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# **Advanced Prostate Cancer: Developing Gonadotropin- Releasing Hormone Analogues Guidance for Industry**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Oncology Center of Excellence (OCE)**

**May 2022  
Clinical/Medical**

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*Contains Nonbinding Recommendations*

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## **Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone Analogues Guidance for Industry<sup>1</sup>**

This guidance represents 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 office responsible for this guidance as listed on the title page.

### **I. INTRODUCTION**

This guidance describes the Food and Drug Administration's (FDA's) current recommendations regarding the overall development program to establish the effectiveness and safety of gonadotropin-releasing hormone (GnRH) analogues for treating advanced prostate cancer.

The recommendations in section III.C., Registrational Trial Considerations, apply to drug product development programs for GnRH analogues in advanced prostate cancer for all dosage forms and routes of administration (e.g., tablets, capsules, injectable suspensions, injectable emulsions, subcutaneous implants). Other sections apply only to extended-release injectable dosage forms.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

### **II. BACKGROUND**

GnRH analogues remain a mainstay for treating patients with prostate cancer. Both GnRH agonists and antagonists are intended to reduce testosterone (T) levels in the blood, a major driver of prostate cancer growth, but they achieve that goal through different mechanisms of action. GnRH agonists cause a transient surge in luteinizing hormone (LH) and T. This surge desensitizes the LH receptors and is followed by a sustained decrease in T levels. Patients whose LH receptors have not been fully desensitized may develop a second surge in T after doses

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<sup>1</sup> This guidance has been prepared by the Division of Oncology 1 in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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subsequent to the first dose (subsequent doses). In contrast, GnRH antagonists bind to the GnRH receptor, suppressing production of LH and follicle-stimulating hormone (FSH) and the resultant production of T. GnRH antagonists' direct suppression of LH and FSH avoid the transient T surges seen with the agonist products.<sup>2</sup>

New drug applications (NDAs) for GnRH analogues typically rely, in part, on FDA's finding of safety and/or effectiveness for a previously approved GnRH analogue, and applicants submit these NDAs through the pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. These 505(b)(2) applications rely on FDA's prior findings of safety and/or effectiveness and also generally include product-specific data from nonclinical general toxicology studies and a clinical trial. This guidance addresses the current regulatory requirements and provides recommendations for the approval of these drug products and the use of a standardized approach to trial design.

### **III. DEVELOPMENT PROGRAM**

#### **A. Drug Product Development**

GnRH analogues typically contain a synthetic peptide similar to naturally occurring GnRH. The drug product is often marketed in the form of a polymer (such as freeze-dried powder (microspheres) that a provider must mix with a solvent in a prefilled syringe to be reconstituted into a suspension) in a single-dose delivery system for intramuscular administration. Chemistry, manufacturing, and controls (CMC) information for this peptide and the excipients and other components of the extended-release formulation can be provided within the application or as a cross reference to a drug master file. The CMC information submitted in the investigational new drug application (IND) during drug product development should follow relevant FDA guidance documents, including the following:

- Guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995)<sup>3</sup>
- Guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003)

For drug products entering clinical trials, the drug product development program should be aligned with the following applicable International Council for Harmonisation (ICH) guidance documents:

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<sup>2</sup> TN Clinton, SL Woldu, and GV Raj, 2017, Degarelix Versus Luteinizing Hormone-Releasing Hormone Agonists for the Treatment of Prostate Cancer, *Expert Opin Pharmacother*, 18(8): 825–832; and LG Gormella, 2009, Effective Testosterone Suppression for Prostate Cancer: Is There a Best Castration Therapy?, *Rev Urol*, 11(2): 52–60.

