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Guidance for Industry

Modified Release Veterinary Parenteral Dosage Forms: Development, Evaluation, and Establishment of Specifications

DRAFT GUIDANCE

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance provides recommendations on the submission of chemistry, manufacturing, and controls (CMC) and pharmacokinetic information, as well as procedures to follow, to support the approval of modified release parenteral drug products intended for use in veterinary species. This information should be filed with the Center for Veterinary Medicine (CVM) to support a new animal drug application (NADA) or an abbreviated new animal drug application (ANADA).[1]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The evolution of parenteral modified release technology provides an opportunity to develop new therapeutic options that were impracticable using traditional tablet or parenteral product platforms. For example, these novel formulations provide a mechanism to deliver a drug over a period of months to years. With some formulations, multi-phasic *in vivo* release characteristics can be achieved such that a single injection provides controlled changes in the drug release characteristics over time. Other formulations allow for drug delivery directly to the site of action, minimizing the adverse effects that accompany systemic drug exposure. But, with these benefits comes the need to establish product specifications to ensure that every batch results in the therapeutic benefits purported on the product label. And for parenteral products intended for use in food-producing animals, these specifications must ensure that violative residues will not

[1]Due to the potential complexities of these modified release formulations, each sponsor should discuss whether its proposed product is appropriate for consideration as a generic. In those situations where CVM determines that a product can be filed as a generic drug application, the same development and CMC information that is requested for new drug applications must be submitted. See FD&C Act, Section 512(n)(1)(G).

occur at the FDA-approved withdrawal time. See the Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 512(d)(1)(F).

In vitro drug-release testing methods provide the information necessary for (1) assuring the adequacy of the proposed process and quality controls; (2) determining stable release characteristics of the product over the proposed product shelf-life; and (3) facilitating an assessment of product modifications (e.g., absence of effect of minor formulation changes, change in manufacturing site or process on product performance). These approaches are detailed in the FDA Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) Guidance for Industry (GFI), "Q8(R2) Pharmaceutical Development" (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH]) *Q8(R2)*) (November 2009).[i] Product specifications are linked directly to the *in vitro* release test method.

Product *in vitro* drug release specifications provide a metric for confirming that the *in vivo* drug release characteristics will be consistent with the intended therapeutic objectives. Empirical (minimal) approaches base product specifications on batch data at the time of registration, and these specifications then serve as the primary means of product control. In this approach, the prognostic potential of the drug-release method is constrained by the limits of the information about which the specifications can be based. In contrast, the systematic (enhanced) quality-by-design (QbD) approach incorporates product specifications as a component of the overall quality-control (QC) strategy. The QbD approach establishes specifications based upon the design space.

A greater understanding of the product and its manufacturing process may create a basis for flexible and innovative regulatory approaches. But the scope of that flexibility will depend, in part, on the relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities that forms the basis for science- and risk-based submissions and regulatory evaluations.

III. SCOPE

This document provides:

- Suggestions for development of an *in vitro* drug release test method
- A discussion of the components of a drug release method
- The role of an *in vivo*/*in vitro* correlation (IVIVC) or an *in vivo*/*in vitro* relationship (IVIVR) in a product application. Throughout this document, we use the term "IVIVC/R" to denote text pertaining to IVIVC and/or IVIVR.
- Methods for establishing IVIVC/R for a parenteral product
- Suggestions for establishing clinically relevant *in vitro* drug release specifications
- Methods for using *in vitro* product specifications for setting expiry and for supporting batch release
- Recommendations for filing information for *in vitro* drug release methods and data as well as material for the Pharmaceutical Development Report, and Chemistry,

Manufacturing, and Controls technical section for modified-release parenteral dosage forms.

This draft guidance does not describe post-approval changes of *in vitro* methods or development of suitable correlation for oral modified release dosage forms and nanotechnology products.

