NEW ENGLAND PDA NEWSLETTER

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Connecting People, Science and Regulation

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On Pre-formulation and Formulation: Defining the Universe of Discourse

By Michael Frid, Ph.D.
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www.wolfelabs.com

Pre-formulation and formulation are integral parts of the drug development process and parenteral drugs require a tailored approach that is different from that for orally-administered or topical pharmaceuticals. In general, pre-formulation refers to the physicochemical characterization of a compound and formulation refers to the development of a customized dosage form for a specific administration route. At some stage in a drug development program precious resources must be dedicated for pre-formulation and formulation work. How can these resources be allocated most effectively and when?

The answer to this question will be different for each organization depending on its scientific culture and business philosophy. Nonetheless, a clear understanding of what issues are addressed during pre-formulation and formulation stages can help in making such decisions. There are four broad subjects with which a formulator of a parenteral pharmaceutical is concerned: solubility of active pharmaceutical ingredient (API), short term or administration stability, dose recovery, and long term or storage stability.

Solubility means the concentration of an API that is achieved in a solution that is administrable to humans. Many parenteral drugs are manufactured as concentrates or solids, and are diluted with, for example, water for injection (WFI) prior to administration. How much API should be delivered, in what volume, and over what period of time may or may not be known accurately prior to the toxicology and animal efficacy studies. Usually, however, a ballpark figure is available and pre-formulation studies can determine whether or not the expectations for solubility of the API are reasonable. Of course, the crux of the solubility problem is that any formulation must be *administrable*, meaning that the amounts of organic components must be below allowable limits, its pH must be acceptable, and, particularly for intravenous administration, osmolality should be close to iso-osmotic.

Other than solubility, short term stability, meaning chemical stability of the API in the dosing vehicle over the time required for administration, is the most difficult and pressing problem tackled during the pre-formulation and formulation studies. Many molecular entities are stable

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Future Topics:

Impact of International Outsourcing on Regulatory and Quality Systems
Mina Gerber and Melissa Smith

Real Life Lessons: HVAC System Validation
Myron Dittmer

Dose Recovery: Identification of a Problem and its Resolution
Nicolas S. Mourier, Ph.D.
Associate Director Pharmaceutical Dev.
Wolfe Laboratories, Inc.

Three Part Series on New OOS Guidance
Mina Gerber
Basic Elements of Statistical Process Control
Stanley N. Deming

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as solids or as concentrates in organic solvents, but become labile on contact with aqueous reconstitution vehicle. Unfortunately, administration times may be as long as 72 hours, for example, in case of dosing by intravenous infusion. Therefore, conditions must be found, subject to the limitations described above, that allow the API to remain chemically stable over a period of time at least twice as long as that projected for administration.

Once the solubility and short-term stability issues have been resolved, a seemingly simple question becomes important: how much of the API present in the administration vehicle actually makes it into the patient? In other words, what is the dose recovery? Experience has shown that some API's are adsorbed onto plastic or even glass surfaces. This situation may arise with a molecule of any structural class but can be particularly important for basic compounds, such as amines. Extensive experimentation and testing may be required to identify the proper administration apparatus, which may include the use of Teflon-coated tubing or silanized containers to ensure adequate dose delivery.

Finally, long-term stability, or stability on storage, requirements vary widely from drug to drug, and can be months to years. Monitoring real-time stability of a product is, of course, ideal but hardly practical for rapid identification of potential stability problems. Accelerated stability testing is used for that purpose, wherein a drug formulation is placed under controlled elevated temperature and humidity conditions. On the basis of accelerated stability testing judgments may be made on the long-term storage form, which can be a concentrated solution, dry powder, or a lyophilized powder.

It is clear that formulation development is not a stand-alone "API comes in, formulation comes out" activity. Every stage in formulation development is guided by the properties of the compound under consideration and the scientific and business judgments of its developers. It is also a two way street, with data on compound's properties and challenges in development of its formulation flowing back and informing future decisions.

