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Message from the Chair

Dear MSE Colleagues,

In the Technical Bulletin section of this newsletter we are giving attention to the fact that process analytical technology (PAT) has come of age, 10 years to be exact. Emil Ciurczak has been so kind to write a review on the PAT technique most applied, his pet being Near InfraRed Spectroscopy. We share with you the good news that we now have a primary focus group covering not only API and API manufacturing, but biologicals and biomanufacturing as well. And we have included a *Meeting Report on the AAPS Symposium on Advances in Analytical and Biotransformational Characterization Methods for Biosimilars*, compiled by Ruta Waghmare and Arya Jayatilaka. Finally not included in this newsletter, but to be distributed as the MSE contribution to the August issue of the *AAPS Newsmagazine* is a high level overview of the importance of quality. Written together with GXP expert Henny Koch, I give in this article a broad overview of the many facets of quality, putting in context the latest hot topics in the quality arena, being quality metrics and quality culture. Any comments on this would be highly appreciated.

In the meantime, we have arrived in the vacation period and the MSE section leadership is already looking ahead to the AAPS Annual Meeting to be held in San Diego, November 2–6. More details will be given in our next newsletter.

I wish you a nice summer vacation.

Tom Sam
My new email: TomSamPhD@gmail.com
MSE Focus Group Updates

Chemical and Biological Active Pharmaceutical Ingredient Manufacturing Technology
http://www.aaps.org/API_Manufacturing_Technology/

**Topic**
The Chemical and Biological Active Pharmaceutical Ingredient Manufacturing Technology (Chem Bio API-MT) focus group was founded in 2009 and has recently undergone some changes. The scope of the group was clarified to include the manufacturing of both small (chemical) and large (biological) molecule active ingredients. Please visit our new webpage and consider volunteering with the group, or collaborating on a programming topic with us!

**Activities**
The Chem Bio API-MT focus group meets monthly and actively participates in monthly supporting section meetings (Analysis and Pharmaceutical Quality, Manufacturing Science and Engineering, and Biotechnology). Our top priority is to move valuable programming forward for our focus group members, and these three sections support us in this effort. Thank you to the Regulatory Sciences section, who has also supported us throughout the years.

Since its creation, the Chem Bio API-MT focus group has organized many successful programs at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition and the AAPS National Biotechnology Conference (NBC), covering a broad range of API-related topics. This year we were pleased to have one program, held jointly with the Process Analytical Technology focus group, presented during the 2014 AAPS NBC: “Advances in Downstream Processing of Biotherapeutics.” Two programs were also accepted for the 2014 AAPS Annual Meeting and Exposition:

- “Case Studies of the Design and Execution of Extractables and Leachables Studies for Container Closure”

In addition to generating programming for meetings, the Chem Bio API-MT focus group also hosts webinars and develops workshops.

To achieve a breadth and depth of programming ideas, the Chem Bio API-MT focus group strives to collaborate frequently with the various sections and focus groups. In 2014, we are excited to welcome new steering committee members associated with the updated scope, and hope to present even more diverse programming on large and small molecules. We would like to acknowledge our appreciation for the passion and work by the biomanufacturing folks who endeavored to increase the representation of biomanufacturing–specific programming within AAPS!

**Chair**
Jaime Marach, Ph.D., is currently a senior scientist in product and process development at Boehringer Ingelheim (BI), developing small molecule and peptide generic medicines. Prior to joining BI, she was a development scientist in the API Technology Center, Analytical Research and Development Department, of Amylin Pharmaceuticals, Inc. developing large peptide drug synthesis, purification, and isolation strategies, as well as analytical characterization method development and formulation troubleshooting. Marach received her doctorate in biomedical sciences from the University of California, San Diego (UCSD), conducting her graduate research primarily on genetic modification of a key protein involved in invasive disease, including mutation, protein
expression in bacterial, mammalian or insect cells, and protein isolation and characterization. Prior to UCSD, she worked in the pharmaceutics division of Amgen, Inc. She has been volunteering with the AAPS Chem Bio API-MT focus group since 2009, and has previously served as website committee chair, secretary, and chair-elect. She began her service as chair in November 2013.

Other steering committee members include: Megan McMahon (past chair), Arya Jayatilaka (past chair), Monica Chuong (secretary), Hui Li (webmaster), and Bryan Chekal (steering committee member). The steering committee will be undergoing a transformation and expansion over the next couple months to better encompass both large and small molecules.