IV. GENERAL CONSIDERATIONS FOR THE DEVELOPMENT OF A DRUG RELEASE METHOD

Accelerated *in vitro* test conditions are necessary if these methods are to serve as a product QC tool; months-long timeframes are generally not practical. Whenever possible, specifications should be established on the basis of a single *in vitro* test method. Because modified release parenteral products are formulated to release drug over a period of days, weeks, or months, the development of a discriminating *in vitro* test method that achieves total drug release within a period of hours or days is challenging. Nevertheless, the *in vitro* method should be sensitive to changes in those drug product quality attributes that can influence *in vivo* product performance. To be an effective prognostic tool, the shape of the *in vitro* profile should be determined by the same rate-limiting factor that determines the *in vivo* drug release profile. This underscores the need to achieve product and process understanding during formulation development.

The *in vitro* drug release test method should be established during the early phases of product development so that it can be used to characterize the preliminary formulations, the formulations used in the Target Animal Safety and Effectiveness studies,[ii] and to provide the assessment of the stability lots. The establishment of product release specifications should be based upon *in vitro* performance of those lots used during the pivotal studies used to demonstrate drug product safety and effectiveness. However, a widening of the specifications may be deemed acceptable based upon additional *in vivo* and *in vitro* data gathered during product development.

Prior to proceeding with development of the drug release method, the following information should be considered and discussed with CVM:

- Formulation development, including assessment of the need for an initial burst release (loading dose) and rate and duration of drug release
- Assessment of the excipient(s) or dosage form that may impact the rate and duration of drug release
- Development of an *in vitro* test that adequately describes the formulation attributes
- Evaluation of the method as a QC test to support batch release at the initial time point and ensure product performance throughout expiry
- Evaluation of the impact of manufacturing process changes on product performance
- Evaluation of the impact of changes in supplier of the active pharmaceutical ingredient and critical excipients
- Substantiation of CMC-associated label claims (such as product drug release characteristics).

V. *IN VITRO* DRUG RELEASE TEST METHOD PARAMETERS:

The *in vitro* drug release method should be capable of identifying formulation differences that affect *in vivo* product performance. This necessitates that the method is sensitive to the rate limiting factor impacting *in vivo* drug release.[iii] Method sensitivity can be confirmed during the formulation screening stage. Often, this evaluation compares the results provided across several *in vitro* release methods. Once a sponsor develops a discriminating system, a consistent set of testing conditions should be maintained across all formulations and manufacturing lots used during target animal safety and clinical effectiveness trials.

In most circumstances, the *in vitro* method should employ sink conditions to reflect the relationship between product formulation and the rate and extent of drug release. In those rare situations where sink conditions cannot be achieved, justification for an assay that does not achieve sink conditions should be submitted in a protocol or with the application.

CVM recommends the following information to support the proposed drug release method and apparatus of choice:

1. Description of the apparatus used: United States Pharmacopeia (USP) chapters <711>[iv] or <724>[v] can be referenced if a sponsor uses one of the USP apparatus. If the sponsor selects a different apparatus, the description should include the vessel (shape, dimension, and its material, etc.), motor, shaft, collection basket or device, water bath or heating device, and how a sponsor performs sampling throughout the duration of the test.

2. Description of physical design and set up conditions of the apparatus. A picture of the equipment and set up with identification of the specific parts of the equipment is helpful. Include the dimensions and tolerances of the specific components and their related position to the whole assembly.

3. Characterization of temperature conditions of the vessel and how they can be maintained consistently during the run.

4. Justification of apparatus suitability:

    a. Determination of the apparatus suitability. This information should include conformance to the measurements (width, length, etc.) and specifications (degree of tolerance) of the specific components.

    b. Performance validation and verification of the apparatus:

        i. If the apparatus is a USP apparatus, follow the USP procedure as described in <711> or <724> to demonstrate the suitability of the apparatus.

ii. If the apparatus is not described in the USP, information from the manufacturer can be used as a point of reference.

iii. Acceptable performance of the apparatus assembly should be verified periodically and the conditions by which the apparatus is deemed acceptable for use should be described.

5. Description of the type of media and justification for its selection.

6 Description of sample and standard preparation, including storage conditions and any precaution in handling and sampling techniques.

7 Description of other assay parameters; i.e., temperatures, mix rates, duration of the test, degradation rate, release rate, sampling points and techniques, etc.

