

2010 Pharmaceutical Sciences World Congress Provides Dissolution Programming with an International Flavor

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In November, the FIP 2010 Pharmaceutical Sciences World Congress was held in New Orleans in association with the American Association of Pharmaceutical Scientists Annual Meeting and Exposition. Some of the latest thinking on dissolution was presented with a distinctly international flavor, since many of the speakers and participants were from outside the United States.

In a Roundtable on **Analytical Instrument**

Qualification: Towards Globalization, Horacio Pappa from the United States Pharmacopeia highlighted the USP Dissolution Toolkit to be used in conjunction with PVTs. Recently, USP introduced several changes with respect to dissolution instrument qualification to reduce testing and make it more robust. **Cindy Busche** from FDA stated that AIQ is the foundation of quality data. She discussed recent Warning Letters and 483s, and indicated that dissolution made the Top 10 list. She also pointed out the importance of a written program for performance qualification and instrument calibration. **Robert McDowall**, McDowall Consulting, discussed the relationship between USP Chapter <1058> and GAMP 5 for computerized instruments. He pointed out the need for an integrated guidance that brings both of these together.

Relevance of Dissolution Testing in a QbD Approach to Drug Release was discussed in a Roundtable. **Patrick Marroum** from FDA said that a goal of QbD is that all batches within the design space should be considered bioequivalent. This may be demonstrated by relating pK or plasma data to in vitro data. Of course, this requires a meaningful in vitro test, one that is discriminating and sensitive to changes in manufacturing parameters. Ideally, sponsors would vary the formulation (perhaps using Design of Experiments) and then generate meaningful in vitro and corresponding bioavailability data. If in vivo data are available, they can be used to evaluate the appropriateness of the design space; alternatively, the f_2 test can be used to compare dissolution profiles.

Ruben Lozano from BMS pointed out that there may be an opportunity to replace dissolution with a surrogate. It is possible that other tests may be more meaningful; upstream control of critical quality attributes could make

dissolution testing redundant. He pointed out that sometimes there is no correlation between dissolution results and bioequivalence (BE) or bioavailability (BA). Surrogate tests might include disintegration, control of API particle size, granule size, blending process, or tablet hardness. Nonetheless, it may be necessary to perform dissolution testing on stability, even if it is avoided as a release test.

An EMA perspective on dissolution and QbD was presented by **Evdokia Korakianiti** from EMA. She pointed out that dissolution testing, media recommendations, and specifications rely on the Pharm Europa chapter on Dissolution and ICH Guidances Q8 (Pharmaceutical Development) and Q6 (Specifications). She also indicated that key documents are under revision, pointing to EMA/CHMP/QWP/202350/10 (1), which attempts to address issues such as in vitro tests that are not biorelevant, and CPMP/EWP/QWP/1401/98 (2), which will provide updated guidance on such as topics appropriate study designs, analytes to be measured, and dissolution test conditions. She also questioned whether dissolution is overdiscriminating in the case of immediate-release products that are BCS Class I and III. With a QbD approach, it is appropriate to examine product performance based on CQAs and to recognize that consistency comes from design and control of the manufacturing processes. The dissolution test should be developed to mimic in vivo performance and may be replaced by a surrogate procedure when appropriate.

In the roundtable discussion that followed the presentations, topics included the FDA stance on alcohol dose-dumping (particularly if in vitro results are different from those observed in vivo), the number of subjects necessary to develop an IVIVC, appropriate situations for use biorelevant methods, and the acceptability of non-compendial dissolution apparatus. When asked how many QbD applications had been received, Marroum indicated FDA had over 30 while Korakianiti said that two or three had used full QbD. On the subject of using biorelevant media to predict food effects, Marroum indicated that in vivo data is required. When asked if surfactants in the media are okay if they are justified, he responded that the method must still be discriminating and the concentration

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of surfactant should be minimized. Responding to a question about dissolution methods for generic modified-release products, Marroum said it was not necessary to follow the monograph method. Regarding the applicability of dissolution to liquid-filled capsules (LFCs), Marroum responded that FDA had accepted the rupture test for some products, while Korakianiti questioned why anyone would want to test dissolution for an LFC.