<sup>3</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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- Guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)
- Guidance for industry *Q1B Photostability Testing of New Drug Substances and Products* (November 1996)
- Guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (November 2005)
- Guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008)
- Guidance for industry *Q3B(R2) Impurities in New Drug Products* (August 2006)
- Guidance for industry *Q3C Impurities: Residual Solvents* (December 1997)
- Guidance for industry *Q3D(R1) Elemental Impurities* (March 2020)
- Guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000)

Because the active ingredient is intended to be released over an extended period (e.g., 1 to 6 months), ensuring adequate and continuous drug release is critical to successful development. During drug product development, sponsors should conduct *in vitro* tests to evaluate and characterize the quality and performance of the proposed drug products. Ideally, the *in vitro* drug-release characteristics should correspond to the *in vivo* drug-release performance, and the sponsor should select clinically relevant drug-release acceptance criteria to ensure consistent quality, efficacy, and safety. The sponsor can also use *in vitro* drug-release testing to evaluate changes in formulation (e.g., polymer and excipient selection) and the manufacturing process (e.g., equipment parameter changes) during drug product development and potential scale-ups. The *in vitro* drug-release tests are often used to monitor the quality of the drug product at release and over time, and the tests are intended to provide evidence that the drug product will perform consistently throughout its shelf life. For drug products for which drug release is expected to occur over a long duration, developing an accelerated *in vitro* drug-release method is an option for drug release and stability testing. Sponsors should characterize *in vitro* drug release early in drug product development and should make it available at initial IND submission for FDA feedback.<sup>4</sup>

When a delivery or mixing device is used, sponsors should describe the drug-delivery device and reference an approved or cleared device or device application. Sponsors should also ensure that the performance characteristics of the syringe are maintained throughout the shelf life. Sponsors should consider in-use testing.

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<sup>4</sup> See the appendix for additional information.

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### **B. Nonclinical Development**

Nonclinical development of anticancer pharmaceuticals is described in the following guidance documents:

- ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010) (ICH S9)
- ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals: Questions and Answers* (June 2018)
- ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) (ICH S6(R1))
- Guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (May 2019)

Sponsors should include pharmacology studies supporting the proposed trial with the initial IND. It is important for sponsors to test the formulation in an animal model for dose finding and chemistry and manufacturing consistency before initiating clinical trials.<sup>5</sup> In general, sponsors should provide nonclinical, general toxicology studies in rodents and nonrodents of up to 1 month's duration to support early clinical development, and they should provide studies of 3 months' duration to support pivotal registration trials. Safety pharmacology and toxicokinetic endpoints can be included in these studies rather than using stand-alone studies. The general toxicology studies should use a route of administration similar to the route of administration in the intended clinical trial and should follow the recommendations described in Table 1 of ICH S9. Consistent with ICH S6(R1), if the 1-month studies show a consistent toxicological profile, then a 3-month study in a single species may be sufficient. Because GnRH analogues are peptides with expected high specificity, secondary pharmacology studies are usually not warranted.

Consistent with the FDA guidance on reproductive testing for oncology pharmaceuticals, no embryo-fetal toxicology study or other reproductive toxicology study is needed to support the indication of advanced prostate cancer (see ICH S9, ICH S6(R1), and guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*). Unless there are unnatural amino acids (i.e., amino acids not normally found in mammals) in the GnRH product, the sponsor does not need to evaluate genotoxicity or carcinogenicity.

In general, it is not necessary to evaluate phototoxicity or immunotoxicity to support developing or marketing GnRH analogues to treat advanced prostate cancer.

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<sup>5</sup> We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

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### **C. Registrational Trial Considerations**

#### *1. Trial Design*

Single-arm trials using T levels as pharmacodynamic/response biomarkers are conducted to support the approval of GnRH analogues. These trials should demonstrate the following:

- Attainment of a castrate (less than 50 nanogram (ng)/deciliter (dL)) T level
- Maintenance of castrate T levels until the end of a dosing interval
- Maintenance of castrate T levels immediately after subsequent doses of the study drug product

To demonstrate these effects of the study drug product on T levels, the treatment period should be at least twice as long as the dosing interval. For drug products that act over a relatively short period (e.g., 1 month), the treatment period should extend over several (three to four) dosing intervals.

Sponsors should discuss with the division randomized designs intended to support comparative claims (efficacy and/or safety) among GnRH analogues.

#### *2. Trial Population*

Participants enrolled in trials intended to support an indication for treating advanced prostate cancer should have normal T levels and either metastatic or biochemically recurrent disease. Sponsors could consider excluding participants with bone metastases in weight-bearing bone who are at risk for developing symptoms associated with T flare. We recommend that sponsors record information concerning the participant's history of prostate cancer, including the date of diagnosis, current stage, extent of metastatic disease at baseline, and prior therapies.

