EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2012
EMA/492713/2012
Quality Working Party (QWP)

Guideline on quality of oral modified release products

Draft

Draft Agreed by QWP	May 2012
Adoption by CHMP for release for consultation	19 July 2012
Start of public consultion	15 September 2012
End of consultation (deadline for comments)	15 March 2013

This guideline together with the Guideline on Quality of Transdermal Patches replaces Note for Guidance on Modified Release products: A: Oral dosage Forms B: Transdermal Dosage Forms. Part I (Quality).

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

Keyword	**Oral dosage form, modified release**

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Guideline on quality of oral modified release products

Table of contents

1. Introduction

1.1. Preamble

Pharmaceutical dosage forms may be developed in which the rate and/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, such as maintaining therapeutic activity for an extended time, reducing toxic effects, protecting the active substance against degradation due to low pH, targeting the active substance to a predefined segment of the gastrointestinal tract for local treatment or targeting active substance release at specified time-points.

This section I document covers the various parts of the application for Marketing Authorization related to quality and should be read in conjunction with section II of this NfG relating to clinical aspects. Furthermore, it is clear that this NfG cross-references 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 Annex I.

1.2. Scope

This NfG concerns quality aspects, especially pharmaceutical development and *in vitro* testing, of dosage forms in which the release of active substance is modified. This guideline only covers delayed release oral dosage forms with the principle of gastro-resistance and prolonged release oral dosage forms. Pulsatile and accelerated release dosage forms are not covered by the current guideline. Delayed release dosage forms with other principles, including those designed to release in a specific area of the gastrointestinal tract in response to a specific trigger (e.g. enzymes) or at specific time(s) after ingestion are not specifically addressed.

Many principles discussed under paragraph 2 with respect to prolonged release oral dosage forms will be relevant to other modified release dosage forms intended for oral administration or via other routes.

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 development of a new drug product. The choice of the composition is normally made early in the development based on small-scale batches and takes into account physicochemical properties of the drug substance, stability and drug absorption characteristics throughout the gastrointestinal tract. As soon as the constituents are chosen, gradual scaling up of the manufacturing process will start. During this period it is reasonable to expect that adjustments will be necessary 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 detect changes which may have an effect on the efficacy or safety of the product.

Pharmaceutical development should establish the link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate.

The formulation chosen in early development should be tested under different dissolution conditions to determine its sensitivity/robustness 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 a Level A *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 absence of a Level A IVIVC the dissolution test can be used only as a quality control method.

After completed scale-up 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 (compared to the laboratory/pilot scale biobatch) in order to verify that the dissolution test conditions chosen are appropriate for the release of clinical materials, scale-up and manufacture (see also 2.1.3. and 2.1.4 and 2.1.5).

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}, t1/2) 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 guidelines on pharmaceutical development.

The following characteristics of the prolonged release system should be described:

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

It should be demonstrated that the prolonged release product maintains its drug release characteristics regardless of relevant variability in physiological conditions. Examples of such variability include gastric and intestinal transit time, food effect, pathological gastrointestinal fluid composition and concurrent alcoholic intake, if and where relevant.

In general, prolonged release oral dosage forms should not have a score line because subdivision or other manipulation of modified release products may adversely affect the modified release properties of the dosage form, possibly leading to dose dumping. Any recommendation on subdivision of a modified release dosage form should be supported by scientific justification that the subdivision does not affect the modified release characteristics, including *in vitro* and/or *in vivo* data as appropriate.

2.1.3. Development of dissolution methods

The release rate should be tested *in vitro* by a dissolution test method. The development of a suitable dissolution test method should be based on the physicochemical *in vitro* and *in vivo* characteristics of the active ingredient and the drug product considering the mechanism of release.

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;

- testing for batch to batch consistency of pivotal clinical, bioavailability and routine production batches;
- determining stability of the relevant release characteristics of the product over the proposed shelf life and storage conditions.

The prolonged release formulation should therefore be tested *in vitro* under various conditions (media, pH (normally pH range 1-7.5; in cases where it is considered necessary pH 1-8), apparatus, agitation, etc.). Testing conditions, including sampling timepoints and frequency providing the most suitable discrimination should be chosen.

If media with a low buffering capacity are used, the pH should be controlled during the dissolution test to be sure that there is no influence of dissolved active ingredient and/or excipients on the dissolution conditions during the test period.

