8 December 2022
EMA/CVMP/QWP/908160/2022
Committee for Veterinary Medicinal Products (CVMP)

Guideline on the quality of modified release dosage forms for veterinary use

Draft agreed by Quality Working Party (QWP)	June 2002
Adopted by CVMP for release for consultation	10 July 2002
Start of public consultation	12 July 2002
Deadline for comments	31 January 2003
Agreed by QWP	12 June 2003
Adopted by CVMP	23 July 2003
Date for coming into effect	1 February 2004
Revision 1*	
Agreed by QWP	23 November 2022
Adopted by CVMP	8 December 2022
Date for coming into effect	17 February 2023

*The current revision consists of administrative changes made in order to align the guideline with Regulation (EU) 2019/6, as amended, and to align with the current EMA template for Guidance. The references to the legislation applicable and other scientific guidelines have also been updated as appropriate. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary. The document reference number is changed to ensure correct document management. The previous document number was EMEA/CVMP/680/02-FINAL

Keywords	***Modified release***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Guideline on the quality of modified release dosage forms for veterinary use

Table of contents

1. Introduction (background)

Pharmaceutical dosage forms may be developed in which the rate of release of active substance(s) has in some way been modified compared with conventional formulations. Modification in release of active substances may have a number of objectives, but the intention of this note of guidance is to cover those products in which release of the active substance is modified in some way in order to maintain therapeutic activity without frequent dosing, reduce toxic effects, minimise stress in animals or reduce the workload of the handler.

The European Pharmacopoeia defines modified release in terms of the rate or site at which the active ingredient is released.

This guideline concerns the quality aspects of products, which are designed to modify the rate of release or to control the timing of release of the active ingredient(s) rather than those formulations affecting the site of release.

The details required in the application for marketing authorisation will reflect:

- the nature of the active substance
- the rationale of the formulation and/or design principle of the device
- the target species
- the route of administration
- the therapeutic intention, for example to achieve sustained drug levels, eliminating peaks and troughs etc.

and consequently

- dose intervals
- possibility of sudden release (dose dumping)

and data must be provided in the various sections of the dossier addressing these aspects.

Guidance is offered covering sections 2A to 2F of an application for marketing. Reference should also be made to other quality guidelines, where relevant.

2. Categories of modified release dosage forms

2.1. Modified release oral dosage forms

2.1.1. Conventional modified release oral formulations

The formulation may be based on the conventional tablet concept; utilising excipients and compression methods to impact slow-release characteristics. Tablets may be coated or uncoated. Capsules containing pellets are another such type of formulation. Such products can be designed to allow an initial rapid release of drug followed by sustained release, over a defined period of time. These preparations generally degrade completely following administration.

2.1.2. Delivery systems (e.g. intraruminal device)

A considerable range of systems to achieve continued or pulsed release are available, utilising different release principles such as diffusion, osmosis, hydrolysis, erosion, corrosion and swelling controlled drug

release etc. Examples include polymer matrix tablets, wax matrices, pulse release devices, soluble glass formulations, resin pellets, gelatine encapsulated needles, solvent activated systems, swellable hydrophilic polymer matrices etc. In many instances part of the device is retained in the animal.

2.2. Intravaginal dosage forms (e.g. vaginal sponges)

These may utilise a matrix which is impregnated with, or through which is uniformly distributed, an active substance. It is slowly made available for local action or for absorption through the vaginal walls.

2.3. Topical presentations

2.3.1. Insecticidal collars, ear tags, strips

In these the drug may be incorporated into a matrix and released by diffusion followed by dispersion through physical contact or released by vaporisation over a period of several months. Other release principles are possible.

2.3.2. Ophthalmic preparations (e.g. ocular inserts)

These consist of impregnated polymers used subconjunctivally.

2.4. Parenteral products

2.4.1. Injections

These may be formulated as depot preparations where e.g. a poorly soluble salt (ester) of the active is suspended in an oily type base releasing the drug slowly for absorption.

2.4.2. Implants

Implants commonly involve the dispersion of a drug throughout a matrix, which may be coated or laminated to achieve controlled drug delivery. This is likely to occur by diffusion. Implants tend to be positioned in non-vascular sites thus aiding retarded release into the blood stream.

