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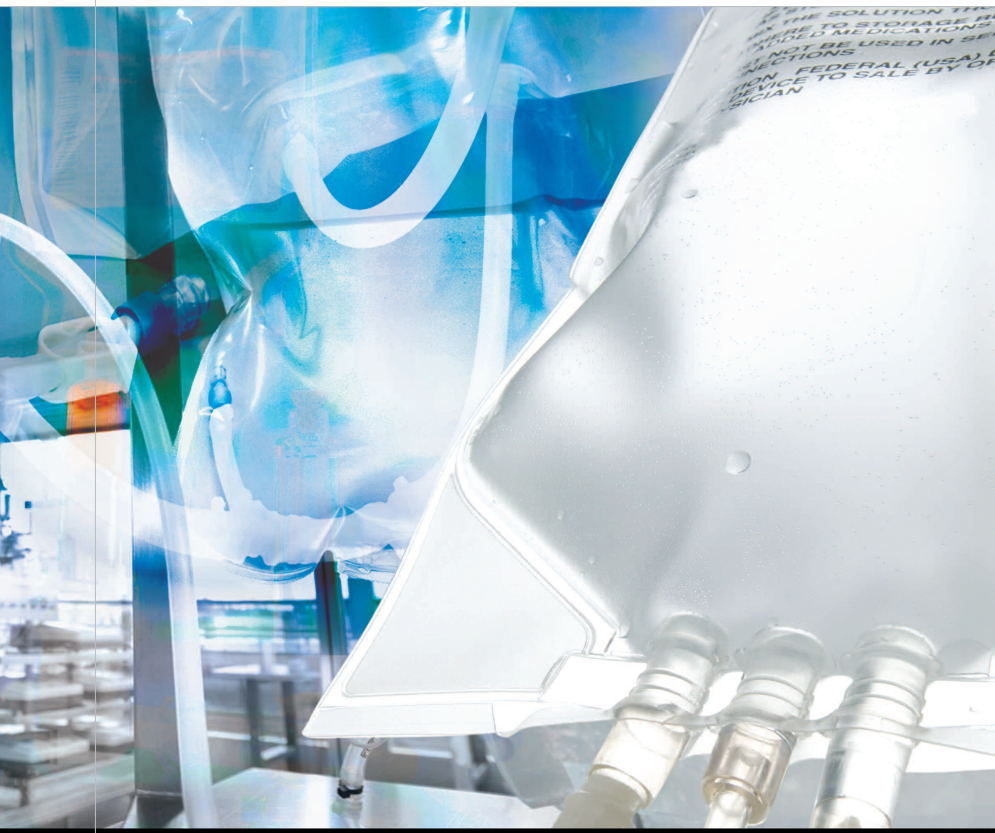
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RTU DRUG PRODUCTS: PART II



should be included in stability submission packages.² In this article, we discuss considerations in designing stability studies, data evaluation, and expiration dating for parenteral products—with an emphasis on intravenous RTU drug products in plastic containers.

Stability Study Design

For U.S. new drug applications, typically three batches per drug product configuration are required with data through 12 months of long-term (25°C/60% relative humidity [RH]), six months of accelerated (40°C/75% RH), and 12 months of intermediate (30°C/65% RH) storage conditions, if applicable. Two of the three

Stability study results help set or refine appropriate specifications and establish the shelf life applicable to all future batches.

Ensure Safety, Efficacy of Ready-to-Use IV Drug Products

Stability considerations are key | BY PAULA YOUNGBERG WEBB, MS, AND RAO CHILAMKURTI, PHD

Editor's Note: This is the second in a three-part series on ready-to-use parenteral products. The first part appeared in our September issue, and the third part will be posted on our Web site, www.pharmaquality.com, when our December/January issue goes online in late December.

Ready-to-use (RTU) intravenous drug products are pre-mixed solutions of drug and intravenous diluents that are typically packaged in 50 mL to 1,000 mL flexible plastic containers. Key considerations in the development of intravenous RTU drug products have been described previously.¹ After the formulation and the container system have been selected and the analytical methods validated, the manufacturer must conduct registration stability studies to demonstrate the product's acceptability over its intended shelf life. These study data are included in the regulatory filing.