**Chemistry, Manufacturing and Controls (CMC)**

http://www.aaps.org/Chemistry_Manufacturing_and_Controls/

The AAPS CMC focus group held an annual face-to-face meeting on June 6, 2014 hosted by Janssen Pharmaceuticals, Inc. in South Raritan, NJ. This meeting is planned by the CMC Focus Group steering team and the goal is to provide a forum for discussing technical and regulatory CMC topics associated with the global development of pharmaceuticals, biopharmaceuticals, and vaccines. This is an interactive meeting, with brief overviews on several hot topics, followed by breakout discussion sessions and summary reports at the end of the day. A key objective of this meeting is to generate in-depth discussions on selected CMC issues, leading to consensus or recommendations for further exploration of these topics.

The Hot Topic sessions for 2014 and agency/industry leaders, facilitated by CMC steering committee members, are provided below:

- **Topic 1:** Breakthrough Therapy Designation Lessons Learned and Opportunities lead by FDA speakers Sarah Pope-Miksinski and Dorota Matecka and Industry speakers Kin Tang and Susan Berlam
- **Topic 2:** Continuous Manufacturing Regulatory and GMP Challenges and Opportunities lead by FDA speakers Celia Cruz and Rapti Madurawe and Industry speakers Elaine Morefield and James Bergum
- **Topic 3:** Risk Based Management Approach for CMC Submissions and Review lead by FDA speakers John Duan and Robert Iser and Industry speakers Leo Lucisano and Eda Montgomery
- **Topic 4:** CMC Considerations for Combination Products lead by FDA speakers Ashley Boam and Scott Furness and Industry speakers Jason Lipman and Stefan Leiner

The program consisted of brief overviews of each topic, followed by interactive breakout sessions. The breakout sessions address questions posed in the overviews and identified fundamental goals and critical steps required for consensus or resolution. Attendees participated actively in all of the discussions and shared their ideas on how they envision future changes in these hot topics.

Overall feedback for the June 6 face-to-face meeting was that it was informative, thought provoking, and the topics were valuable and offered a good variety. Some topics could be discussed in more depth at future meetings e.g., breakthrough therapies and continuous manufacturing.

Slides from the face-to-face meeting are now available on the CMC focus group webpage under “Announcements” and at the link provided below:

http://www.aaps.org/Sections_and_Groups/Focus_Groups/Chemistry,_Manufacturing,_and_Controls/Resources/Presentations/
MSE Open Forum

Streamlining Manufacturing and Scale-up to Support "Breakthrough Therapy" Designation for Solid Oral Dosage Forms

Tuesday, November 4, 2014
6:30 PM–9:30 PM

Held during the 2014 AAPS Annual Meeting and Exposition

Register today! »
An additional fee is required to attend the open forum.

| Target Audience | • Scientific staff responsible for tech-transfer, scale-up, and commercialization  
|                 | • Pharma and Biotech company project managers, and scientific staff managing CRO/CMOs  
|                 | • Business development groups of CRO/CMOs |
| Lead Contacts   | • Bhavishya Mittal, PhD (Senior Scientist I, Formulation Sciences, Takeda)  
|                 | • Cynthia A. Oksanen, PhD (Senior Director, Drug Product Design, Pfizer) |
| Meeting Format  | A moderated forum with up to four speakers that will present case studies that discuss the novel scale-up strategies that are currently employed for rapid development programs for solid oral dosages. There will be a Q&A session with the audience after the presentations. |
| Description     | Over the past 10-15 years, a tremendous amount of effort has been placed in developing high potent, oncology-based drug products in numerous pharmaceutical companies. In the meanwhile, FDA has issued information on “Breakthrough Therapy” designation with the intention to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. A breakthrough therapy designation conveys all of the fast track program features, as well as more intensive FDA guidance on an efficient drug development program. |
| Speakers        | • Dr. Raymond Skwierczynski (Sr. Director, Formulation Sciences, Takeda)  
|                 | • Dr. Dan Blackwood (Sr. Principal Scientist, Pfizer)  
|                 | • Dr. Marco Verwijs (Associate Director, Formulation Sciences, Vertex)  
|                 | • Dr. Sarah Pope-Miksinski (Division Director, CDER, FDA) |
| Moderator       | Bhavishya Mittal, PhD (Senior Scientist I, Formulation Sciences, Takeda) |
| Sponsor         | Takeda Pharmaceuticals International Company |
Webinars and Conferences of Interest

- "Scratching the Surface": Surface-Surface Interactions and Their Impact on Processing, Stability and Performance of Pharmaceuticals
  Webinar, August 14, 2014
- Out of the Box Talks: How Are the Rings of Saturn Like a 155,000 Mile Diameter Granulator?
  Webinar, August 21, 2014
- Regulatory Considerations for PAT and RTRT—An FDA Perspective
  Webinar, August 28, 2014
- FDA/PQRI Conference on Evolving Product Quality
  Conference, North Bethesda, MD, 09-16-2014 - 09-17-2014.
- Hands-on Course in Tablet Technology(3)
  Course, Oxford, MS, 09-21-2014 - 09-26-2014
- Tablets & Capsules Hands-On Short Course
  Course, Baltimore, MD, 10-20-2014 - 10-24-2014

MSE Technical Bulletin

How has PAT Affected Near-Infrared?
What a Difference a Decade Makes.