2.5. Others (including novel formulations)

Any dosage form designed to give modified release, which does not fall into the afore mentioned categories 2.1 to 2.4. One example might be a hollow bit for horses, in which case the active substance is gradually eluted through its perforations by heat from the horse's mouth and salivary action.

3. Development Pharmaceutics *(refers to section 2A of the marketing authorisation dossier)*

3.1. Therapeutic objectives

The therapeutic objectives and rationale for developing the product should be provided. Pharmacokinetic (e.g. AUC, C_{max}, T_{max}, $t_{1/2}$, etc.) 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) or device should be given. Reference is made to the Guideline on Development Pharmaceutics for Veterinary Medicinal Products.

3.2. Principle of the modified release system

The modified release system should be described in terms of:

- the manner in which release is intended to be achieved (membrane type, matrix, etc.);
- single non disintegrating unit, multi-unit pelletised preparation, single eroding unit etc.;
- release mechanism and kinetics (diffusion, erosion, osmosis, etc. or combinations of these).

3.3. Establishment of release patterns

Because of the wide variety of veterinary modified release preparations, the diversity of principles by which release is achieved and the differences in duration of action, finished product testing in comparison with conventional formulations may play a somewhat subsidiary role monitoring release patterns of the finished product. Instead greater emphasis will have to be placed on development pharmaceutics and process validation. Product development studies should be designed to ascertain the influence of critical parameters (including excipients and device components) and the impact of process parameters and variables on the final release characteristic of the finished product.

Such studies should identify those parameters crucial to, and indicative of, the subsequent release pattern. Furthermore it should be evident from the submission that such parameters are well controlled during the manufacturing process of the product thus ensuring batches with reproducible release characteristics. Where possible the interaction between these parameters and the changes in the *in-vitro* and *in-vivo* release profiles should be shown, in order to establish *in-vitro*/*in-vivo* correlation.

One example might be an intraruminal device effecting pulsatile-release through corrosion by ruminal fluids of its metallic elements, which leads to sequential release of the constituent units. In this case an *in-vitro*/*in-vivo* correlation may be established regarding the alloy composition vs. the rate of corrosion in fistulated animals, being predictable to release time intervals.

These crucial parameters thus established may form the basis for in process and or routine finished product testing. However, the test procedure and controls proposed must be firmly anchored in the development pharmaceutics studies.

Evidence should also be submitted addressing the risk of dose dumping.

4. Testing of the modified release systems *(refers to section 2B of the marketing authorisation dossier)*

4.1. Conventional modified release oral formulations

The principles elaborated in the CHMP Guideline on quality of oral modified release products are also relevant.

If, however the described testing for conventional formulations is not feasible, section 4.2 should apply.

4.1.1. *In-vitro* testing

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 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.

Test conditions providing the most suitable discrimination should be chosen.

The dissolution apparatus should preferably be one of those described in the European Pharmacopoeia. The continuous flow through method of the European Pharmacopoeia monograph may be of particular value in testing poorly soluble drugs. The use of methods other than the official methods in the European Pharmacopoeia should be justified and validated.

The choice of rotation speed should be justified by carrying out the test at different speeds and the speed giving an appropriate degree of discrimination as a quality control tool and ideally between batches with acceptable and unacceptable bioavailability should be chosen.

The test medium should preferably be aqueous based; organic or aqueous organic media should be avoided. For poorly soluble drugs, a minimal content of an appropriate surfactant may be added. Buffer solutions at a number of pH values spanning the physiological range should be used to determine the relationship between dissolution and pH. The data obtained could usefully be represented using three-dimensional dissolution profiles (i.e. % dissolved as a function of time and pH).

In order to achieve adequate discrimination, it may be necessary to limit the solubility of the drug and still achieve sink conditions in the dissolution medium. It may also be necessary to consider the ionic strength and surface tension of the medium. The volume of medium used should preferably ensure sink conditions, which may be assumed if the amount of drug in solution does not exceed 30% of the saturation concentration. The solubility of the drug in the chosen dissolution medium should be stated. Identical test conditions should be used for different strengths of the same product.

The robustness of the dissolution test should be determined by examining the effect on the dissolution rate of variations in temperature, pH and speed of rotation.