Integrating dissolution testing with permeability to predict product performance was discussed in a roundtable session. **Bertil Abrahamsson** from AstraZeneca highlighted the influence of formulation factors on systemic exposure and the importance of dissolution and permeability modeling to predict formulation performance in industry. Several examples were presented, including the influence of particle size on absorption and the effect of changes in C_{max} and AUC for the establishment of safe space and IVIVC. He described the use of absorption software to explore the likelihood of attaining safe space for the development of IVIVCs by probing the role of physiological factors like gastric emptying and permeation rate in relation to the dissolution rate. Then he noted that the in vitro testing of permeability and solubility is essential in early assessment of colonic absorption potential. He also discussed the use of TIM model for the combination of dissolution and permeability. The advantages of computer modeling were emphasized. In a question about appropriate in vitro testing, he noted that dialysis could also be used.

James Polli from the University of Maryland started his presentation with a discussion about the quality of target product profiles and the setting of specifications. With the hypothesis that modest changes in dissolution have no in vivo consequence for IR dosage forms whose overall absorption is not dissolution-controlled, he posed the questions of when BE studies can be waived for these IR products and what is needed to show that dissolution is not kinetically dominating. Then he highlighted that the deconvolution-based approach for IR formulations is very conservative when permeability is high and inappropriate when permeability is low. On the other hand, the convolution-based approach is appropriate when permeability is very high. He pointed out that the factor(s) controlling overall absorption kinetics and dosage form performance can be elucidated from in vitro dissolution–in vivo absorption relationships, and he discussed the underlying reasons for “no correlation” (i.e., made no effort, no good understanding of the product, dissolution not rate-limiting, in vitro test truly not sensitive to variables that are important, complex PK).

Shinji Yamashita from Setsunan University presented a BCS study of 311 marketed drugs to show that permeability (P_{eff}) but not dose number (D_o) limited the fraction absorbed (F_a) for most oral marketed drugs. He noted the importance of evaluating the developability of poorly soluble compounds as early as possible. An in vitro system to assess both dissolution and permeation processes

simultaneously (D/P system) and its predictability for some compounds was presented. Further improvement of the system was discussed (i.e., the addition of the function of the stomach, especially for basic compounds, gastric retention). He emphasized the importance of understanding the process of oral drug absorption that occurs in the GI tract in vivo and of building a system that can represent this in vitro or in silico. Questions and a discussion of the accuracy of in vitro systems and how the surface area is accounted for in permeability studies followed.

In Vitro Release of Drugs from Non-Oral Dosage Forms was discussed in a symposium. **J. Michael Morris** from the Irish Medicines Board presented a review of the FIP Special Dosage Forms Guidance. He discussed the harmonization of compendial methods and emphasized that compendial methods should be used if possible. He pointed out that the concept of drug release testing is referred to as in vitro drug release testing rather than dissolution testing. The dosage form taxonomy approach for solid oral dosage forms and non-oral dosage forms (topical preparations, eye preparations, suppositories, parenteral, inhalation, formulations for local effect, drug-eluting stents) was presented. Finally, the benefits of in vitro release testing were discussed and the preparation of the FIP paper on the up-to-date overview of release testing of novel and special dosage forms was noted.

Neal Davies from Washington State University discussed issues for Inhalation Products. He questioned what dissolution for these products is, and which apparatus should be used. He emphasized that inhalation products are not mentioned in BCS. The lung membrane passage and factors affecting absorption in lungs were presented. The importance of the choice of predictive in vitro tools in combination with the categories and tiers of inhalation dosage forms for the development of IVIVCs was highlighted. An example of dissolution testing of corticosteroids with media containing phospholipids (DPPC) in a modified flow-through cell was described. The commercial apparatus from Copley Scientifics for dissolution of inhaled products and the membrane cassette used were noted.