In addition, stability study results help set or refine appropriate specifications and establish the shelf life applicable to all future commercial batches. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q1A (R2) guidance document offers guidance on stability testing for new drug substances and products and provides directions on what

batches placed on stability should be manufactured at “not less than 10%” of the intended commercial batch size (at least at pilot scale); the third batch may be smaller.

Using multiple active pharmaceutical ingredient lots and exposing some batches to worst-case processing conditions such as maximum hold times and sterilization temperature and time should be considered when manufacturing stability batches. The batches should be manufactured at the proposed site for commercial production, using equipment equivalent to commercial use.

For proposed products with multiple presentations, manufacturers may consider a matrixing or bracketing design approach described in ICH Q1D.³ Both designs offer potential cost savings, either by decreasing the need for testing or reducing the number of batches needed. These designs are amenable to products with the same constituents, the same container materials, and similar attributes.

A bracketing study design involves testing only samples from the extremes of the proposed product configurations, with the assumption that the extremes repre-

sent the stability of the intermediate configurations. Table 1 (see below) provides an example of a bracketing approach for 12 product presentations, reducing the number of registration batches from 36 to 12.

A matrixing study design includes all samples being tested at the initial and final time point, with only a subset of samples tested at any given time point in between; the assumption is that the stability of the tested samples represents the stability of all of the samples at a given time point. Table 2 (see below) provides an example of a matrixing test design. This design can be risky: If results indicate a difference among the configurations

tested, then the untested configurations will be assigned the shortest dating determined until actual configuration testing confirms what is appropriate.

Manufacturers must evaluate aqueous-based drug products packaged in semi-permeable containers, such as flexible plastic containers, for potential water loss, in addition to the physical, chemical, biological, microbiological, and functional attributes of the container. These products must demonstrate the ability to withstand low relative humidity environments. We describe the storage conditions for room temperature products packaged in semi-permeable containers in Table 3,

along with the typical test intervals for each condition and the minimum amount of data required for the submission.

The duration of the storage period at room temperature (25°C) and corresponding test schedule must cover the intended shelf life of the proposed product and demonstrate its stability profile. Testing intervals should be at a sufficient frequency to characterize the degradation profile adequately. Typically, samples stored at the intermediate condition are not tested unless a significant change is observed at accelerated conditions. (See reference 2 for the definition of significant change.)

If significant change is observed, the manufacturers should conduct an intermediate storage condition study. For frozen products, the long-term storage condition is -20°C. Short-term thawed testing, which generally consists of storage at 5°C for up to 30 days or for up to three days at 25°C after thawing, is also performed at various long-term frozen intervals. Due to the nature of frozen products, the length of the study at each storage condition will be specific for each drug product.

Tests Performed During Studies

Selection of specific tests/assays is based on the technical understanding of the solution product and the container system. The test schedule should focus on the parameters controlling shelf life or those parameters likely to change, in addition to meeting regulatory requirements regarding test type. The typical tests performed on parenteral drug products include appearance, color, potency, degradation products, pH, particulate matter, sterility, pyrogenicity, and container leachables. For products in semi-permeable flexible plastic containers, it is essential to monitor water loss as well.

The critical product attributes or those likely to change, such as potency, degradants, pH, and water loss should be monitored at each test interval. Attributes expected to remain stable, such as excipients or sterility, may be tested less frequently, perhaps every six or 12 months during the course of the study. To characterize the stability profile of a particular parameter, it may be necessary to schedule additional intervals (e.g., one, three, five, six, seven, or nine months) depending on its rate of change.

Additional studies may be needed once the product is removed from the overpouch, because the water loss rate

Table 1. Example of a Bracketing Study Design

	1.0 mg/mL	2.0 mg/mL	3.0 mg/mL
100mL	∅	0	∅
200mL	0	0	0
400mL	0	0	0
500mL	∅	0	∅

(0) Represents proposed products
 (∅) Represents proposed products to be placed on study

Table 2. Example of a Matrixing Study Design

Batch	1			2			3		
Size (mL)	10	20	50	10	20	50	10	20	50
Schedule	1	2	3	2	3	1	3	1	2
0	∅	∅	∅	∅	∅	∅	∅	∅	∅
3	∅	0	0	0	0	∅	0	∅	0
6	0	∅	0	∅	0	0	0	0	∅
9	∅	0	∅	0	∅	∅	∅	∅	0
12	0	∅	0	∅	0	0	0	0	∅
18	0	∅	∅	∅	∅	0	∅	0	∅
24	∅	∅	∅	∅	∅	∅	∅	∅	∅