8. Demonstration of sink conditions: Provide data that defines the volume of fluid necessary to insure that the concentration of drug in the medium at 100% release does not exceed one-third of the saturation concentration, where saturation concentration is defined by the maximum mg/mL of drug that can be solubilized in the release medium.

9. Specification of timing of measurements: Ideally, the drug release test should take no more than 2 days to perform, thereby expediting the lot release process and minimizing the risk of degradation of the *in vitro* test system. The test time points, generally four, are expressed in hours. Samples should be withdrawn within a tolerance of ±15 minutes or ±2% of the stated times (where criteria used for tolerance are determined on the basis of when the sample is taken relative to the duration of the test and may differ across the four selected time points). Deviation from the tolerance will need to be justified.

10. Description of the instrumentation used to quantify drug concentrations used to assay sample aliquots collected from the designated time frame. A description of the analytical system should include details, such as the type of chromatography, column, detector, mobile phase, etc. Validation of this type of system typically follows the elements and criteria as specified in USP <1225>[vi] and VICH GL2[vii] which should include measures of specificity, linearity, accuracy, precision, range, limit of detection, limit of quantitation, robustness, and system suitability.

11. Discussion of procedures and criteria for determining discriminative ability of the test. The method should allow differentiation in the profile with formulation involving some change in the manufacture of the batch used in the safety and effectiveness trials (such as composition, process, equipment, excipients) or age of the product (new as compared to aged or expired product).

12. Any additional data analysis or supporting data needed to determine release rate or specifications from the batches used to fulfill requirements associated with the Safety and Effectiveness technical sections.[ii]

13. Detailed calculation of % drug release.

14. Proposed specifications (time = 0 and t = stability throughout expiry) and justification.

VI. THE ROLE OF THE IVIVC/R IN A PRODUCT APPLICATION:

An IVIVC describes a quantitative (generally linear) relationship between *in vivo* and *in vitro* release characteristics while an IVIVR reflects a relationship that can be described by something other than that of a straight-line.[viii] CVM recommends that at the very least, sponsors demonstrate an IVIVR to support the biological relevance of the *in vitro* release method.

Generally, an estimation of in vivo drug product release characteristics is based upon blood level profiles. When establishing the blood level profile that will be used to support the generation of an IVIVC/R, the intended *in vivo* release characteristics of the proposed product need to be considered. For example, early concentrations (i.e., blood captured within the first 1-8 hours after drug administration) may be needed to characterize an initial burst of drug release, irrespective of whether or not such a burst in drug release is intended. Profiles for products targeting zero order release characteristics should allow for a determination of the duration of that zero order release. Characterization of *the in vivo* profile generated for products that exhibit multiple peaks throughout the dosing interval may need more frequent blood samples, where the definition of "frequent" will be based upon the rate at which these bursts are observed and/or the proposed duration of drug release. Therefore, the blood sampling profile used when establishing the IVIVC/R needs to be tailored to the intended product.

In some instances, an IVIVC/R has been developed with only a single formulation in order to predict blood level profiles generated within that formulation. For example, D'Souza and DeLuca (2005)[ix] and Rawat et al (2012)[x] demonstrated that accelerated *in vitro* test conditions can be developed that adequately describe complex, multi-phasic *in vivo* drug release patterns. However, from the perspective of using *in vitro* data to extrapolate across formulations (i.e., to enable the *in vitro* release test results to substitute for an *in vivo* bioequivalence study), CVM believes that the IVIVC/R needs to be established on the basis of data generated across at least three formulations exhibiting differences in their respective rates of *in vivo* drug release. While describing the *in vivo* release characteristics across these formulations, the same blood sampling schedules should be employed in order to define the relationship between *in vitro* and *in vivo* product performance.

For the *in vitro* component of the IVIVC/R, no fewer than 12 replicates for each of the 3 different formulations should be tested. Due to unique attributes of modified release formulations, 12 replicates could, for example, reflect 1) 12 individuals units, such as 12 individual implants from a given production batch; 2) 12 replications of an aliquot from a production batch of a liquid formulation, such as a suspension and *in situ* gels; or 3) 12 replications of multiple unit products, such as implantable pellets. In the latter situation, separate

tests of 12 replicates each should be performed when with pellets are designed to exhibit different *in vivo* release characteristics and the modifications necessary to establish the IVIVC/R should provide a test of product critical quality attributes (CQAs) without altering the mechanism controlling drug release.