References:

Pharmaceutical Preformulation and Formulation; Mark Gibson Ed., IHS Health Group, 2001, Denver, CO, USA

USP 29 – NF 24; United States Pharmacopeial Convention, Official from January 1, 2006

http://www.fda.gov/search/databases.html

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New England Chapter News:

Wednesday, June 13, 2007
Networking, & Dinner Meeting
Hilton Garden Inn, Burlington, MA

Tour of Millipore facility in Billerica

PDA TR40 Sterilizing Filtration of Gases: A Comparison with TR26
Leesa McBurnie
Sr. Microbiologist
Meissner Filtration Products, Inc

PDA TR26 Sterilizing Filtration of Liquids: An Overview and Update
Jerold Martin
Sr. Vice President, Scientific Affairs
Pall Life Sciences

Don't forget to SIGN UP!!
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How about some of Myron Dittmer's Favorite Links for organizations?
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ISO:www.iso.org/isoonline.frontpage
WHO: www.who.int/en/

Want to look up Elements of preformulation studies?
www.pharmainfo.net/

Did you Know?
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Audit Procedure
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Audit Report
And 7 other downloads
www.emea.eu.int/Inspections.JAP.html

NEW ENGLAND PDA PRESIDENT'S MESSAGE

Louis Zaczkiewicz

The 2007 PDA annual meeting was a great event to be part of in March. Besides the great presentations, interest group meetings, chapter council meeting and networking events, this was a special meeting as the PDA awards night recognized one of our own: Dr. Mark Staples. We should all be very proud of Mark as he received the distinguished Volunteer Award for his years of dedicated service to the PDA and the New England Chapter. Mark was part of the core group of people who founded this chapter in 1988 and has been serving it in many ways for as long as I can remember. Some recent examples of his work include chapter President, meeting presenter, technical reviewer for some international guidance documents, and active participant in the planning committee. During Mark's tenure as NEPDA President, our chapter was recognized as chapter of the year. I urge each of you to congratulate Mark and thank him for the tremendous work he has done for the PDA. We plan to have Mark as the guest of honor at our June 13 meeting.

Also at the Annual Meeting, many people came up to me to congratulate our chapter for being one of the most active chapters in North America. Our February meeting at the Charles River Laboratory was a particularly successful event. Not only did we get to witness firsthand the state-of-the-art work that CRL does for clinical trials studies, but we also had 2 great presentations on Chromatography Validation. By the time you read this, will have completed our April 11 meeting on Cold Chain Management along with a tour of the Sypris ship test facility in Burlington. At this event we rolled out new, experimental pricing changes. We will be charging retired or unemployed PDA members and active college students only $10 to attend our dinner meetings. Although this pricing will be a financial loss for the NEPDA, we feel it is important to encourage these groups to attend the section meetings.

Additional events that we have confirmed for this year include the June 13 meeting on filtration and the November 14 meeting on the PDA TR1, Steam Sterilization Validation. Our September 12 meeting is still in the planning stages, but the possibilities currently include a meeting on Project Management or on the soon to be published PDA technical report on glass defects.

We are very lucky to have a strong group of people active in making these great events happen. As always, you are encouraged to come to our planning committee / business meetings held on the second Wednesday of every other month. Feel free to contact me with suggestions on how to keep making this chapter even stronger.

One of Louis' favorite links is a Pharma discussion group:

www.pharmweb.net/pwmirror/pwq/pharmwebq2.html

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IF METHOD VALIDATION IS A SNAPSHOT, LET'S SEE THE MOVIE! By Melissa Smith

Often method validation is described as a snapshot view of method status, yet how often is the 'age' of this snapshot questioned? Method validations have roles beyond that of fulfilling the ICH Q2R(1) requirements for a Type II quantitative test, for instance. It is these areas that touch upon the validation, that rely upon the validation, and that are part of the expansive life cycle of validation that this article will try to delineate.

While one part of method validation is to ensure all the appropriate sections in ICHQ2R(1) have been tested, it is beneficial to stand back and view the validation in a wider frame than the immediate snapshot.

PRODUCT PHASE TRANSITIONS

There have been a few articles on the progression of validation from Phase I/II to III. Planning ahead for the review of validations in Phase III in preparation for commercial filing is a task not to be underestimated, especially if the validations were conducted in Phase II, if the method has been transferred from one CRO to another, if there have been Out of Trend or Out of Specification incidents, if the frequency of invalids is higher than desired, or if there have been changes to the method over time. The Assay Technical Team, comprised QC and AD members with assay technical expertise, review issues in execution, equipment, materials, reliability, system suitability criteria, sample validity criteria, standards, controls and specifications that they feel warrant further discussion. Particular attention to the details of Potency Assay and Stability Indicating Assay Validations are needed as well as the adequacy of the statistical criteria of all parts of the Validation Reports. The Method Validation Package is part of an overall package of trending, OOS investigational support, CRO transfer/backup vendor preparation, and the justification of specifications as well as providing analytical links to clinical lots and early reference standards.