Diane Burgess from the University of Connecticut discussed approaches of in vitro dissolution for Complex Parenteral Products. The question was posed that there may be more than one approach and different methods for different dosage forms and different APIs for in vitro drug release of MR parenteral forms. A review of different methods for in vitro testing of dispersed systems (i.e., continuous flow technique, membrane diffusion technique, sample and separate technique, in situ) was presented. An example of the use of the flow-through method for microspheres was shown, in which a six-week in vitro release was well correlated with in vivo data. The convenience of an accelerated in vitro method (increased temperature) was discussed. She highlighted that the use of USP 2 for the in vitro release testing of microspheres leads to more aggregation. For in vitro release testing of

liposomes, the dialysis sac, the reverse dialysis sac, and the flow-through method can be used. Better data can be obtained with the reverse dialysis sac because with the dialysis sac, violation of sink conditions may occur. Finally, she noted that a dialysis adapter that can be used in USP 4 apparatus. In a question about how invasive the accelerated methods are, she indicated that it is difficult to obtain an IVIVC with an accelerated method.

Kazuo Maruyama from Tokyo University gave a presentation about **Targeted Intracellular Drug Delivery with Liposomes**. The liposomal drugs on the market in Japan were shown. He emphasized that ideally, drugs in nanocarriers (liposomes) should not only accumulate in the interstitial space inside tumors but should also be internalized by the target cells, which creates high intracellular drug concentration and allows multidrug resistance to be bypassed. Targeting intracellular delivery systems have to be stable in vitro and in vivo, moving from blood to tumor tissue, and binding to tumor cells. A transferrin-PEG-liposome these liposome for treatment of different types of cancer was presented. In vitro and in vivo stability, a prolonged circulation time, an extravasation from blood to tumor tissue (ERP effect), binding to tumor cells, and high intracellular drug concentration were shown for this system. The applicability of this system as an ideal carrier for passive and active targeting was emphasized.

In Vitro Release and Dissolution Testing Focus Group Meeting

The annual face-to-face meeting of the IVRDT Focus Group was led by incoming Chair **Alger Salt**. Salt reviewed the role of the Focus Group in proposing and supporting the dissolution programming for the Pharmaceutical Sciences World Congress (PSWC) and in fostering publications in the field, including an AAPS Journal Issue on the Role of Dissolution in QbD and Drug Product Life Cycle and papers on alcohol dose dumping, selection of dissolution media, targeted dissolution media, and dissolution instrument calibration. The group also supported a themed issue of Dissolution Technologies on semi-solids and sponsored a poll on current approaches to dissolution instrument calibration. You can find more detail in the Newsletters posted on the Focus Group website (http://www.aaps.org/inside/focus_groups/InVitro/index.asp). They also discussed 2011 Objectives, which include proposals for the 2011 AAPS Annual Meeting and a Dissolution Workshop or Webinar, newsletters, collaboration with other focus groups, international outreach, and student outreach in university chemistry programs.

BCS and BDDCS-Based Strategies for Oral Drug Development were discussed in a mini symposium. **Leslie Z. Benet** from the University of California discussed the major differences between the two classification systems, pointing out that the main purpose of BCS is the biowaivers, and that of BDDCS is the prediction of drug disposition and interaction. The basis of BCS is the extent



IVRDT Leadership: Left to right, Greg Martin (Chair, elect), Steve Mayock (Past Chair), Alger Salt (Chair)

of absorption whereas that of BDDCS is the prediction based on permeability rate. In both classification systems, the criteria for high solubility are the same, whereas the criteria for high permeability are defined differently: the extent of absorption >90% of dose for BSC, and an extent measure versus a rate measure for BDDSC. The implications of BDDCS were discussed. For marketed drugs, prediction of permeability from metabolism can be made; metabolism should be limited to CYP450 processes and phase 2 enzymes that require absorption to occur. The BDDCS predicts the relevance of enzymes and transporters in the gut and liver and the potential for DDIs. He presented a study on the accuracy of animal models at predicting human behavior with several Class III compounds and points for Class II drugs and food effects.