Depending upon the nature of the information generated during product development (i.e., the ability to establish an IVIVC or an IVIVR) and the purpose of subsequent *in vitro* release test data (e.g., its use in supporting pre- or post-market changes versus development of product quality release specifications), once a target *in vitro* profile has been established (based upon the lots used in the clinical field trial) and product specifications have been established, subsequent profiles may be evaluated on the basis of:

- The ability of a subsequent profile (i.e., multiple time point release specification) to meet established product specifications. This information should be used to support batch release and product stability (see VIII. Establishing Drug Release Specifications).

- The ability to demonstrate comparability to the target profile based upon use of the f_2 criterion where an f_2 value between 50 and 100 suggests that 2 profiles are similar (see the glossary and the FDA CDER GFI, "SUPAC-MR: Modified Release Solid Oral Dosage Forms" (September 1997)[xi] for definition). For profile comparability (as defined by f_2) to support a waiver of *in vivo* relative bioavailability study requirements, the magnitude of formulation change that can be supported by *in vitro* release data depends upon several factors:

    - If the change has the potential to alter what constitutes the rate-limiting factor,[2] then an *in vivo* relative bioavailability study will be necessary to support the safety and effectiveness of the new formulation.

    - If the proposed formulation change falls within SUPAC Level 1 changes or if the change in product composition or manufacturing is unlikely to alter *in vivo* product performance (e.g., a change in ingredient supplier or substitution between two similar excipients), then the f_2 test can be applied to support the biowaiver as long as an IVIVR has been established.

    - If a major change in formulation occurs (for example, a deletion or addition of ingredients that may be critical to the *in vivo* release characteristics of the formulation), then CVM can only render a decision of product bioequivalence if an IVIVC has been established.

[2]Examples of rate-limiting steps include: for a lipophilic solution, the rate of partitioning between the lipophilic layer and interstitial fluid is a rate-limiting step; for an *in situ* forming gel or implant, the rate of drug movement through the gel to the surface is the rate-limiting step; for a suspension, the rate at which the particles dissolve and the particle size and surface to volume ratio is a rate-limiting step. For more discussion please refer to Martinez M., Rathbone M., Burgess D., Huynh M., 2008. *In vitro* and *in vivo* considerations associated with parenteral sustained release products: a review based upon information presented and points expressed at the 2007 Controlled Release Society Annual Meeting. *J Control Release*, 129:79-87.

When systemic drug concentrations are measurable, the *in vivo* characterization should be based upon blood concentration/time profiles. However, there exist situations where it is not feasible to measure drug concentrations in the systemic circulation. Within the framework of veterinary medicine, it may be feasible to establish the IVIVC/R on the basis of an explant study. When explant data are utilized, the method should capture the amount of drug remaining in the injection site as a function of time. Optimally, these data would be collected as a component of other ongoing investigations (e.g., as part of the Target Animal Safety study). Ravivarapu et al. (2000) have shown that such explant studies can provide valuable information on the relationship between product formulation, *in vitro* performance and *in vivo* drug release.[xii] Alternatively, for safety reasons, there may be times when it is important to evaluate residual drug remaining prior to subsequent administrations. Sponsors should discuss methods for capturing these data with CVM as early as possible in drug development.

VII. DEFINING AN IVIVC OR IVIVR

To demonstrate an IVIVC/R, both internal and external validations are necessary. The internal validation examines the ability of the model to predict *in vivo* performance using the *in vitro* data that originally went into the model development. Also needed is an external validation where a formulation, with known bioavailability but that was not used in the development of the model, is used to evaluate the overall prediction error of the test method.

