NEW ENGLAND PDA NEWSLETTER

12 Sept 07 Volume 2, Number 3

Connecting People, Science and Regulation

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Editorial Board

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Dose Recovery: Identification of a Problem and its Resolution

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Intravenous (IV) administration is a common route used clinically for delivery of parenteral dosage forms. Distinctions are often made between *bolus injection*, *slow intravenous injection*, and *intravenous infusion*. These modes of administration involve a variety of administration sets, supplied by different providers, which need to be evaluated for dose recovery. Briefly, dose recovery is a measure of how much of the drug substance present in the administration vehicle is delivered into the patient upon administration using a given administration apparatus. Dose recovery is an important issue for a new chemical entity (NCE) but becomes critical for generic drugs that must deliver the same amount of drug substance as a brand-name product. Non bioequivalence of a generic preparation is a potential source of rejection by the Food and Drug Administration (FDA). Furthermore, dose recovery testing is necessary for co-administration of two or more drugs.

The studies designed to address dose recovery and related issues typically are performed using a high-pressure liquid chromatography (HPLC) technique designed for monitoring solution concentration of the compound under investigation. A stability-indicating HPLC method should be available for a compound in clinical development. Therefore, analysis of the drug concentration on loading into an administration set, from any part of the set, and on exit from the set will provide a picture of its physical stability (solution concentration) and chemical stability as a function of time.

Commonly, the active pharmaceutical ingredient is stored in a concentrated form either as a liquid, neat or in solution, or as a solid. The removal of the drug substance from its primary packaging involves dilution of a liquid, dissolution of a powder, or

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Please remember the date!
The next NE PDA meeting is
November 14th!

reconstitution of a lyophilized solid. The dilution/reconstitution vehicle generally is introduced through the system closure using a syringe and needle, and the resulting solution is diluted further into larger dosing containers such as IV bags or evacuated containers.

Among the typical diluents are solutions of 5 % Dextrose, 0.9 % Sodium Chloride, Ringer's solution, and Sterile Water for Injection (sWFI). A compatibility study with these diluents and administration sets from various providers can reveal losses in dose recovery when the test article is evaluated for up to 48 hours at the targeted high and low concentrations. Occasionally, the residual fluid from the sterilization process in evacuated containers may be responsible for drug incompatibility. A compatibility study at high and low concentration including the order of mixing (drug or diluent first) may help to ensure that the evacuated container from the selected provider is fully compatible with the investigational drug substance.

Co-administration of the test article with other drugs is a convenient method for drug delivery that is used frequently in the clinic. The solutions of co-administered drugs mix via a Y-site connection. Simulated Y-site co-administration should be evaluated rigorously as problems such as precipitation of the drug substances, color changes, decomposition, or adsorption can occur. This study typically is carried out by adding the drug at the required concentration with a variety of FDA approved drugs in different mixing order and diluents. Physical appearance, pH, and dose recovery are assessed for up to 48 hours.

Many remedies are available if a problem with dose recovery is identified. When occurring at the initial stage (incomplete recovery on sample preparation) a methodical testing of all materials used needs to be performed for all the studied concentrations. Often, replacement of plastic components by glass or siliconized parts will resolve the dose recovery problem.

Assessment of compatibility with administration sets manufactured from different materials is done similarly. Siliconized IV bags are available as are coated lines.

The remedy of last resort is reformulation in a different vehicle. Incorporation of a complexing agent or a surfactant into a drug formulation may obviate the need for deployment of unusual administration sets or development of complex instructions for clinical use.

References:

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Guidance for Industry: Container Closure Systems for Packaging Drugs and Biologics-Chemistry, Manufacturing, and Controls Documentation. US Food and Drug Administration, May 1999: www.fda.gov/cder/guidance/1714fnl.htm

PRESIDENT'S MESSAGE

From Lou Zaczkiewicz, NEPDA President

We hope you don't treat us as SPAM

I bring you greetings from your PDA chapter. There are lots of great things happening with the PDA at both the local and global levels. Global PDA has been working on and releasing many new and revised technical reports including the recently revised TR1. Global also has many fine conferences and training programs (see www.pda.org). Locally we meet monthly alternating between business meetings and educational / networking presentations.
At both levels we have active programs for students. The PDA offers three scientific programs designed to provide maximum networking, presentation and career building opportunities for biopharmaceutical or pharmaceutical students including:
1. Annual Graduate Research Symposium
2. Student Poster Sessions
3. Pre-Doctoral Fellowship Program – Students can earn up to $40,000 in available funding!
PDA student membership only costs $30 / year.

Locally we have a greatly reduced price for the dinner meetings and would like to start student chapters at local colleges (contact us if you'd like to help). However we need your help in getting the word out about these and other events. Some companies are contracting with email management services (notably Barracuda Spam Firewall) that now treat the emails that announce our programs as SPAM. At the end of August, for example, none of our members at a large pharmaceutical company received the notice of our September Project Management workshop.

We need your help. Please contact your IT department to ensure that our email announcements keep getting to you (coming from lzaczkiewicz@hyaluron.com). If you do not want to receive notices about local meetings and this newsletter, please send me an email to remove your name from our distribution list.

Regards,
Louis Zaczkiewicz
NEPDA President

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The New England Chapter of the PDA is pleased to announce the ***availability of advertising opportunities in our newly launched newsletter.*** Since its inception in 1988, our chapter has seen a significant growth in membership and participation. Our newsletter has the following reach:

- Our direct e-mail distribution reaches over 1,200 contacts throughout New England.
- Our membership includes people from manufacturing, research, QA, QC, engineering, contract manufacturers, consultants, regulatory, ***etc.***
- The newsletter is promoted at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-100 attendees.
- The newsletter is posted to our chapter's website at Global PDA (www.pda.org), an organization that has over 10,000 members.

We offer vendors, consultants, operating companies and other organizations the opportunity to promote themselves and also support the NE PDA Chapter by purchasing advertising in our newsletters

Upcoming Publication Schedule:

Issues	Cost	Deadline
Prior to **November 7 Meeting (vol. 2/no. 4)** **Venue/Topics:** Tour TBD, TR-1 Steam Sterilizer Validation	**$100** per ad	**Oct 1**

Artwork Format/Submission:

Business card (2" H x 3.5" W) ads are $100/issue, 2 ads/issue maximum

Full color, 300dpi or better, TIF, PDF or JPG *only*

Individual files not to exceed 3MB (zip files accepted)

E-mail artwork to melissa@mjqualitysolutions.com

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Questions:

About the newsletters and articles? E-mail Melissa at Melissa@mjqualitysolutions.com

About advertising opportunities or artwork? E-mail *lzaczkiewicz@hyaluron.com*

Thank you from the New England PDA!

Louis Zaczkiewicz, ***President***