If a surfactant is used in the dissolution medium, the amount needed should be justified. The choice of the surfactant should be discussed and its consistent batch to batch quality should be ensured.

The inclusion of enzymes in the media is acceptable, and even encouraged, when justified (e.g., colonic delivery). If enzymes are added to the dissolution media, a rationale should be given for the type and concentration of enzymes added. Further, consistency of the batch to batch quality of the enzymes should be ensured including activity (IU/mg or IU/ml) or concentration (mg/ml) as appropriate. Note that the enzyme concentration of the SGF / SIF media prescribed in the Ph.Eur. are much higher than physiologically relevant values.

Justified enzyme concentrations should be used when the enzymes constitute part of the dissolution control mechanism. The use of biorelevant media may improve the correlation to *in vivo* data and may detect a potential food effect.

The volume of medium should preferably ensure sink conditions.

For formulations having a zero order release kinetics (with or without lag time) a specification of the dissolution rate over time (per cent of label claim per hour) for a given interval may be suitable instead of the cumulative amount dissolved at a given time point (see also section 2.2). For this type of product, a graphical presentation of the dissolution rate versus time should be additionally presented in order to justify that the product can be regarded as a zero-order release formulation. For additional details with respect to the choice of apparatus, testing conditions, validation/qualification and acceptance criteria, reference is made to the Ph. Eur.

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, individual dosage unit results, the mean value and a measure of variability (e.g. standard deviation or 95 % confidence interval) should be presented at each time point. Use of other statistical approaches must 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. Discriminatory power of the dissolution test

It should be shown that the dissolution test under the chosen test conditions is able to discriminate between batches with acceptable and non acceptable *in vivo* behavior.

Showing discriminatory power may be achieved in one of the following approaches in order of priority:

- It is best practice to include batches which have failed to show acceptable pharmacokinetic parameters in vivo. Based on the dissolution results, meaningful specifications may be set to reject such batches due to their dissolution data. This may be supported quantitatively though a validated IVIVC, which has been developed under consideration of batches with unacceptable pharmacokinetic parameters;
- In cases where there are no non-acceptable batches available, the dissolution data may be compared to the average results of the pharmacokinetic parameter (point estimates) of the in vivo studies. These data may be compared by checking the rank order of the results;
- If neither of the first two approaches is feasible, the discriminatory power may be shown by deliberately varying an attribute of the active ingredient (e.g. particle size distribution), composition and/or manufacturing process parameters, in order to produce different in vitro dissolution behavior, without generating in vivo data for these batches. However such test procedures may lead to over-discrimination, i.e. even batches with acceptable in vivo performance may be rejected by the quality control method.

2.1.5. Bioavailability study

A summary of the bioavailability studies should be given. The data should include information on pharmacokinetics (AUC0 → t(last), AUC0 → ∞, C_{max}, and other relevant parameters; for generic products also the point estimates and 90% confidence intervals), manufacturing sites and dates, batch sizes and numbers, formulations and dissolution results of the batches used.

Bioavailability studies should be performed with batches of 100,000 units or at least 10% of full production scale, whichever is greater, 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, for example, 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.

2.1.6. 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 or in case of a biowaiver for different strengths. Similarity of dissolution profiles should be established with at least 12 individual values per time point. Consideration should be given to the sampling timepoints and frequency, taking into account the physicochemical *in vitro* and *in vivo* characteristics of the active ingredient and the mechanism of release of the drug product.

In cases where the biowaiver is to be applied for approval of different strengths, if not all strengths of a test drug product are compared *in vivo* versus the reference, the dissolution of the other strengths of the test product will be compared to the strength of the test product used in the bioequivalence study.

The profiles should be compared and their similarity may also need to be demonstrated by statistically justified methods using model-independent or model-dependent methods e.g. linear regression of the

percentage dissolved at specified time points, statistical comparison of the parameters of the Weibull function or calculation of a similarity factor.

2.1.7. *In vitro-in vivo* comparison

In vitro dissolution testing is not only important as a necessary quality assurance for batch-to-batch consistency but also to indicate consistency within a batch (i.e. that individual dosage units 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. The variability of the data should be reported and discussed when establishing a correlation. In general the higher the variability in the data used to generate the *in vitro-in vivo* correlation (IVIVC), the less confidence can be placed on the predictive power of the correlation.