Four types of correlations have been described (see CDER GFI, "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In vitro/In vivo Correlations" (September 1997)).[xiii] The extent to which each of these can be used to support changes in formulation will depend both upon the formulation in question, the pharmacokinetics of the active pharmaceutical ingredient(s) (API), the therapeutic window for of the API, and the type of correlation that has been established. A helpful description of how these relationships can be established and support product development throughout the product development process has been described elsewhere.[xiv]

Level A

The Level A correlation should usually be estimated by a two-stage procedure: deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. A correlation of this type is generally linear and represents a point-to-point relationship between *in vitro* drug release rate and the *in vivo* input rate (e.g., the *in vivo* dissolution of the drug from the dosage form). Because the rate of drug release from parenteral modified release products is accelerated under the *in vitro* test conditions, the *in vitro* drug release and *in vivo* input curves would need to be rendered superimposable with a scaling factor.

Whatever the method used to establish a Level A IVIVC, the model should predict the entire *in vivo* time course from the *in vitro* data. In this context, the model refers to the relationship between *in vitro* dissolution of a modified release dosage form and an *in vivo* response such as plasma drug concentration or amount of drug absorbed. To generate this level of correlation, *in vivo* pharmacokinetic data should be provided for an immediate release dosage

form so the clearance and volume of distribution associated with the drug itself can be used to facilitate the estimation of absorption rate and fraction absorbed from the formulation. Using convolution (or other appropriate modeling techniques), the fastest and slowest allowable *in vitro* release rates should be determined based upon modeled plasma concentration time profiles that exhibit a maximal difference of 20% in the predicted C_{max} and AUC values.

With regard to the *in vitro* dataset, the time points should cover the early, middle, and late stages of the dissolution profile. The last time point should be the time point where at least 80% of drug has dissolved. If the maximum amount dissolved is less than 80%, then the last time point should be the time where the plateau of the dissolution profile has been reached. CVM believes parenteral modified release dosage forms have a greater risk of long-term accumulation than oral dosage forms. For products in which accumulation is potentially a concern, CVM may request time points in which the maximum percentage of drug release is greater than 80%.

It should be noted that a Level A correlation is extremely difficult to obtain, and is particularly difficult when applied to parenteral modified release formulation where a very long duration of release and multifunctional absorption characteristics complicate the ability to obtain a Level A correlation.

Level B

The Level B relationship is based upon principles of statistical moment analysis. The mean *in vitro* release time is compared either to the mean residence time or to the mean *in vivo* release time. Similar to Level A, the Level B uses all of the *in vitro* and *in vivo* data. However, because it is not a point-to-point correlation, the Level B relationship does not uniquely reflect the shape of the *in vivo* concentration-time profile.

Level C

Level C relationships do not reflect the complete shape of the plasma concentration time curve and often use less than the full complement of *in vitro* release data. Rather, the Level C relationship describes a single point relationship between a dissolution parameter—for example, the percent dissolved in 4 hours—and a pharmacokinetic parameter (e.g., time to 50% AUC). This one time point may be used to establish the specification such that there is not more than a 20% difference in the predicted AUC and C_{max}. At other time points, the maximum recommended range at any dissolution time point specification should be within ± 10% of label claim deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Reasonable deviations from this ± 10% standard may be acceptable if the range at any time point does not exceed 25%.

Multiple Level C

A multiple Level C relationship relates one or several pharmacokinetic parameters of interest to the amount of drug dissolved at several time points of the dissolution profile.

VIII. ESTABLISHING DRUG RELEASE SPECIFICATIONS

To maximize the relevance of the outcome of *in vitro* drug release tests, CVM prefers at least four time points with associated specification limits within a drug release profile. Future reduction of time points for routine *in vitro* release testing will be evaluated post-approval. Any justification for a different number of points should be based on the complexity of the pharmacokinetic and *in vitro* release profiles for the formulation.

Setting Drug Release Test Specifications with an IVIVC/R

An IVIVC/R adds *in vivo* relevance to *in vitro* product release specifications and can be used as more than a tool for batch-to-batch QC. The *in vitro* drug release test is used as a meaningful predictor of *in vivo* performance of the formulation, and the release specifications may be used to minimize the possibility of releasing lots that have different *in vivo* performance. It can also influence expiry if product release characteristics change over time.