Emil W. Ciurczak

It is an understatement to say that NIR was a slow starter. Discovered in 1800 (the first outside of the visible range), there were no application papers published until the 1870s. There was a brief interest in NIR in the late 1930s, but the advent of World War II, mid-range infrared (MIR) was found to be a better tool in the synthesis of rubber (since natural materials were scare because of U-boat activities). Unfortunately, NIR remained an oddity for several more decades. In fact, by 1970, only 50 papers had been published using NIR as the main technology.

Commercial NIR instruments began to be built in the 1970s with the interest of USDA scientists, using it for agricultural products. Methods of analysis, at that time, consisted of Karl Fischer titrations for water, Soxhlet extractions for oil, and Kjeldahl distillations for nitrogen (protein). These were time-consuming and expensive to run. Farmers had to wait days before getting payment for produce and were made to stay nearby until analyses were run. All these were made a memory with the introduction of NIR by pioneers such as Karl Norris (US) and Phil Williams (Canada). Now these day long tests could be performed in a minute. By 1980, all shipments of grain leaving the US were analyzed by NIR.

It had also become quite popular in other industries: tobacco, textiles, polymers, and petrochemicals, to name a few. However, the pharmaceutical industry was mired in HPLC and, as is well-know, the industry is very, very slow to adopt any new technology. However, one small EMEA (now EMA) “suggestion” changed so much. The EMEA “suggested” that incoming raw materials be qualified on a 100% basis. That meant that every container of every material needed to be tested. Since I was at Sandoz, a Swiss corporation, at that time, it was relayed to us to follow that dictum. There was one small problem: our raw materials were not the same as European raw materials.
Chemically, yes; physically, yes; but US lacks something that is ubiquitous in Europe: trains. The US is heavily dependent on trucks for delivery, so a typical delivery of, say lactose, could easily consist of over 200 bags. A delivery in Switzerland could be made with 2-3 large containers, delivered by railcar. That meant a set of compendial tests (for example, the EP) would take Sandoz, Basle, a few days to run. In Sandoz, US, those same tests could take weeks. Since we had just undergone major expansion and spent quite a bit of money on equipment, a second shift in QC was out of the question. Enter NIR.

I was approached by a salesman from Technicon (later became Bran + Leubbe) who promised “no work, no anything; anyone can run the instrument.” I had him escorted off the property. Later, I was contacted by someone who actually worked with their NIR and asked me to come in to the symposium they were running. I did and saw that almost all the speakers were talking about wheat, cotton, and such. However, I made the leap that, if a successful calibration could be made for an uncontrolled “synthesis” such as farming, it should be “child’s play” to use near-infrared for heavily tested and controlled pharmaceutical materials.

At that time, the only other pharmaceutical scientists (that I was aware of) who were “playing” with NIR were John Rose (Squibb, US) and Ken Lieper (Glaxo, UK). When I spoke with the people at Technicon, alter that day, I asked the obvious questions, if I wanted to use the device for raw materials. “Can I take it to the warehouse?” No. “Does it have a fiber optic probe?” No, we are working on that. “Do you even have qualitative software?” No, but Howard Mark is working on it. “Then why should I buy it?” Trust us.

OK, I did and, happily, the Mahalanobis Distance software developed by Howard (using me as the beta site) worked quite nicely. By 1984, we had validated the method and by 1985, were testing every container of all the lots of API and excipients arriving at the site. As a side benefit, we also noticed “strange” spectral variations. The baseline offset, seen in diffuse reflection, led us to use the phenomenon to calibrate for mean particle size. Other shifts in the intensities and wavelengths led to the ability to measure crystallinity or polymorphic changes. All these facts are very interesting, but not yet useful for any process work.

When the PAT Guidance was introduced, a number of changes took place in a number of places. One of the earliest “PAT-friendly” events was the work performed at Pfizer (Sandwich, UK), where the first self-contained, wireless NIR unit was developed for blend uniformity confirmation. The fact that both raw materials and powder blends could now be measured in real time spurred instrument companies to vie for sales. This, in turn, meant they had to offer something more than a “sample and bring back to the lab” paradigm for raw materials and a large, expensive unit for blend uniformity. Thus, smaller units arrived on the scene.