VALIDATION AS PART OF DAILY QC LIFE

Validations, if viewed as an end in themselves, are often not a visible part of daily QC work. QC should have as part of their method training an overview of the basis of the method, the critical steps and materials, and the behavior of the method as reviewed in the method validation report. When the reports are designed with summary sections in the front of the report, this is easily achieved. If they are not summarized in this way, then their usefulness as a quick guide is diminished.

WHAT DOES THE NEW OOS GUIDANCE SAY ABOUT VALIDATION

The OOS Guidance issued in Oct 2006 states that in the Phase I investigation of an OOS, the laboratory supervisor reviews data to determine if there was laboratory error or if the result may be due to problems in the manufacturing process and that part of this assessment is to "evaluate the performance of the test method to ensure that it's performing according to the standard expected based on method validation data and historical data". So here is another reference to the use of the method validation along with historical (trending) data by QC to ensure that the test method is behaving as intended. Method trending files should be reviewed on a routine basis by the Quality group with reference to the validation parameters and the capability of the method to monitor the process within the specification set-or in other words, is the method still behaving as it was intended when the specifications were set, has there been a drift, to what could this be attributed, and

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how can it be addressed. Frequently these reviews can have associated ties to the budget cycle so that method improvements involving capital equipment can be planned within the annual budget cycle so that the equipment in the Quality lab remains reliable, up to date, and efficient. With an Assay Technical Team in place with joint attendance by QC and AD, this review is part of their scope.

Method Technical Review should occur during phase III and a Gap Analysis performed. Historical data is reviewed as well as the state of the equipment, the reliability of the CRO (if applicable), the vendor/testing backup plan if using a CRO, the reference standard and controls inventory, and any potential/ foreseeable comparability exercises due to process changes… Many of these can have an impact on validation and it can be argued that a new assessment, for example, of precision may be beneficial to the overall method package.

TRENDING-LIFE AFTER VALIDATION

Trending of method parameters is a topic that often causes angst. However, trending files serve as a basis for monitoring method behavior and process over time, for aiding the ability to detect an Out of Trend and potentially reduce downtime, for helping draft appropriate acceptance criteria in Phase III validations, and for ensuring specifications are appropriately set so that the process is capable of meeting the specifications given the know variations in the process and the method. Their usefulness is many fold and is reduced the longer it is put off starting them. Validations and Method Technical Reviews should yield critical trending parameters to be used in the setup of the trending files.

Revalidation is often looked upon as an indication that the original validation was in error in some way rather than an execution to obtain additional information to ensure the future has less 'bumpy roads'. Method Technical Reviews should encompass the Trending Files, Method Validations, Quality Control Equipment, CRO status review (and backup plan), desired changes to methods such as equipment, materials and specific executable steps, and OOT, OOS, and deviation reviews. This should take place in Phase III and on an defined basis thereafter to ensure that you are on top of the methods instead of being in a situation where fighting fires takes the place of proactive review.

BY THE WAY-HAVE YOU READ THIS USP CHAPTER?

The USP has a General Chapter called Analytical Data-Interpretation and Treatment <1010> which I encourage you to read if you have not already. It covers typical calculations done for validations such as mean, standard deviation, confidence intervals, outlier, t tests and has an appendix on control charts, precision, an outlier study and two sections on comparison of methods where examples of data are used to explain the use of the charts and formulas. It has a good explanation of some of these terms and their uses in validation activities.

IN CONCLUSION

Overall, Method Validation is just a snapshot for a look at the methods behavior at the time-and through various activities such as trending files, annual method reviews, and investigations there is an ongoing reference to and use of the validations to ensure they remain relevant to the method at hand and useful as one of the tools in the QC toolbox.

Validations need to keep current with the operational reality of the method and to ensure that they still bear a solid relationship with the capacity to aid OOS investigations, to behave in a controlled manner within all process parameter ranges expected in long term production, to be able to distinguish the expected variation from the method from variation due to operational drift as the number of operators and laboratories are added, and to know its relationship to the specification window. Validations should be poised to provide an current snapshot to its behavior throughout the lifetime use of the method. Revalidation should be expected as a useful tool in the methods lifetime.

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- The newsletter is promoted at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-100 attendees.
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Thank you from the New England PDA!
Louis Zaczkiewicz, ***President***