One of the challenges associated with establishing the *in vivo* relevance of the *in vitro* release test is that these data are generated under conditions that markedly accelerate the rate of *in vitro* drug release. Therefore, a confirmation of the relationship can be obtained through the generation of *in vivo* and *in vitro* data across a range of formulations (e.g., variation in curing time, different source of excipients, and differing composition). To achieve this, CVM recommends that the sponsor submit information generated throughout the period of formulation development (thereby eliminating the need to purposefully generate inequivalent drug products). Confirmation of an IVIVC/R allows the use of the *in vitro* test method for establishing clinically-relevant release specifications and for setting product expiry.

Setting Drug Release Test Specifications without an IVIVC/R

Without an IVIVC/R, the *in vitro* drug release test is applicable solely for QC purposes; *in vivo* bioequivalence cannot be determined on the basis of *in vitro* drug release tests. In the absence of an IVIVC/R, CVM may accept proposals for *in vitro* release specifications based on averages of drug release results from lots used for clinical studies. When the *in vitro* test is used as a QC test without any *in vivo* significance, we recommend drug release percentage limits that at all time points are no more lenient than the average release ± 2 standard deviations. Exceptions may be considered based on evidence that proposed ranges represent those of safe and effective lots. Widening specifications based on scale-up, stability, or lots for which bioequivalence would be difficult to support without information about *in vivo* effects of this greater variability.

IX. FILING INFORMATION FOR CMC SUBMISSIONS

A. Early Information

Sponsors developing a drug release method or considering the establishment of an IVIVC/R may wish to consider the submission of background information or early study information as part of an early information submission. The submission of early

information is an additional tool that allows CVM an opportunity to have discussions with sponsors earlier in the process.

B. Protocol

CVM recommends that sponsors submit a method protocol before finalizing the *in vitro* drug release test method and prior to conducting the pivotal target animal safety and effectiveness studies so both CVM and sponsor may agree on expectations for the method. Likewise, CVM recommends that a sponsor wishes to pursue an IVIVC/R, a protocol covering both *in vivo* and *in vitro* components should be submitted for CVM concurrence. In so doing, the conditions associated with the *in vitro* method will be defined prior to manufacture of the safety and effectiveness study batches; agreement obtained on the information needed to support product specifications based upon study batch(es); and concurrence reached on the corresponding analysis of those data for generating *in vitro* product specifications. Sponsors may also request a meeting to discuss the development of early and final formulations and to gain CVM's current thinking on the proposed dosage form and formulation.

C. Pharmaceutical Development Reports (PDRs)

CVM encourages sponsors to provide PDRs that describe the scientific rationale for the chosen manufacturing process(es) and controls for modified release drug products (section 2.3.P.2 entitled "Pharmaceutical Development" in CVM's Question-based Review format). A sponsor's ability to demonstrate process understanding in this section of the drug application can be factored into CVM's risk-based decision making for the Good Manufacturing Practice (GMP) component of drug approval. Suggestions for PDRs can be found in CDER/CBER GFI, "Q8(R2) Pharmaceutical Development" (ICH Q8(R2)).[i]

Pharmaceutical development of a modified-release parenteral product may include some or all of the following elements:

- Defining the quality target product profile as it relates to quality, safety, and efficacy. Considerations for the quality target product profile could include:
    - Intended use in clinical setting, route of administration, dosage form, and delivery systems.
    - Dosage strength(s).
    - Container closure system.
    - Therapeutic moiety release or delivery attributes affecting pharmacokinetic characteristics (for example, *in vivo* release, drug partitioning characteristics, potential barriers/obstacles to *in vivo* drug release and/or target site delivery) appropriate to the drug product dosage form being developed.
    - An explanation of why the drug substance may be a good candidate for modified release dosage forms.