#### *3. Dose Selection*

The study drug product dose used in the clinical trial should be informed by nonclinical testing. Sponsors should consider using early dose-finding studies or enrolling participants at multiple dose levels in the registrational trial. The adequacy of data for the selected dose for the new drug product will be assessed based on one or more clinical trials that demonstrate an adequate bridge to support the ability to rely on the safety and effectiveness of the listed drug for the new drug product.

#### *4. Trial Procedures and Timing of Assessments*

GnRH agonists are expected to achieve castrate T levels by Day 28, and T levels should be measured at this time. GnRH antagonists are expected to achieve more rapid development of castrate T levels than GnRH agonists. To document when castrate T levels occur, sponsors should consider weekly assessment of T levels until Day 28. Although the final analyses should



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use T levels assessed at a central laboratory, T levels should also be assessed at local laboratories so that participants who do not have castrate T levels (on or after Day 28) can be promptly removed from the trial for safety reasons.

To ensure that castrate T levels are maintained over the dosing interval, sponsors developing GnRH agonists or antagonists should measure T levels before each dose of the study drug product. Sponsors could consider additional measurement of T levels at other time points, including the midpoint of the dosing interval, to help guide further drug product development if the predose level fails to show castrate T levels.

To assess for potential T surges following subsequent doses of a GnRH agonist, sponsors should obtain T levels at 1 hour, 4 hours, and 3 days after subsequent doses in all trial participants and provide these results as supportive efficacy data. Sponsors could consider an additional T measurement between 3 and 7 days after the additional dose. Sponsors should justify and discuss the appropriateness of the timing of T-level assessments with FDA before initiating the study.

We recommend that sponsors assess the effect of the study drug product on tumors by measuring prostate specific antigen at a central laboratory and reviewing bone scans and scans of known sites of disease (e.g., computed tomography (CT) scans). For participants with metastatic disease, tumor measurements would normally be obtained every 3 to 6 months during the treatment period, and we recommend that these results be included in the application database.

Sponsors should collect information on the dates of use and dose of herbal medications and dietary supplements, if they were used, at trial entry and throughout the treatment period because some herbal or alternative medications may affect T levels. Sponsors should also provide participants with a list of medications that they should not use during the trial period.

Adverse event collection should solicit events using open-ended questions and known adverse events for this class of drugs, such as hot flushes, breast pain, bone pain, difficulty sleeping, and injection site reactions. After collecting data on injection site reactions, sponsors should report all terms related to this concept (e.g., injection site swelling, redness, pain) under a single term. The incidence of injection site reactions has varied markedly between trials, and this may be related to a lack of uniformity in ascertainment and assessment. Sponsors should assess adverse events throughout the treatment period and for 30 days after the end of the dosing interval. For example, sponsors should assess adverse events for 4 months after the last dose of a 3-month formulation of a GnRH analogue.

Safety monitoring should include measurement of hemoglobin A1C and a lipid panel at screening and at the end of treatment, at minimum. Multiple trials have demonstrated an association between GnRH agonist use and adverse effects on insulin sensitivity and dyslipidemia, which may increase the risk of cardiovascular disease.<sup>6</sup> If the treatment period

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<sup>6</sup> GN Levine, AV D'Amico, P Berger, PE Clark, et al., 2010, Androgen-Deprivation Therapy in Prostate Cancer and Cardiovascular Risk: A Science Advisory From the American Heart Association, American Cancer Society, and American Urological Association: Endorsed by the American Society for Radiation Oncology, *Circulation*, 121(6):833–40, doi: 10.1161/CIRCULATIONAHA.109.192695.

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exceeds 1 year, these tests should be repeated annually. If the treatment period exceeds 2 years, bone density should also be measured at baseline and every 2 years.

Before trial initiation, sponsors should discuss with the division the potential use of patient-reported outcomes (PRO) to support labeling claims.<sup>7</sup>

### *5. Pharmacokinetics and Pharmacodynamics*

Plasma T levels have been used as pharmacodynamic/response biomarkers leading to traditional approval<sup>8</sup> of GnRH analogues for advanced prostate cancer in the 505(b)(2) pathway. Therefore, a robust bioanalytical method for measuring plasma T levels is critically important. Sponsors should employ a fully validated bioanalytical assay for the analysis of plasma T levels.<sup>9</sup> The bioanalytical methods used to measure plasma T levels should be accurate, precise, specific, sensitive, and reproducible.