Shinji Sakuma from Setsunan University presented the background for the design and the principles for BE studies. The high variation in AUC and C_{max} that is often observed was highlighted. His talk provided an understanding of the risk factors that incur bioinequivalence of IR solid oral dosage forms in BE studies. The first consideration is that low solubility and permeability may be risk factors. The number of subjects is not correlated with permeability and solubility, indicating that variation in drug absorption is dominated by other factors. The second consideration is that low oral BA and high total body clearance are risk factors; an approach on the relation of $AUC/dose$ and the number of subjects based on BCS was presented. A well-regulated correlation was observed for BCS Class I and III compounds but not for BCS Class II and IV compounds. Validation of the use of this parameter ($AUC/dose$) was presented, and the analysis supported the appropriateness of biowaiver of BE studies for IR formulations containing not only BCS Class I compounds but also Class III drugs. He noted that the expansion of biowaiver of BE studies into IR solid oral dosage forms containing BCS Class II drugs is currently impractical, and that analytical methods that predict in

vivo dissolution will be required in this case. He concluded that the combination of BCS and *AUC*/dose enables the prediction of difficulties in proving BE of IR solid oral dosage forms containing BCS Class I and Class III drugs. This understanding will allow pharmaceutical industries to design BE studies with a practical (i.e., efficient and cost-saving) strategy.

Panos Macheras from the University of Athens presented the evolution of drug absorption analysis and described the road to BCS and the BCS FDA guideline. He pointed out the concerns of the meta-BCS period for dissolution and solubility, emphasized the importance of hydrodynamics in dissolution, and indicated the reconsideration of the diffusion-layer model in which the dose is taken into account. Then the QBCS system was presented and the central role of dose–solubility was noted. He discussed that the high solubility criteria in the FDA guidance may be too strict for weakly acidic compounds. The difference between kinetic and intrinsic solubility was emphasized, and it was shown that classification changes because kinetic solubility is higher than intrinsic solubility. Supersaturated solubility data of sparingly soluble drugs are more physiologically relevant for biopharmaceutic classification purposes, and he suggested that solubility–dissolution studies be carried out toward this end. He also pointed out that the mechanism of dissolution in vivo is not known and that it is better to use model-independent methods. The permeability considerations by the introduction of BDDCS and the drug transporters era in the meta-BCS period were also shown.

Open Forum on Establishing Clinically Relevant Dissolution Specifications in the Quality by Design World: Practical Implications and Regulatory Challenges.

The moderators of this Open Forum were **Nagesh Bandi** and **Steve Colgan**, both from Pfizer. The first talk was by **Christine Moore** of the FDA. Her topic was **Overview and Mission of Setting Clinically Relevant Specifications**. She outlined a possible Quality by Design (QbD) approach to dissolution release specification setting:

- Develop an initial quality target product profile.
- Perform an initial estimation of the relationships between the critical quality attributes (CQAs) and in vivo performance.
- Determine aspects of the formulation and process that are critical to the release profile.
- Determine the sources of variability and optimize the formulation.
- Use models to understand potential changes in material and manufacturing operations.

She defined real-time release testing (RTRT) as the ability to evaluate and ensure the quality of in-process and final product based on process data. This approach can be

facilitated by fast assays or surrogate assays for dissolution release testing. She offered alternatives to dissolution testing, the disintegration test and surrogate models. The remaining gaps are computational and experimental methodologies, complex dosage forms, and patient variability. The regulatory aspects of the remaining challenges are the need for increased scientific dialogue, the detail and placement of information in the application, and international acceptance and harmonization. She concluded by stating that QbD approaches can lead to a fundamental paradigm shift for pharmaceutical development and manufacturing, providing a linkage between patient, product, and process and a more risk-based approach to regulatory oversight.

The second speaker was **Ganapathy Mohan** of Merck on the topic of **Developing Meaningful Clinically Relevant Specifications: A CMC Perspective form Industry**. He discussed the traditional approach to dissolution where dissolution specifications are driven by regulatory and compendial expectations, geared primarily toward quality control of the products and ensuring batch-to-batch consistency. The dissolution specifications are mainly based on statistical evaluation of developmental, formal stability, and study batches and failure rates. The desired state would be to develop meaningful methods that can correlate to in-vivo performance and leverage mechanistic understanding for selecting tests and specifications that will demonstrate clinical relevance throughout the product shelf life. The path to achieve the desired state would be the development of a new strategy for in vitro specification setting and the establishment of systematic processes that link all development phases to specification setting, including leverage of pre-clinical and clinical studies. He pointed out the early stage of development is not ideal for establishing clinically relevant specifications, but that Phase 2 is about the right time to start collecting the information to show clinical relevance.