Simultaneously, another movement started when the telecommunications industry imploded in the 1990's. One of the best materials for NIR detectors is Indium Gallium Arsenide (a.k.a., InGaAs), however, being used so extensively by the communications industry, the price was beyond what a typical instrument company could spend...and make an affordable instrument. One manufacturer told me (in 1991) that an InGaAs diode-array detector would cost $10,000...in bulk! I wouldn’t want to think of buying a single one. With the collapse, the cost of detectors (now in excess) dropped dramatically.

In addition, there were a number of device makers, formerly working with telecomm companies, who now needed an outlet for their products. Their products were built to absorb and emit light in many wavelengths...rapidly. Since some devices were meant to be repeaters for trans-oceanic communications, with numerous simultaneous users, speed and accuracy were critical. It didn’t hurt that the specifications called for operation for several decades, without replacement (it is difficult to replace a part several miles under the ocean). This gave us small, low-powered, accurate, and, of course, rugged spectrometers for process work.

Another force shaping the use of NIR was the phenomenal growth in computer power. The computer used for the first Mahalanobis algorithm had no resident memory (just a dual “floppy” disk drive), so was equipped with a 4 MByte Winchester disk drive. The early program took a minimum of overnight to generate a single equation. Not only has computing power increased, but storage has gone through the roof. Even the smallest laptops routinely have 3-500 GBytes of memory.

Why is computer speed and memory so valuable? With tablets being made at rates of many thousands per hour, the speed of the spectrometer is moot without some way of handling these spectra. In addition, newer algorithms (while Partial Least Squares and Principal Components Analysis/Regression became commercially available in 1987) need the computing power of newer computers to make the “magic” happen. Newer systems can take the inputs from disparate measuring units (pressure, temperature, flow rates, NIR’s, et.) and, using specialized MVA (multi-variate analysis) software control the end product formation.
Perhaps the biggest assist (albeit indirectly) was the pressure on drug companies to bring prices into a competitive mode. Numerous countries passed laws that regulated prices and told manufacturers that, if they wanted approval for a newer, more expensive drug, it must work better than existing products, if it is priced higher than those already marketed. In addition, with the expansion of the Chinese and Indian production capacities, European and American manufacturers were looking for ways to lower their Cost of Goods Sold (COGS). The obvious way was PAT and QbD.

While the idea of QbD and its accompanying Design Space were excellent, it cannot be run without constant and reliable monitoring. The bottom line here is that few companies can afford many $100,000+ devices throughout their facilities. The need for smaller, faster, sturdier, and most importantly, less expensive instruments has driven the NIR industry for years and continues at an increasing pace. There have been a number of rugged devices, costing less than $200 to build, made to be placed on platforms, such as “smart phones.” These newer devices mean FINALLY moving from D.R.I.P. to D.P.I.R.

That is “Data Rich, Information Poor” massive, multi-purpose instruments (as we use in an analytical lab) will be replaced by smaller, less expansive and expensive, almost single purpose units (or, Data Poor; Information Rich). For example, the most commonly measured analyte in any industry is water. Do we really need a $100,000, explosion-proof unit to measure H2O? This could be the case where a one or two filter unit, costing (perhaps) $1,000 would suffice. In time, the entire production line will be covered with dozens of (nearly) disposable units, each checking one or two parameters of the product. The time and money and materials saved will be enormous (just in calibration time alone; we could simply replace modules like spark plugs, light bulbs, or tires and use pre-calibrated units, sending the old ones back for repair or disposal).

The biggest effect on NIR because of PAT? We are advancing design and performance at a pace that is exponentially faster than had PAT not happened. Thank you, PAT.

Meeting Reports

AAPS Symposium on Advances in Analytical and Biotransformational Characterization Methods for Biosimilars: Demonstrating Comparability and Equivalence

Speakers and topics:
Opportunities in the Advanced Analytic Profiling of Complex Biologic Therapeutics
Shiaw-Lin Wu, Ph.D., Head of Analytical Sciences, BioAnalytix

Bioanalytical Approaches for the Development of Monoclonal Antibody Biosimilars
James Hulse, Ph.D., Managing Scientific Director- Discovery & Development Solutions, EMDMillipore

Similarity Assessment of a Proposed Biosimilar PF-05280014 and Innovator Product
Chee-Keng Ng, Ph.D., Senior Principal Scientist, Pfizer Inc.