Dissolution profiles should be determined for:

- each strength of the modified release product if more than one strength is to marketed;
- halved tablets where the release mechanism permits tablets to be broken in half for dosage purposes;
- any changes in the composition and/or manufacturing process of the product during development, if relevant.

At each time point in the dissolution test 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.

The definitive dissolution profile and the corresponding specification will be based on *in-vitro* results of batches used in *in-vivo* testing and will provide an assurance that batches will routinely give the desired *in-vivo* behaviour. It may be necessary to validate the specification for any variations in the

drug or excipients, e.g. the particle size or polymorphic form of the active substance, the gelling properties or particle size of the release controlling excipients or a variation in the manufacturing process.

The content of any key excipient, which has a determining effect on the release of the active substance, should not vary outside validated limits. These limits should be established on a case-by-case basis during the development of each product.

4.1.2. *In-vivo* testing

A summary of the bioavailability testing should be given. The data should include information on pharmacokinetics (AUC, C_{max}, T_{max}, t1/2, etc.), batch numbers, formulation (if different from the proposed marketing formulation) and dissolution results of batches used in *in-vivo* studies.

Bioavailability studies should preferably be performed on at least pilot or production scale batches. Where these are not available, studies could be performed on laboratory scale batches provided it is demonstrated that subsequent product batches (manufactured after registration) show similar bioavailability characteristics, by using valid *in-vitro* testing methods.

4.1.3. *In-vitro/In-vivo* comparison

To justify the specification limits of the *in-vitro* dissolution test, an attempt should be made to establish a meaningful correlation between *in-vitro* release characteristics and *in-vivo* bioavailability parameters. In order to accomplish this, a number of techniques may be employed. These include, in order of decreasing predictive power:

a) comparison of the *in-vitro* dissolution curve of the product with the *in-vivo* dissolution curves generated by deconvolution of plasma level data or by other appropriate methods.;

b) comparison of the mean *in-vitro* dissolution time with the mean *in-vivo* dissolution time of the product derived by using the principles of statistical moment analysis;

c) comparison of the *in-vitro* dissolution time (e.g.TD90%) or *in-vitro* AUC to one mean pharmacokinetic parameter, e.g. T_{max} , AUC, etc.

Tolerance limit is defined by a maximal difference of 20% in the predicted parameters. Limits based on a difference greater than 20% should be justified.

Other approaches are acceptable especially if the above methods fail to demonstrate a correlation. Examples of other approaches may include demonstrating bioequivalence of the proposed formulation to formulations with dissolution profiles at the upper and lower limits of the specification, or alternatively, the specification limits may be derived from the spread of *in-vitro* dissolution results of batches used in bioavailability testing. Reference is made to the Guideline on the conduct of bioequivalence studies for veterinary medicinal products EMA/CVMP/016/2000.

The choice of approach should be justified by the applicant.

4.2. Other modified release dosage forms

On the account of diversity in non-conventional formulations, general rather than specific guidance is offered. This is to reflect the philosophy rather than the practicality of testing and for this reason this section is brief. However, the elements of *in-vitro* testing elaborated on in Section 4.1.1, 4.1.2 and 4.1.3 should be taken into consideration as far as possible.

Where these products are concerned, to ensure batch-to-batch reproducibility, reliance is more likely to be placed on a tightly controlled formulation, ingredients specifications and manufacturing process rather than on finished product testing itself (see Section 3.3.). However, the finished product specification is expected to contain some element addressing batch-to-batch consistency, except in exceptional and justified cases

5. Manufacturing process validation *(refers to section 2B of the marketing authorisation dossier)*

Precise details of the manufacturing process should be given. Critical process parameters that can significantly affect the release of the drug (e.g. tablet hardness, coating procedure, moisture content) should be identified. If an *in-vitro*/*in-vivo* correlation has been established, limits for the critical parameters should be validated by dissolution testing of the product made under different processing conditions to demonstrate that allowable variations in these parameters do not result in unacceptable changes in the dissolution profile.

If the manufacturing process has been validated using laboratory scale batch size, the effect of scale up on the dissolution characteristics of the product should be established, prior to approval.

The validation of the manufacturing process should be made in accordance with the corresponding guideline (Guideline on process validation for finished products – information and data to be provided in regulatory submissions).

All or some of these points may already have been addressed in the development section and appropriate cross-reference may be made.