- Drug product quality criteria (for example, sterility, purity, stability, and drug-release) appropriate for the intended marketed product.
- Identifying potential CQAs of the drug product, so that those product characteristics that have an impact on product quality can be studied and controlled.
- Determining the CQAs of the drug substance and excipients, and selecting the type and amount of excipients to deliver drug product of the desired quality.
- Selecting an appropriate manufacturing process.
- Defining a manufacturing control strategy.
- Optimizing analytical tests, especially the *in vitro* drug-release test.
- A description of which excipients in the formulation are release controlling.
- Experience with similar release-controlling excipients that were not a part of the final formulation.
- Development of a reconstitution vehicle, if appropriate.
- Physical properties of the formulation, such as partitioning characteristics that may affect drug-release rate.
- Discussion of the effect of particle size on release characteristics, if appropriate.
- Manufacturing considerations, such as unusual processes or equipment.
- A comparison to an immediate-release formulation, if one exists.
- Method development for the drug-release assay, such as buffers and apparatus or new release-measurement technology.
- Risk analyses linking design of manufacturing process to product quality.

D. Other Information

This section offers an overview of the information that would typically be submitted and the corresponding section in CVM's Question-based Review format.

1. Section 2.3.P.4 Control of Excipients: If appropriate, references to Type IV master files with information about release-controlling excipients may be provided in the product quality section pertaining to excipient control.

2. Section 2.3.P.5 Control of Drug Product:

    - The proposed drug release method
    - Appropriate validation for the drug release method
    - Information that describes the IVIVC/R associated with the proposed test method.
        - Product expiry;
        - Setting product specifications at product release(time = zero) and expiry; and
        - Changes in specifications beyond the ranges supported by the product batches used during the safety and effectiveness trials.

3. Stability: Justification of the proposed stability specifications.

X. GLOSSARY

AUC: Area Under the *C*urve; the integral of the plasma concentration vs. time curve.

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits as per 21 CFR 210.3(b)(2).

C_{max}: Maximum plasma concentration.

Critical quality attributes (CQAs): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[i]

Drug product: A finished dosage form containing a drug substance, usually, but not necessarily, in association with one or more other ingredients as per 21CFR 314.3(b).

Drug Release Test: An *in vitro* assay that assesses the percentage of the full dose released from a modified-release parenteral product over time. The performance of drug release tests is generally similar to dissolution tests used for solid oral dosage forms, but CVM recognizes that the term "dissolution" is not an adequate description of how many parenteral modified-release dosage forms are intended to function.

Explant: Removal of the tissue at a given time point from the site of injection and subsequent assay for remaining active ingredient(s).

f_2: A parameter that defines the similarity of two *in vitro* drug release profiles—

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

where n = number of sampling time points, R = dissolution at time point t of the reference, and T = dissolution at time point t of the test.[xv]

Formulation: The ingredients and composition of the dosage form.

***In vivo*/*in vitro* correlation (IVIVC)**: A predictive mathematical model describing the relationship between an *in vitro* property of a modified release dosage form (usually the rate or extent of drug release or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed.

***In vivo*/*in vitro* relationship (IVIVR)**: A relationship between *in vivo* bioavailability and the *in vitro* release profiles, which can be described by a relationship other than that of a straight line.

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits as per 21 CFR 210.3(b)(10).

Mean residence time (MRT): The mean time that the drug resides in the body. MRT may also be the mean transit time. MRT = AUMC/AUC.

Modified-release parenteral dosage form: A parenteral dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional injectable dosage form.

Non-release-controlling excipient: An inactive ingredient in the final dosage form that does not significantly affect the release of the active drug substance from the dosage form.

Release-controlling excipient: An inactive ingredient in the final dosage form that functions primarily to extend the release of the active drug substance from the dosage form.

Release rate: Amount of drug released per unit of time as defined by *in vitro* or *in vivo* testing.

Sink conditions: A situation in drug release methods in which the solubility of the drug in the dissolution medium does not limit the rate at which the drug may partition to the dissolution medium from the dosage form. This is defined as the volume of fluid necessary to insure that the concentration of drug in the medium at 100% release does not exceed one-third of the saturation concentration.

Statistical moments: Parameters that describe the characteristics of the time courses of plasma concentration (area, mean residence time, and variance of mean residence time) and urinary excretion rate.

$\mathbf{T_{max}}$: time to peak concentration.

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