Biosimilar Comparability Conundrum - How Similar is Similar?
Robert Bell, Ph.D. President / Owner- Drug and Biotechnology Development LLC

Session Chairs:
Ruta Waghmare, Ph.D (EMD Millipore)
Arya Jayatilaka, Ph.D (Pfizer Inc.)
Introduction:

Figure 1: The Upcoming Biotherapeutic Patent Expirations

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Patent Expiry (US / EU)</th>
<th>2011 Sales ($Bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epogen / Procrit</td>
<td>Amgen / J&amp;J</td>
<td>2013 / exp</td>
<td>3.7</td>
</tr>
<tr>
<td>Neupogen</td>
<td>Amgen</td>
<td>2013 / exp</td>
<td>1.4</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Amgen</td>
<td>2012 / 2015</td>
<td>7.9</td>
</tr>
<tr>
<td>Rituxan</td>
<td>Roche</td>
<td>2016 / 2013</td>
<td>6.6</td>
</tr>
<tr>
<td>Humalog</td>
<td>Lilly</td>
<td>2013 / 2013</td>
<td>2.4</td>
</tr>
<tr>
<td>Remicade</td>
<td>J&amp;J</td>
<td>2018 / 2014</td>
<td>7.2</td>
</tr>
<tr>
<td>Aranesp</td>
<td>Amgen</td>
<td>2014 / 2016</td>
<td>3.0</td>
</tr>
<tr>
<td>Erbitux</td>
<td>Lilly / BMS</td>
<td>2015 / 2014</td>
<td>1.8</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Roche</td>
<td>2019 / 2015</td>
<td>5.8</td>
</tr>
<tr>
<td>Lantus</td>
<td>Sanofi</td>
<td>2015 / 2015</td>
<td>5.2</td>
</tr>
<tr>
<td>Neulasta</td>
<td>Amgen</td>
<td>2015 / 2017</td>
<td>4.0</td>
</tr>
<tr>
<td>Humira</td>
<td>Abbott</td>
<td>2016 / 2018</td>
<td>7.9</td>
</tr>
<tr>
<td>Avastin</td>
<td>Roche</td>
<td>2019 / 2022</td>
<td>6.6</td>
</tr>
</tbody>
</table>

These patent expirations of biopharmaceutical products have initiated the introduction of a new generation of drugs, called 'Biosimilars' (Figure 1). There are several names generally associated with this category of drugs including Biosimilars, Biogenerics, Follow-on-Biologics, Subsequent Entry Biologics and Similar biotherapeutic Products.

Last year, a symposium was organized on the “Challenges and Strategies of Biosimilars Manufacturing” on 15<sup>th</sup> October, 2012 at the AAPS Annual meeting held in Chicago, IL. Our aim was to be able to discuss the challenges the pharmaceutical industry is facing in manufacturing biosimilars and characterization and demonstrating comparability of them with the audience. The session was very interactive and well attended with around 200 attendees. The feedback from the audience was also very informative.

Given the success of the session last year, and to continue the discussion on the characterization and demonstration of comparability of biosimilars, a session was organized on 12<sup>th</sup> November 2013 at the AAPS Annual Meeting with the aim of developing further on the theme of Biosimilars—namely Advances in Analytical and Biotransformational Characterization Methods for Biosimilars. This year, we had around 125 attendees for the session.

In this report we are aiming to bring some of the discussion points to interested readers who may not have been able to attend the session.

We would like to thank MSE and APQ sections of the AAPS for their support. This session was organized by the PAT focus group and API Manufacturing technology focus group.

Opportunities in Advanced Analytic Profiling of Complex Biologic Therapeutics.

Protein drugs are often complex in structure, particularly highly glycosylated proteins. The development of such complex glycosylated proteins as biologic drugs or biosimilars therefore presents a high degree of challenge as to reproduce them with accurate and consistent profiles. Often, comparability to the original product or to different
lots is required in order to maintain and claim similar quality and efficacy profiles. Further, demonstrating a highly similar product may significantly reduce or even eliminate its clinical requirements for approval as described in recent FDA draft guideline for biosimilars. Advanced analytics such as fingerprint technologies with orthogonal approaches may have the opportunity to provide such profiling capabilities to assure the highly similar nature between products or lots.

In this talk, several advanced analytical techniques, strategies and examples from profiling various innovator and biosimilar drugs were discussed including approaches for accurate mapping of biologic sequence variation, glycosylation, and disulfides. For example, in the sequence variation analysis, orthogonal to multi-enzyme digestion strategies for accurate determination of variation sites, an advanced approach using top-down analysis provided direct evidence of two mutations occurring in the same gene. In the analysis of O-linked glycosylation, a set of unique sample preparation protocols combined with effective electron-transfer dissociation (ETD) in mass spectrometry mapped out multiple sites of O-glycosylation, enabling accurate site characterization and occupancy comparison for different lots. Further, an advanced LC-MS top-down analysis using ultra-high resolution mass spectrometry revealed stoichiometry of glycosylation patterns in intact proteins, with capabilities to assign complex disulfides using ETD.

Overall, the talk provided a review of how these new approaches and orthogonal techniques can enable faster and more accurate characterization that can be applied in assessing and ensuring comparability between products or lots throughout biologic or biosimilar drug development.