6. Control tests

6.1. Control of starting materials (refers to section 2C of the marketing authorisation dossier)

Where the modified release may be inherent in the active substance itself, the excipient or a device, additional specifications on the active substance, the excipients or the device (e.g. particle size, functionality tests) should be presented in section 2C.

It is necessary to ensure that the specifications for these starting materials (active substance, excipient or device) appropriately control the critical properties that influence the rate of release.

For example, it may be necessary to control the particle size profile of an active substance used to manufacture an insecticidal collar.

In case of a device, in addition to including limits to tightly control dimensions, it might be important to include in the specifications a test and limits to control the performance of the device. The proposed tests and limits should be detailed and justified.

6.2. In process controls (if necessary) (refers to section 2B of the marketing authorisation)

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, an explanation for the methods used and limits chosen should be provided.

6.3. Finished product (refers to section 2E of the marketing authorisation dossier)

In the case of non-conventional oral formulations (Section 2.1.2.) the approach to finished product control will have to be evaluated on a case-by-case basis as elaborated on in Section 3.3.

The finished product specification must include a parameter indicative of drug release except for non-conventional dosage formulations where it has been established that no such parameter exists. This is not only important to ensure consistent drug release from batch to batch at time of manufacture but also to set acceptance limits for the product during its shelf life. The control parameters should be deduced from the profile(s) obtained during the development of the product, and revalidated with at least pilot production scale batches. Selection of specifications should take into account pharmacokinetics, pharmacodynamics and *in-vitro* assay variability.

All dosage units tested should comply with the 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 (In the case of conventional formulations (Section 2.1.1.) dissolution limits at a minimum of three points should be included in the specification: 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 drug has been released (generally more than 80%dissolved). Where both upper and lower limits are specified at any time point, the difference between them should not usually exceed 20 % of the labelled content of active substance in the formulation unless wider limits have been shown to provide reproducible and acceptable *in-vivo* performance.

Where an *in-vitro*/*in-vivo* correlation has not been satisfactorily established or when there is no *in-vitro* test method available, it may be necessary to carry out additional control tests on the finished product. For example, the content of any release determining excipients may need to be controlled within an upper and lower limit on each batch of product (see note for guidance "Specifications and control tests on the finished product'')

One example might be the determination of the level of a plasticiser in a PVC-based insecticidal collar.

Routine testing of the finished product is always necessary unless it can be demonstrated that this is not possible or justified. In certain cases, routine testing of intermediates (e.g. cores, pellets) may be acceptable. One example might be the determination of the dissolution rate of single tablets of intraruminal devices containing several of these tablets, before final assembling of the devices.

6.4. Validation of the dissolution assay

The assay method of the active substance in dissolution samples should be validated according to the relevant VICH guidelines “Validation of analytical procedures” and “Validation of analytical procedures: Methodology”, taking into account the stability of the active ingredient dissolved in the medium and effects from the excipients.

6.5. Batch results

Ideally, batch analysis results should be provided for 3 production scale batches. In addition, for products intended for use in food-producing species, a summary of the batch analysis results for the batches used in the residue studies should be provided

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.

7. Stability *(refers to section 2F of the marketing authorisation dossier)*

It must be demonstrated that the release profile of the active substance is maintained within specification throughout the proposed shelf life of the product. The results of release testing should include mean values of individual dosage units together with maximum and minimum values for all the batches undergoing the stability tests.

In the case of non-conventional formulations, the previous paragraph should apply if possible. For these formulations, the stability of the active substance must be addressed, evidence should also be provided that the release mechanism/delivery system is unaffected by storage over the proposed shelf-life. Parameters identified in process development and utilised in finished product testing may also prove a useful guide in this instance.

8. Changes to products

Where the release specification has been correlated with *in-vivo* results, minor changes to the data may be acceptable on the basis of *in-vitro* testing. Minor changes include changes to the composition (e.g. nature and/or quantity of excipients which do not influence the release characteristics), method or site of manufacture or manufacturing equipment. Other changes may, however, necessitate further *in-vitro*/*in-vivo* correlation studies or *in-vivo* bioavailability studies. Reference should also be made to Commission Regulations on variations and respective guidelines.

9. Samples

Because of the individual nature of modified release delivery systems, a sample would be desirable for illustrative purposes but a technical drawing and/or a technical description should be supplied in any case.