The third speaker of the session was **Jack Cook** from Pfizer, whose topic was **Developing Meaningful Clinically Relevant Specifications: A CMC Perspective form Industry**. He discussed pre- and post-approval manufacturing changes for a drug, asking what would be an efficient QbD path for exploring the potential impact of formulation (or dosage form) changes on in vivo performance. He started by observing that recent techniques and advances have allowed pharmaceutical scientists to measure the impact of changes in process and materials on in vitro formulation performance. However, our ability to interpret the relevance of any effect is often challenged by a lack of understanding of how in vitro changes are reflected in vivo. How does one establish this link between dissolution and in vivo performance? He suggested that the disintegration test may be adequate to judge first-in-human formulations. One point was for the scientist to become less of a frequentist: use fewer assumptions with individual study focus to a more Bayesian view, learn from previous studies, and use Design

of Experiments (DOE) frequently. Now IVIVC is still avoided, but the reality is that without one, there will always be another BE study, slowing down development. FDA is increasingly requesting companies to do an IVIVC. He summarized by stating that the BCS system can be used to assess the relationship between the dissolution test and product performance. With high solubility drugs, there is a region of bioequivalence, and with low solubility drugs, an IVIVC is possible. In order to judge the impact of a formulation change on in vivo performance, one needs a measured in vitro test or parameter that is predictive of in vivo performance. He also explained that the most efficient QbD path is through developing models using routinely collected data.

The last speaker was **Elaine Morefield** from FDA, who spoke on **Performance-Based Specifications**. She began by discussing the regulatory aspects of the product specifications, stating that traditionally, the product specification describes the tests and acceptance criteria used to judge the quality of the product. However, the current emphasis is on quality being designed into a product (QbD); quality cannot be tested into a product. The role of specifications should be to assure that products meet clinical performance and to confirm that the processes are performing as expected. She defines clinically relevant dissolution specifications as those specifications that help to determine consistent in vivo performance as proven by their ability to reject batches with inadequate in vivo performance. It is important to establish clinically relevant dissolution specifications to provide consistent safety and efficacy profiles for the marketed product relative to those achieved by the clinical trial formulation and to assure optimal rate of delivery and optimized drug therapy to the patient. The challenge to obtaining clinically relevant specifications is

that there are a limited number of clinical trials during development to provide linking information. In addition, there is limited ability to assess clinical consequences of changes in the manufacturing processes and formulation. Lastly, there is limited availability of in vitro models that can predict in vivo performance. Therefore, there is a need for methods that can predict the impact that changes in the manufacturing processes or formulation may have in vivo. Clinically relevant dissolution methods may have unconventional technologies, with complex media or apparatus design, yet conventional methods may be sufficient in most cases. She discussed three different scenarios for setting dissolution specifications. In Scenario 1, there are no data linking in vitro dissolution to plasma levels; in Scenario 2, there are data establishing the range of release characteristics that result in bioequivalence; and in Scenario 3, data are available to establish a predictive and robust in vivo—in vitro correlation. She ended by stating that the development of a clinically relevant dissolution method is critical to the setting of clinically relevant specifications and that clinically relevant specifications can increase regulatory flexibility.

REFERENCES

1. *Concept paper on the revision of the note for guidance on quality of modified release oral dosage forms and transdermal dosage forms: Section I (quality)*; EMA/CHMP/QWP/202350/10; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency: London, 2010.
2. *Recommendation on the Need for Revision of (CHMP) <Note for Guidance on the Investigation of Bioavailability and Bioequivalence>*; CPMP/EWP/QWP/1401/98; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency: London, 2007.