### Bioanalytical Approaches for the Development of Monoclonal Antibody Biosimilars

The regulatory documents outline a step wise approach for the development of biosimilars. These steps include:

- **Structural Characterization**
  - Primary structure (amino acid sequence)
  - Secondary, tertiary and quaternary structure
  - Post-translational modifications (e.g. glycoforms)
  - Potential variants (e.g. deamidation)

- **Functional Characterization**
  - In vitro potency
  - Target binding (Mabs)
  - Binding to FcR
  - Complement binding
  - Functional assays – ADCC, CDC, complement activation

- **Animal Studies**
  - Comparative toxicology study, including TK
  - PK / PD (maybe)
  - Immunogenicity (mainly for interpretation of TK)

- **Clinical Studies**
  - Bioequivalence – head-to-head
  - PK / PD expected
  - Immunogenicity
  - NAb assay should be available

The overall summary of the talk was that there is increasing interest in Biosimilars. The regulatory path is becoming clearer with release of EMA and FDA Guidelines. The comparability assessment includes Analytical,
Analytical Similarity Assessment of PF-05280014, A Proposed Trastuzumab Biosimilar

The development of a biosimilar monoclonal antibody begins with an in-depth understanding of the structure and function of the reference product, followed by iterative process development that enables the manufacture of a similar product. Upfront understanding of the attributes of the target reference product involves a comprehensive application of state-of-the-art robust orthogonal analytical characterization methods that, in totality, are capable of revealing the structural details and biological activity of the reference product, while also monitoring lot-to-lot variability. In the analytical similarity assessment presented, the side by side comparison of the reference product lots sourced from different global regional markets and the proposed biosimilar forms the cornerstone of the characterization strategy. Dr. Ng’s presentation showed side-by-side analytical similarity data on primary sequence confirmation, biochemical and biophysical attributes, and biological activity for PF 05280014, a proposed trastuzumab biosimilar.

The techniques discussed for demonstrating this biosimilarity included confirming the amino acid sequence between PF-05280014 and licensed products by NanoESI QTOF MS, comparative N-Linked oligosaccharide profiling, charge heterogeneity assessment using iCE and CEX-HPLC, determination of aggregation species levels by SE-HPLC and activity and biological functional assessments.

Biosimilar Comparability Conundrum - How Similar is Similar?

The Patient Protection and Affordable Care Act (Affordable Care Act) amends the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products (Biologics Price Competition and Innovation Act of 2009 (BPCI Act)) that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product. The BPCI Act describes a new regulatory pathway that would require the manufacturer of a “biosimilar” version of an approved biological to demonstrate to the FDA that there are no clinically meaningful differences between the two products in terms of the safety, purity, and potency, they are highly similar in molecular structure (excluding minor differences in clinically inactive components) and that they share the same mechanism(s) of action. Similarity between a biosimilar and its reference biotherapeutic product should be evaluated in all quality, safety and efficacy aspects.

Biosimilarity has been defined by the EMA, WHO and USFDA (Figures 2 and 3) and is typically described as a test biologic being similar to an approved or reference product in terms of quality, safety and efficacy. However, identifying the chemical or biological dissimilarity and understanding its' structure activity effect (if any) on pharmacokinetic, pharmacodynamic, clinical outcomes is essential.
Definitions

**Biosimilar or Biosimilarity:**
- **EMA**
  - A biosimilar medicinal product is a medicinal product which is similar to a biological medicinal product that has already been authorized (the 'biological reference medicinal product'). The active substance of a biosimilar medicinal product is similar to the one of the biological reference medicinal product.
- **WHO**
  - A biotherapeutic product similar to an already licensed biotherapeutic product in terms of quality, safety and efficacy.
- **USFDA**
  - A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency.

So this begs the question, how similar is similar? Is there an appropriate metric that adequately defines similarity? There does not appear to be an adequate regulatory answer to this conundrum and has to be addressed on a case by case basis. It is desired that the biosimilar have the same critical quality attributes of the reference protein such as the primary, secondary structure and post-translational modifications. Identifying and justifying the “bio-dissimilarity” or difference between the reference and test product chemistry and biology characteristics are key to the reference / test comparability exercise.

The biosimilar developer utilizes the usual analytical techniques for comparability such as spectroscopy, electrophoresis, chromatography and binding properties to note similarities and differences. Most if not all modern analysis equipment such as spectral integrators include purity and identity algorithms that can be used for comparability. There is existing acceptance (as well as comparability) criteria for ligand binding assays, non-clinical, human pharmacokinetic, pharmacodynamic and clinical studies. This information, in conjunction with the analytical comparability exercises, form the basis of comparability. Compilation and analysis of the multivariate data will reveal similarity and dissimilarity - both observations should be justified.