(0) Represents all possible testing points
 (∅) Represents planned testing

Table 3. Storage Conditions for Solutions in Semi-Permeable Containers

Study	Storage Condition*	Typical Test Intervals	Min. Data at Submission
Long Term ¹	25°C/40%	0, 3, 6, 9, 12, 18, 24 months, then yearly until expiry	12 months
Intermediate ²	30°C/35%	0, 6, 9, 12 months** (**Only if significant change observed)	12 months
Accelerated	40°C/NMT 25%	0, 1, 3, 6 months	6 months

*Temp = +/- 2°C; RH = +/- 5%

¹The applicant decides whether to use 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH

²If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition

(Ref. 3 - ICHQ1A)

may increase with the overpouch. Or, in the case of oxygen-sensitive products, rapid ingress of oxygen into the container may result. Manufacturers should conduct a photostability study per ICH Q1B to demonstrate the product's stability when exposed to light and the effectiveness of the packaging system, as appropriate.⁴ Manufacturers should also conduct temperature cycling studies to demonstrate the effects of temperature variation that the product might undergo during shipping and distribution. The number of replicates per test depends on the variability of the method and the expected change over time of the attribute. Typically, three samples are scheduled: one for potency, one for degradants, and pH testing to facilitate statistical analysis.

Using statistics to establish shelf life provides a higher degree of confidence that all future batches will meet the acceptance criteria.

Data Evaluation

Once available, the stability data are evaluated to set the appropriate expiry date. The ICH Q1E guidance document provides direction on how to assess stability data, including the use of statistics to estimate product shelf life.⁵ To ensure that the drug product will remain within acceptance criteria through its shelf life, product expiration dating must consider the following: stability data from registration batches, formulation development data, manufacturing process data, analytical variability, release and stability specifications, and stability data supporting in-use conditions. Each attribute should be evaluated separately—and an overall assessment

used—to propose a shelf life. The shelf life should not exceed that predicted for any single attribute.

As indicated in ICH Q1E, chemical attributes, such as potency or degradants, generally follow zero-order kinetics during long-term storage. Zero-order kinetics can also estimate water loss for products packaged in semi-permeable containers. Using statistics to establish shelf life provides a higher degree of confidence that all future batches will meet the acceptance criteria. When statistics are performed, if the rates from different batches meet the criteria for poolability, a mean rate is used to establish shelf life. If the rates cannot be pooled or cannot be considered statistically the same, then the worst-case rate predicts the expiration date.

Intravenous RTU products that survive terminal sterilization and exhibit minimal change in potency and degradation products over time often have their shelf life based on water loss. The water loss rate through the semi-permeable container system is linear over time. In some cases, dating may be determined by pH, which may change due to lack of formulation buffer or due to low levels of container-related leachables.

For aseptically filled room temperature products, the level of degradation products is often the shelf life-limiting parameter. For aseptically filled frozen products, manufacturers must evaluate the change in potency, pH, and degradants on frozen storage stability as well as on thawed stability at 5°C and room temperature to determine the appropriate expiration dating for the product.

Extrapolation to extend shelf life beyond the period covered by the available long-term data can be proposed if no significant change is observed at the accelerated storage condition. A proposed shelf life based on extrapolation should always be confirmed by additional real-time long-term stability data as soon as the

data become available. The post-approval commitment batches should be tested at a point in time that corresponds to the extrapolated shelf life.

In the end, the key to a successful RTU pre-mix drug stability program is developing and implementing study designs based on scientific understanding of the formulation stability and container properties—specifically flexible plastic containers—along with applicable ICH guidelines. Stability study data are evaluated to establish appropriate expiration dating periods for the products. Well-designed studies fully characterize the stability profile of the RTU pre-mixed product and ensure that it is safe and efficacious and will meet its requirements through expiry while in the market. ■

Youngberg Webb is senior director, stability operations, and **Dr. Chilamkurti** is senior director, pharmaceutical technology, at Baxter Pharmaceuticals & Technology. Reach Dr. Chilamkurti at rao_chilamkurti@baxter.com.

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