t_{1/2}$, therapeutic index, first pass-effect) and physico-chemical properties of the drug substance (e.g. molecular weight, partition coefficient, local tolerance). The site of application on the skin should be given.

Different types of TDDS could be distinguished, e.g.:

- active substance(s) incorporated in the adhesive matrix
- active substance(s) incorporated/dissolved in a (semi-solid) reservoir, release through a membrane

The following items should be discussed:

- description of the TDDS including material, function, dimensions of different parts and compatibility with the other components of the TDDS (active substance(s), excipients)
- description of development manufacturing process
- description of the excipients responsible for the pressure-sensitive adhesion
- description of any penetration-enhancer used and its relation with drug absorption
- drug load versus total amount released from the TDDS over the intended period of use
- possibility of crystallisation/precipitation of the active substance in the TDDS during the intended period of use and the impact on drug absorption
- adhesive properties of the TDDS covering the intended period of use including information on local tolerance and waterproofness if relevant
- residual solvents
- proportionality of different strengths if relevant
- occlusion

### 4.2 Control tests

#### 4.2.1 In process (if necessary)

A dissolution specification applied to intermediate products (e.g. semi-solid matrix) may be the same as or different from that of the finished product. If different, a justification for the limits chosen should be given.

#### 4.2.2. Finished product

Release characteristics of the active substance from the TDDS should be tested with a suitable dissolution method. Different methods can be used (disc assembly, cell or rotating cylinder) depending on the composition, dimensions and shape. Special attention should be paid to any membrane used in relation to the kinetics of the active substance and its possible interference with the performance. Reference is made to the Ph.Eur. "Dissolution test for transdermal patches".

The specification for drug release characteristics should be derived from batches used in the clinical trials showing acceptable *in vivo* performance. Dissolution *in vitro* should be tested at least up to a time point at which a steady state release is achieved and the intended period of time for treatment should preferably be covered. Testing over shorter periods should be justified.

Normally, the release characteristics are expressed as the amount active substance(s) released per surface area per time unit.

Results of individual dosage units ($n \geq 6$), the mean value and a measure of variability should be presented.

TDDS comply with Ph.Eur. test C for uniformity of content of single-dose preparations, unless otherwise justified.

### 4.3 Variations to products

Type I variations are applicable to TDDS provided the necessary information is submitted to support the change. Since TDDSs are highly variable dosage forms (inter- and intra-individual), any variation in the composition (drug reservoir, pressure-sensitive adhesive) and dimensions should normally be supported by *in vivo* data unless extensively justified.

**ANNEX 1**
**Glossary**

Biobatch:

Batch used in a bioavailability/bioequivalence study or in clinical testing showing acceptable performance; the size of this batch is at least pilot scale, i.e. for oral solid dosage forms at least 10 % of full production scale or 100.000 units, whichever is larger

Conventional release dosage form:

Preparations showing a release of the active ingredient which is not deliberately modified by special formulation and/or manufacturing method. In case of a solid dosage form, the dissolution profile of the active ingredient depends essentially on the intrinsic properties of the active ingredient.

Equivalent term: Immediate release dosage form

Convolution:

Prediction of plasma drug concentrations using a mathematical model based on the convolution integral, e.g. the following convolution integral may be used to predict plasma concentration (c(t)) resulting from the absorption rate time course ($r_{abs}$); The function $c_\delta$ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and is typically estimated from i.v. bolus data:

$$c(t) = \int_0^t c_\delta (t-u)\, r_{abs} (u)\, du$$

Deconvolution:

Estimation of the time course of drug input (usually *in vivo* absorption or dissolution) using a mathematical model based on the convolution integral; e.g. the absorption rate time course ($r_{abs}$) that resulted in the plasma concentration (c(t)) may be estimated by solving the following convolution integral for $r_{abs}$. The function $c_\delta$ represents the concentration time course that would result from the instantaneous absorption of a unit amount of drug and is typically estimated from i.v. bolus data:

$$c(t) = \int_0^t c_\delta (t-u)\, r_{abs} (u)\, du$$

Delayed release dosage form:

Modified release dosage forms showing a release of the active ingredient which is delayed. Delayed release is achieved by special formulation design and/or manufacturing method. The release of the active substance is delayed for a predefined period after administration or application of the dosage form and then releases as a conventional dosage form resulting in a lag time without any change in other pharmacokinetic parameters.

External predictability:

Evaluation of predictability using a new data set then the ones on which the IVIVC is established (how well predicts the model the data)

Internal predictability:

Evaluation of predictability using the initial test data set on which the IVIVC is established (how well describes the model the data used for establishing the IVIVC)

Laboratory scale:

Batches produced at a size of 100-1000x less than full production scale.

Mean absorption time:

Time required for drug top reach systemic circulation from the time of drug administration = mean time involved in the *in vivo* release and absorption processes as they occur in the input compartment:

$MAT = MRT_{oral} - MRT_{i.v.}$

Mean *in vitro* dissolution time:

The mean time for a drug to dissolve *in vitro*:

$$MDT_{vitro} = \frac{\int_0^{\infty}(M^{\infty} - M(t))dt}{M^{\infty}}$$

Mean *in vivo* dissolution time:

The mean time for a drug to dissolve in vivo:

$MDT_{solid} = MRT_{solid} - MRT_{solution}$

Mean in vivo residence time:

The average time for a drug to reside in the body:

MRT = AUMC/AUC

Modified release dosage forms:

Preparations where the rate and/or place of release of the active ingredient(s) is different from that of the conventional dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing method. Modified release dosage forms include prolonged release, delayed release, pulsatile release and accelerated release dosage forms.