Many years back, primarily for simplicity's sake, the following "biosimilarity factor" was proposed for biosimilars or to demonstrate therapeutically equivalent biologics (Bell 1998-2006):

$$\text{PE/PS} + \text{BE(PK/PD/CS*)} + \text{IA} + Q = \text{TE},$$

where PE/PS is pharmaceutical equivalence / similarity, BE is bioequivalence, PK is pharmacokinetic, PD is pharmacodynamic, CS is clinical similarity, IE is immunologic assessment, Q is quality, TE is therapeutic equivalence and * is if required. Since the diversity of proteins range from simple unmodified, to modified,
glycolsylated to monoclonal antibodies, there is no one size fits all metric for biologics and similarity should be examined on a case by case basis; however, the general concept is applicable to all proteins. Comparisons between the products should include the usual statistical metrics and any differences noted and justified. It is important to demonstrate similarity but more importantly identify the differences, the dissimilarity, between the products, and assure the dissimilarity results in no clinically meaningful difference.

Reference:


Must We Celebrate All Diversity? Regulatory Drivers and Perspectives on Differences in Requirements for Dissolution Release Methods and Specifications That Lead to Global Inconsistencies

Talia Flanagan, on behalf of the QbD and Product Performance Focus Group

The dissolution test has always been important from a manufacturing perspective. It can be the basis of some critical decisions, such as determining the suitability of batches for release to patients as part of the product specification, or assessing the impact of changes in process parameters on product performance in the post-approval environment. As such, it is to be expected that the rationale behind the choice of dissolution test and specification is closely scrutinized during review of the marketing application. Under the QbD paradigm, there has been a renewed focus on the role of dissolution test in assuring in vivo performance, i.e., an increased emphasis on the clinical relevance of dissolution methods and specifications. This requires the discriminatory power of the method and this proposed specification to be considered in the context of the available in vivo understanding for the product – can the test detect failure modes which would affect in vivo performance? Conversely, will it fail batches which would be acceptable in vivo? Generating clinical data to understand the in vivo impact of process and formulation changes can be immensely helpful in this context, to develop understanding of the in vivo impact of changes in in vitro performance, thereby enabling a dissolution test with appropriate discriminatory power and a clinically relevant specification to be selected.

The desirable scenario from a commercial supply perspective is to have a single global release test and specification, i.e., avoiding the need for multiple tests and acceptance limits for different markets. In practice, the marketing application for a drug product is often submitted to several different health authorities in parallel, each
of whom closely scrutinize the proposed dissolution method and specification as the test which links manufacture and *in vivo* performance. These parallel discussions sometimes have different outcomes, which can lead to the same product having different specifications and sometimes even dissolution methods approved in different territories. This can complicate release testing during commercial manufacture and the subsequent supply chain.

To explore this issue, the QbD and Product Performance Focus Group hosted a round table discussion at the AAPS 2013 annual meeting entitled ‘Must We Celebrate All Diversity? Regulatory Drivers and Perspectives on Differences in Requirements for Dissolution Release Methods and Specifications That Lead to Global Inconsistencies’, moderated by Jack Cook and Paul Dickinson. Three expert panel members, representing the US, Europe and Japan, were invited to present their perspective on the discussion topic as food for thought before the Q&A session.

**Angelica Dorantes** of US FDA emphasized that the goal of dissolution is to ensure bioequivalence between manufactured batches and those used in the clinical studies. Dr Dorantes highlighted the importance of understanding which factors can influence drug release in vitro and in vivo, noting that this does not always necessitate the use of complex biorelevant media. She also emphasized that in vivo data are essential to enable selection of a relevant method with an appropriate discriminatory power, and to enable the setting of a clinically relevant specification. Three approaches to specification setting were described; Approach 1, where the acceptance limit is based solely on the *in vitro* performance of batches in pivotal pharmacokinetic and clinical studies, may not always assure clinical relevance or appropriate discrimination, and can result in a tighter design space under the QbD paradigm. Approaches 2 and 3 both reference *in vivo* exposure data from dosing formulation/process variants with different *in vitro* dissolution profiles. Approach 2 referred to the situation where a range of dissolution profiles which result in bioequivalent exposures has been established; this enables selection of a clinically relevant method and specification, although in practice flexibility may be limited to the failure mechanisms tested in the clinical study. Approach 3 refers to the scenario where changes in *in vitro* dissolution lead to changes in *in vivo* exposures, enabling an *in vivo-in vitro* correlation (IVIVC) to be established; this approach also enables clinically relevant tests and specifications to be defined, and is established in FDA guidance to allow requirements for future bioequivalence studies to be waived.