Given the use of a pharmacodynamic/response biomarker (i.e., T level) in the clinical trial to support approval, sponsors need not demonstrate pharmacokinetic (PK) bioequivalence of the proposed drug product to the listed drug on which the sponsor intends to rely in a proposed 505(b)(2) application. However, sponsors should collect samples of the drug product and the listed drug in a pilot study or a subgroup within the registration trial to characterize the PK of the drug product relative to the listed drug. Characterizing the PK profile of the drug product can also illustrate the drug substance release from the drug product, estimate the accumulation potential of the drug substance after multiple doses, and describe the relationship between pharmacokinetics and plasma T cells for the drug product.

### *6. Efficacy Endpoints*

Plasma T level is used as a surrogate endpoint to assess the efficacy of GnRH analogues. A T level less than 50 ng/dL is considered castrate level. The timing of T-level assessments is discussed above. To accommodate T-level assessments at the end of a dosing interval, sponsors should extend the trial period for at least two dosing intervals for long-acting (3 to 6 months) formulations and three to four dosing intervals for short-acting (1 month) formulations.

Assessing mean T levels would not provide an adequate measure of efficacy because averaging T levels will not reveal the participants who did not benefit (i.e., achieve castrate levels);

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<sup>7</sup> See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) and the draft guidance for industry *Core Patient-Reported Outcomes in Cancer Clinical Trials* (June 2021). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>8</sup> The term *traditional approval* denotes the longstanding route of drug product approval based on the demonstration of clinical benefit or an effect on a surrogate endpoint known to predict clinical benefit. That term is distinguished from accelerated approval, which is associated with use of a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit to support drug product approval.

<sup>9</sup> The guidance for industry *Bioanalytical Method Validation* (May 2018) provides recommendations on bioanalytical method validation.

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therefore, it is critical to show that a high percentage of participants achieved and maintained a T level less than 50 ng/dL. The percentage of participants who achieved and maintained a T level less than 20 ng/dL should also be included as a secondary endpoint and included in labeling. Particularly for randomized trials seeking to demonstrate a comparative benefit between two alternative GnRH analogues, PROs can be included as secondary endpoints. Sponsors should discuss their PRO assessment strategy with the FDA review division.

### *7. Statistical Considerations*

The primary analysis for the single-arm trial described above should be the calculation of the proportion of participants who achieve and maintain castrate T levels from Day 28 through the end of the treatment period. To demonstrate efficacy, the lower bound of the 95 percent confidence interval for this estimate should be greater than 90 percent (i.e., less than 10 percent treatment failures). The Kaplan-Meier method is recommended to calculate the estimate and its 95 percent confidence interval. For this method, an event is defined as a treatment failure, which is a noncastrate T level (i.e., T level greater than or equal to 50 ng/dL) at any time from Day 28 through the end of the treatment period. Although noncastrate T levels before Day 28 are not considered treatment failures, participants who fail to achieve a castrate T level at Day 28 should be considered to have an event at Day 28 in this analysis.

The following recommendations for handling missing data after Day 28 in participants who successfully achieve a castrate T level by Day 28 should be considered when the Kaplan-Meier method is used:

- 1) Participants who leave the trial for reasons other than a noncastrate T level should be censored at their last T level assessment.
- 2) Participants with one or more consecutive missing T levels and a noncastrate T level after the missing time point should be considered to have had a treatment failure at the first missing time point.
- 3) Participants with castrate T levels immediately before and after a single missing T level should not be considered to have had a treatment failure or censored at the missing time point.
- 4) Participants with two or more consecutive missing T levels (across more than 1 day) and castrate T levels immediately before and after the missing time points should be censored at their last T level before the missing data.

Sponsors should conduct a sensitivity analysis in which participants who leave the trial and participants with two or more consecutive missing T levels, regardless of T levels before and after those missing time points, are considered to have had treatment failures. Sponsors should plan for approaches to handle missing data in participants who have other types of missing patterns not captured above and should consider additional missing data sensitivity analyses. Sponsors also should conduct sensitivity analyses with different approaches for handling

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participants who received concomitant medications and herbal supplements that could possibly affect T levels.