An established Level A IVIVC may reduce the number of *in vivo* 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. Furthermore, establishment of a Level A IVIVC gives confidence in the use of dissolution testing as a change control tool.

Validation of a Level A IVIVC involves showing that it is sufficiently predictive. A Level A IVIVC is established based for example on a deconvolution technique, in which *in vivo* absorption or *in vivo* dissolution can be predicted from *in vitro* data and not C_{max} and AUC (detailed in Annex 2). A validated Level A IVIVC allows the use of the associated *in vitro* dissolution test as a surrogate for an *in vivo* study, as the resulting *in vivo* concentration-time profile can be predicted using the *in vitro* dissolution data and the IVIVC equation. Implicit in this approach is that (1) such an IVIVC can only be reliably used for interpolation (explained below) and (2) a single IVIVC model must be applicable to all formulations used in its development and validation.

Note that an IVIVC cannot serve as a basis for claiming bioequivalence between products from different MA applicants, based on *in vitro* data only.

An IVIVC model should be used for interpolation within the range of data used in its development, rather than extrapolation outside of the range over which it is known to apply. This principle is particularly important for regulatory applications, such as justification of dissolution specification and biowaivers. This has important implications for the choice of formulations to be included in an IVIVC study.

It is generally recommended to use formulations with widely varying *in vitro* dissolution profiles for IVIVC development and validation, since utilising formulations with only small differences in their *in vitro* dissolution profiles will limit the scope for widening of the specification range and the range for which a biowaiver can be justified. However, it is acknowledged that different release mechanisms or other biopharmaceutical factors may come into play at the formulation extremes, impacting on the relationship between *in vitro* and *in vivo* drug release and precluding generation of a single IVIVC equation which describes the behavior of all formulations within the range proposed for a biowaiver. Therefore, formulations should be chosen such that the same release mechanism is likely to control both the *in vitro* and *in vivo* release of drug. This will tend to limit the range of *in vitro* dissolution profiles used in practice for IVIVC development and validation.

If an extreme formulation (i.e. one with the fastest or slowest *in vitro* dissolution of the formulations used in the IVIVC) is subsequently chosen for further development, it is advisable to extend the IVIVC validation range by generating *in vivo* data for another formulation (yet faster or slower, as the case may

be) and using these data for external validation of the existing IVIVC or for redevelopment and validation of a new IVIVC.

2.2. Setting specifications

The specification should be set using a discriminatory dissolution test.

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 and/or to characterise a loading/initial dose (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 85% dissolved i.e. Q=80 %).

For drug products showing a zero order release a specification of the dissolution rate/time for a given time interval may be more appropriate than the cumulative amount dissolved at a distinct time point. In cases where a zero order release kinetic is combined with a variable lag time, such a specification is mandatory.

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 range 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 or a validated IVIVC.

b. Established Level A IVIVC:

The specification should be set using a discriminatory dissolution test. A validated Level A IVIVC allows *in vitro* dissolution data (in this case, proposed rather than observed data) to be used as a surrogate to an *in vivo* study of formulations at the proposed dissolution specification limits. Dissolution profiles are generated from the proposed limits using an appropriate mathematical function (Weibull function, Hill, etc as justified by the behaviour of formulations tested during product development) or, normally less usefully, based on release at different time points. The entire plasma concentration-time profile is calculated for the proposed upper and lower dissolution limits and the observed *in vitro* dissolution data for the to-be-marketed (reference) formulation utilising the validated IVIVC. The corresponding C_{max} and AUC values are calculated for the proposed lower and upper limits and the reference formulation and the ratios calculated (upper to lower, upper to reference and lower to reference).

The guiding principle of specification setting is that all batches within the lower and upper dissolution specification limits should be bioequivalent to one another. When bioequivalence is based on *in vivo* data, the acceptance range for the maximum difference in comparative data is 80-125%, based on confidence intervals around the mean C_{max} and AUC. Although some methods of IVIVC analysis quantify biological variability (and allow prediction of confidence intervals), most methods predict mean concentration-time data only. Therefore, for BE predicted based on mean data (by use of dissolution data in lieu of *in vivo* data and supported by an IVIVC), the criteria for BE limits must necessarily be tighter i.e., the difference between the C_{max} and AUC for the mean *in vivo* concentration-time data predicted for the upper and lower dissolution specification must be less than 20%. Limits based on a

difference greater than 20% between the predicted C_{max} and AUC for the upper and lower dissolution specifications must be justified.