**Evangelos Kotzagiorgis** of EMA started by describing the European pharmaceutical perspective on dissolution testing - this is focused on methodological considerations associated with performing the test - apparatus, media, rotation speed, sampling times etc. – but contains little discussion of the clinical relevance of the test or the result. He contrasted this with the EMA guidelines, which focus on the more engaging aspects of dissolution that lead to it being the focus of such intense debate – namely that the intention of dissolution testing is to reflect the likely *in vivo* performance of the product. The choice of test should take in vivo data into consideration, to enable a meaningful acceptance criterion to be set, and should also have suitable discriminatory power. Dr Kotzagiorgis also raised the question of whether it is always feasible for one method to fulfil all of these needs.

**Shunji Nagata** (Hiroshima International University, Japan) focused on differences in dissolution apparatus and media between the Japanese Pharmacopoeia and US/European pharmacopoeias, which could present barriers to complete method harmonization in some cases. While the majority of tablet dissolution methods in the JP use the paddle apparatus at 50rpm, which easily lends itself to globally acceptable methods, more complex apparatus, namely the flow-through cell and reciprocating cylinder, are not listed in the JP. Additionally, simulated biorelevant fluids are not listed in the JP. In particular, the addition of pepsin to overcome the effects of cross-linking of gelatine capsules in dissolution, is not permitted, due to clinical evidence that this phenomenon could impact *in vivo* absorption in subjects with higher gastric pH (a condition particularly prevalent in Japan).

A lively Q&A session followed the speaker presentations with numerous questions from the audience. These ranged from detailed questions on more unusual dosage forms, such as appropriate methodology for lozenges, to more conceptual questions, such as why IVIVC (Approach 3) is perceived to be the ideal way of linking dissolution to clinical performance, given that products which fit Approach 2 (i.e., a range of dissolution profiles is established which are bioequivalent) carry a much lower risk of a change in dissolution impacting clinical performance.
Approaches for opening dialogue with regulators on the appropriateness of the proposed dissolution method and specification were also discussed; for EMA, the Scientific Advice process was recommended as a forum to discuss the scientific basis of the dissolution test and get a harmonized view across member states; in the US, the dissolution method development report can be appended to the IND. A common theme in the responses was the importance of demonstrating how the proposed method relates to in vivo data, with greater product-specific in vivo understanding providing a stronger basis for dialogue with regulators and potentially leading to greater flexibility.

Dissolution is a key test of product performance, and as such is likely to continue to be a hot topic of discussion during review. Currently, best practice in the development of clinically relevant dissolution methods and specifications and what this means in routine manufacture is still an evolving area in some respects, and it’s likely that this is what leads to the different interpretations between health authorities that are sometimes seen during review. However, this roundtable discussion made it clear that even if sponsors are not yet seeing a consistent approach in some of the detailed discussions during review, there is a clear and common purpose across the territories represented - namely that the QC test and specification should ensure suitable in vivo performance, so that safety and efficacy continues to be assured throughout routine commercial production. This requires a dissolution test with an appropriate degree of discrimination, based on an understanding of which process and formulation parameters could impact in vitro performance, and the setting of a clinically relevant specification, which ensures that product performance is maintained in a region where these factors do not impact in vivo. This common aim provides a basis for dialogue with health authorities on the most appropriate way to achieve this for a given drug product, and for a discussion of how the in vitro and in vivo understanding gained during product development translate into the proposed dissolution method and specification. Ultimately, this should result in tests which can provide appropriate assurance of suitable in vivo performance without being unnecessarily burdensome in routine batch testing and release.

We are not at the end of the journey toward establishing clinically relevant dissolution methods and specifications as common practice, and further work is needed to make this a reality. While IVIVC (Approach 3) is discussed in bioequivalence and post approval change guidelines, Approach 2 is not, making its use in a regulatory context less clear to sponsors. Ideally, publication of a harmonized approach across health authorities, such as a position paper or guidance, would provide a clear path for development of globally acceptable clinically relevant methods and specifications, and a basis for dialogue during review. Before this can happen, further discussion is needed to establish a common view of best practice in this area across health authorities and industry, including more product-specific examples of the application of Approaches 2 and 3 in the context of a QbD development. Publication of examples demonstrating the benefits of Approaches 2 and 3 over the ‘traditional’ route (Approach 1) are also needed, to help scientists in industry convince resource holders of the benefits of performing such studies. Discussion and examples of how in silico modelling can be used in the development of clinically relevant methods and specifications would also be welcome; for example, whether it is always necessary to perform a specific relative bioavailability study to support development of an IVIVR, or if the use of existing clinical data augmented by an in silico model could also be acceptable in a regulatory context. Only by continuing the dialogue between scientists from across industry, academia and regulatory bodies will we continue to move this area forward.