In determining the sample size of the trial, sponsors should anticipate and account for the possibility of participants leaving the trial prematurely. Sponsors should make every effort to avoid missing data.

### **D. Labeling Recommendations**

The CLINICAL STUDIES section of labeling should include a summary of the clinical study or studies that provide the primary support of effectiveness of the drug product.<sup>10</sup> This section should provide information on the percentage of participants who achieved and maintained a castrate T level, which is necessary for demonstrating substantial effectiveness of a GnRH antagonist for the treatment of advanced prostate cancer.<sup>11</sup> This section should also include the percentage of trial participants who achieved and maintained a T level less than 20 ng/dL during the treatment period. Additionally, if the applicant proposes to describe the time course of achieving castrate T levels, this information should be presented in this section as the percentage of participants treated with GnRH antagonists who achieved castrate levels at Day 14 or 21. Presenting mean T levels over time can be misleading because the mean value may mask a clinically important incidence of treatment failures; therefore, applicants should not include mean T level results in product labeling.

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<sup>10</sup> See 21 CFR 201.57(c)(15) and the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

<sup>11</sup> 21 CFR 201.57(c)(2)(iv).

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### APPENDIX

The following are general comments regarding the *in vitro* drug-release method development, acceptance criteria, and data submission that applicants should provide in new drug applications.

#### **1. In Vitro Drug-Release Method Development Report**

- a. Provide a detailed description of the *in vitro* drug-release method being proposed to evaluate the drug product. Provide data to support that the selected *in vitro* drug-release method development parameters are the most appropriate for the proposed *in vitro* drug-release method (e.g., testing apparatus, dialysis chamber, *in vitro* release medium conditions, temperature). An accelerated drug-release method can be developed for quality control purposes. The testing conditions used for each test should be clearly specified. The release profile should demonstrate complete drug release or a plateau (i.e., no increase over three consecutive time points). We recommend the use of at least six samples per testing variable during method development.
- b. Provide complete *in vitro* drug-release profile data (individual, mean, standard deviation). The data should be reported as the cumulative percentage of drug released with time (the percentage is based on the drug product's proposed labeling claim at different time points).
- c. Submit data to support the discriminating ability of the selected *in vitro* drug-release method. In general, the testing should compare the *in vitro* drug-release profiles of the target drug product and proposed drug products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes and process parameters (i.e., plus or minus 10 to 20 percent change to the specification ranges of these variables).
- d. Provide supportive validation data for the *in vitro* drug-release method (i.e., method robustness, etc.) and analytical method (e.g., precision, accuracy, linearity, stability).
- e. Provide a list of critical material attributes and critical process parameters affecting *in vitro* drug release.

#### **2. In Vitro Drug-Release Acceptance Criteria**

The complete *in vitro* drug-release profile data (e.g., 0.5, 1, and 6 hours, then 1, 2, 4, and 6 days, etc., n = 12) from clinical and registration/stability batches should be used for setting the *in vitro* drug-release acceptance criteria. Adequately validated and fully documented analytical methods should be used. FDA recommends a minimum of three time points to set the acceptance criteria (i.e., sampling time points and acceptance limits) for extended drug-release products from the lots used in the clinical trials and primary stability batches. These time points should cover the early, middle, and late stages of the drug-release profile. The last time point should be where at least 80 percent of the drug product is released. If the maximum amount released is less than 80 percent, the last time point should be the time when the plateau of the drug-release profile has

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been reached. In general, the selection of the drug-release acceptance criteria ranges is based on mean target value plus or minus 10 percent and greater than 80 percent for the last sampling time point. Wider criteria ranges may be acceptable if they are supported by an approved in vitro–in vivo correlation or physiologically based pharmacokinetic model.

### **3. Data Submission**

The complete in vitro drug-release profile data for the clinical and stability batches of the drug product should be presented in tabular and graphical formats. The tables and plots of mean and individual vessel data for the clinical and stability batches should include profile data at release (time-zero) and throughout the duration of stability testing under long-term storage conditions.