(It should be noted that pulsatile and accelerated release dosage forms are not covered by the current guideline)

Percent prediction error:

%PE = [(observed value - predicted value) / observed value] x 10

Prolonged release dosage forms:

Modified release dosage forms showing a slower release than that of the conventional release dosage form administered by the same route. Prolonged release is achieved by special formulation design/and/or manufacturing method.

Equivalent term: extended release dosage form

Release controlling excipient:

Excipient with determining effect on the release of the active substance

Side batch:

Batches representing the intended upper and lower *in vitro* release specification derived from the defined manufacturing process by setting process parameters within the range of maximum variability expected from process validation studies

Sink conditions:

May be assumed if the amount of substance in solution at the end of the dissolution test does not exceed 30% of the saturation concentration

Statistical moments:

These are parameters that describe the characteristics of the time courses of plasma concentration (area, mean residence time and variance of mean residence time) and of urinary excretion rate (Journal of Pharmacokinetics & Biopharmaceutics, vol 6(6), 547, 1978)

**ANNEX 2**

## 1. *In-vivo - in-vitro* correlations (IVIVC)

A number of techniques may be employed in order to establish an IVIVC. The following levels can be defined:

Level A: representing a point-to-point relationship between the *in vitro* dissolution curve of the product and the in vivo dissolution curves generated by deconvolution of plasma level data or by other appropriate methods (Wagner-Nelson, Loo-Riegelman, numeric deconvolution*)*

Level B: representing a one point relationship between: a) the mean *in vitro* dissolution time of the product and either the mean in vivo residence time or the mean in vivo dissolution time by using the principles of statistical moment analysis; or b) the *in vitro* dissolution rate constant versus the absorption rate constant derived

Level C: representing a one point relationship between the amount dissolved *in vitro* at a particular time and one mean pharmacokinetic parameter, e.g. AUC, $C_{max}$ or $T_{max}$; if one or several pharmacokinetic parameters correlate to the amount of drug dissolved at various time points of the dissolution profile, a multi-level C correlation has been established

## 2. Developing an IVIVC

### 2.1 Level A

Generally, one formulation tested at different dissolution conditions should be compared with a plain aqueous solution of the active substance. Ideally, the formulations should be compared in a single study with a cross-over design.

*In vitro* conditions producing a dissolution profile which is similar to the *in vivo* input rate are chosen. If the *in vitro* dissolution is either faster or slower than the *in vivo* input rate, the introduction of a uniform time scaling factor can be considered.

### 2.2 Level B and C

Generally, level B and C correlations are not useful for supporting major variations in the composition or manufacturing process of the product but can be useful in setting specifications

If a linear correlation can be established based on a minimum of on the one hand three time points, between the amount dissolved or three MDT's and on the other hand the corresponding AUC, $C_{max}$, MRT or any other suitable pharmacokinetic parameter (multi level C), *in vitro* data can be used to predict *in vivo* performance. It should be noted that if a multi level C correlation is achievable, then also the development of a level A correlation is feasible.

## 3. Evaluating the predictability of a Level A or C IVIVC

In view of the use of an IVIVC as a surrogate marker for *in vivo* performance, it should be verified that the predictability of the *in vivo* performance of a product based on its *in vitro* dissolution profile is valid for the *in vitro* dissolution rates covered by the specification. This evaluation should focus on the estimation of the predictive performance or, conversely, prediction error.

In this evaluation, two basic concepts are important:

- the less data available for development and evaluation of the IVIVC, the more additional data needed for the complete evaluation of the predictability of the IVIVC

- the formulations studied should differ adequately in release rate (e.g. ³10% dissolved) resulting in substantial difference in the pharmacokinetic parameters of interest

It should be noted that the evaluation of the predictability is an active area of investigation and that definitive recommendations regarding methods and criteria cannot be given.

## 4. Methods for evaluation of predictability

Any appropriate mathematical method can be used to estimate the magnitude of the error in prediction of the *in vivo* results from *in vitro* dissolution data, if fully justified.

Here, one approach is given as an example.

### 4.1 Internal predictability

Predict the plasma concentration profile for each formulation used to define the IVIVC. The predicted profile is then compared with the observed profile according to the equation (a) for the percent prediction error:

(a) %PE =[(observed value - predicted value) / Observed value] x 100

Criteria for considering the predictability of the IVIVC as acceptable are:

- average absolute percent prediction error (%PE) ≤10% for $C_{max}$ and AUC, plus %PE for each formulation ≤15%

If these criteria are not met, external evaluation should be performed.

### 4.2 External predictability

An additional data set of a formulation not used in developing the IVIVC (however, within the model of the product and of the same MA applicant/manufacturer) should be used. Criteria for considering the predictability of the IVIVC as acceptable are:

- %PE ≤10% for $C_{max}$ and AUC

If the %PE is between 10-20% again additional data are needed. All the data should be included in the evaluation. A %PE > 20% indicates unacceptable predictability.

**ANNEX 3**
**Similarity factor**

A similarity factor can be defined as:

$f_2 = 50.\log\{[1+(1/n)\Sigma_{t=1}^{n}(R_t-T_t)^2]^{-0.5}.100\}$

In this equation $f_2$ is the similarity factor, n is the number of time points, R(t) is the mean percent drug dissolved of e.g. the current formulation, and T(t) is the mean percent drug dissolved of e.g. the changed composition.

The evaluation of similarity is based on the conditions of:

- a minimum of three time points
- 12 individual values for every time point
- not more than one mean value of >85% dissolved
- that the standard deviation of the mean should be less than 10% from the second to last time point

An $f_2$ value between 50 and 100 suggests that the two dissolution profiles are similar.