For drugs that are absorbed throughout the gastrointestinal tract, the AUC is often similar for formulations of widely varying dissolution rates and the specification is driven by C_{max}, rather than AUC. In this case, the advantage of utilising an IVIVC for specification setting is that limits wider than +/- 10% in cumulative dissolution at particular time points may be possible, as not every time point has the same impact on C_{max}. The sensitivity of C_{max} to changes in dissolution depends on the pharmacokinetic properties of the drug (the shorter the half-life the greater the sensitivity to changes in dissolution) and the shape of the IVIVC relationship (i.e., whether *in vitro* or *in vivo* dissolution is faster).

2.3. Control strategy

General regulatory guidance on the establishment and justification of a control strategy for the drug product is given in other relevant guidelines. Particular attention should however be paid to the control of drug release from modified release drug products.

Pharmaceutical development should establish the link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate.

In an enhanced pharmaceutical development environment, compliance with the dissolution requirement could be demonstrated by real time release testing (see

Guideline on Real Time Release Testing EMA/CHMP/QWP/811210/2009-Rev1). As the drug release rate may be susceptible to scale-up effects, it is particularly important that the drug release rate prediction algorithm is verified at the commercial scale.

2.4. Variations to products

The supporting data requirements for variations to the Marketing Authorisation will depend upon the significance of the change, whether or not a Level A 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 IVIVC has been established and the release specification is not changed, changes may be accepted on the basis of *in vitro* data, the therapeutic index of the drug substance and predictive capability of the IVIVC. In this case, waiver of a bioequivalence study should be based on comparison of the predicted plasma concentration-time profiles and associated pharmacokinetic parameters (Cmax, AUC and a shape parameter) for the formulations before and after changes, calculated utilising the *in vitro* data and the validated 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

Several delayed release dosage forms have been identified by the Ph.Eur.: gastro-resistant capsules, tablets and granules. In this section, specific guidance is provided for gastro-resistant dosage forms. Products based on other principles can also often be classified as delayed release dosage forms, including those designed to release in a specific area of the gastrointestinal tract in response to a specific trigger (e.g. enzymes) or at a specific time after ingestion. Although the principles described herein for the pharmaceutical development, specifications and control strategy are also generally relevant for other

delayed release dosage forms, specific guidance for those dosage forms would have to be developed based on the relevant formulation principle and mechanism of release.

Note that in addition to the points addressed below, many of the principles discussed under paragraph 2 are also relevant to delayed release dosage forms.

3.1. Development pharmaceutics

A summary of the bioavailability studies should be given. The data should include information on pharmacokinetics (AUC0 → t(last), AUC0 → ∞, C_{max}, and other relevant parameters; for generic products also the point estimates and 90% confidence intervals), manufacturing sites and dates, batch sizes and numbers, formulations and dissolution results of the batches used.

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 local treatment, etc.

The mechanism of release and choice of the excipient(s) responsible for the delayed release should be discussed e.g. targeting release at a given pH, susceptibility to enzymatic attack, erosion with time etc.

Pharmaceutical development should establish the link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate.

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 containing multiple units of pellets.

The development of single unit non-disintegrating gastroresistant dosage forms is generally discouraged for gastroresistant products since their residence time in the stomach is unpredictable and in general longer than disintegrating dosage forms which contain multiple units of pellets. Therefore, such single unit non-disintegrating dosage forms are liable to a higher risk of dose-dumping and/or erratic concentration profiles.

If the SmPC requires the co-administration with food or does not exclude the co-administration with food, gastro-resistance should also be tested at a higher pH (e.g. in the range 3-5) for both single unit non-disintegrating and disintegrating dosage forms with multiple units to determine resistance to release in the fed stomach. Most meals will temporarily buffer the pH in the stomach to 3 or above, so pH 2 would not be a sufficiently challenging test.

3.2. Setting specifications

At least two points should be included in the specification on *in vitro* dissolution of a gastroresistant product: an early time point to exclude release in the acidic medium (less than 10% dissolved after 2 hours) and one to ensure that the majority of the active substance has been released in a (near) neutral medium (see Ph. Eur.) It is emphasized that gastroresistance must be demonstrated for two hours or more. With regard to acceptance criteria for continued testing, reference is made to the Ph. Eur..

3.3. Control strategy

Regulatory guidance on the establishment and justification of a control strategy for the drug product is provided elsewhere. Particular attention should be paid to the control of critical quality attributes that are responsible for the delayed drug release, e.g. the integrity of a gastro-resistant coating.

Pharmaceutical development should establish the link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate. In an enhanced pharmaceutical development environment, compliance with the dissolution requirement could be demonstrated by real time release testing (see Guideline on Real Time Release Testing EMA/CHMP/QWP/811210/2009-Rev1). As the principle for controlling the drug release in a delayed release dosage form may be susceptible to scale-up effects, it is particularly important that the design space is verified at the full commercial scale.

3.3 Variations to products

Since the *in vitro* test on gastro-resistance for delayed release dosage forms is considered relevant to the *in vivo* situation, changes 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.

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 (rabs); The function cδ 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:

$$c(t) = \int_0^t c\delta\,(t-u)\,rabs\,(u)\,du$$

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 (rabs) that resulted in the plasma concentration (c(t)) may be estimated by solving the following convolution integral for rabs. The function cδ 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 oral solution, suspension or rapidly releasing immediate release dosage forms data:

$$c(t) = \int_0^t c\delta\,(t-u)\,rabs\,(u)\,du$$

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.

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*:

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

$$M^{\infty}$$

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 100

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)

Zero order release

The drug release rate is independent of time.

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 (Wagner-Nelson, Loo-Riegelman, numeric deconvolution) or by other appropriate methods (e.g., modeling approaches based on convolution or differential equations using average data or population pharmacokinetic modeling).

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 several time points of the dissolution profile, a multiple Level C correlation has been established.

2. Developing an IVIVC

2.1. Level A

Recommendations and considerations around the design of an IVIVC study and subsequent IVIVC data analysis can be found in Section II of this Note for Guidance (Pharmacokinetic and Clinical Evaluation; CPMP/EWP/280/96 Corr). Generally, two or more formulations with sufficiently different dissolution profiles and an appropriate reference formulation (for the purpose of deconvolution) with fast drug release (e.g., intravenous administration, oral solution or immediate release formulation) are administered in a cross over study in healthy volunteers. Parent drug levels are quantified as a function of time in blood or plasma. The IVIVC can be modeled directly using plasma concentrations (one step approach) or after deconvolution of the modified release formulation concentration-time profiles relative to the immediate release formulation (two step approach). In order for *in vitro* dissolution test to serve as a surrogate marker for *in vivo* behaviour and to be used as a change control tool normally a level A IVIVC is required.

Initial testing of the formulations in a variety of different dissolution tests/conditions at the time of product release allows identification of the dissolution test that provides the most suitable discrimination. The *in vitro* dissolution testing time points for the formulations used in the IVIVC study should be of sufficient frequency to fully characterise the dissolution profile, including the plateau (e.g., three consecutive points differing by less than 5%). Fewer time points may be chosen for QC testing, but the converse is not true: QC time points are not appropriate for the *in vitro* component of the IVIVC data set since (1) sparse data may not allow accurate interpolation between points and (2) sampling stopped prior to reaching a plateau translates into incomplete drug release and compromises IVIVC validation.

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 in setting specifications, multiple level C correlations could be supportive.

A multiple level C correlation is developed through if a linear correlation can be established based on a minimum of on the one hand three time points, between the amount dissolved at three or more timepoints or three MDT's and on the other hand the corresponding AUC and, C_{max} for a number of formulations with different *in vitro* dissolution rate profiles, MRT or any other suitable pharmacokinetic parameter (multiple level C), *in vitro* data can be used to predict *in vivo* performance. It should be noted that if a multiple level C correlation is achievable, then also the development of a Level A correlation is feasible. A Level A IVIVC allows prediction of the entire plasma concentration-time profile (giving valuable insight into the shape of the profile and time of maximum concentration) in addition to summary pharmacokinetic parameters, such as C_{max} and AUC, while only the summary pharmacokinetic parameters are predicted from a multiple level C correlation. As such, a Level A is the preferred approach. Additionally, it should be noted that if a multiple level C correlation is achievable, a Level A correlation is likely to be feasible.

3. Evaluating the predictability of an 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 IVIVC. 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.≥ 10% dissolved) resulting in substantial difference in the pharmacokinetic parameters of interest.

Methodology and reporting of predictability analysis are further discussed in Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic And Clinical Evaluation); CPMP/EWP/280/96 Corr).