Pharmaceutical equivalence, therapeutic equivalence and the role of analytical science

The assumption that pharmaceutical equivalence is predictive of therapeutic equivalence has become increasingly contested. This topic was examined in depth at a recent meeting reported by David Elder, Director, Scinovo, R&D, GlaxoSmithKline and JPAG committee member, and Richard Kaye, Senior Investigator, Pharmaceutical Development, R&D, GlaxoSmithKline

Introduction
The greater complexity of medicinal products and their global sourcing clearly challenges the underlying belief that pharmaceutical equivalence is predictive of therapeutic equivalence. JPAG (Joint Pharmaceutical and Analysis Group) in collaboration with TOPRA recently held a symposium that examined the role of analytical science in characterising and establishing therapeutic equivalence, utilising experts in the field from industry, academia and regulatory agencies. The meeting was held at the Royal Society of Chemistry, London, UK.

Critical review of current bioequivalence guidelines
Speaker: Sean Jones, MHRA, UK.

Mr Jones highlighted some recent scientific publications covering bioequivalence of new formulations or generic products, exemplifying that bioequivalence is a hot topic within the industry. He reminded the audience that any directives regarding bioequivalence testing are there to protect patient safety and not to hinder new product development (including generic medicines) or instigate unnecessary human or animal testing. Mr Jones explained the historical considerations for bioequivalence by highlighting the differences in marketing authorisation requirements for a generic product compared to an innovator product. Provided that the generic product has the same qualitative and quantitative composition, the same pharmaceutical form and has been demonstrated as being bioequivalent, bridging to the supporting nonclinical and clinical data are typically straightforward. This ensures the generic product has the same summary of product characteristics (SmPC) as the originator. However, it is also important to highlight that the active substance can be a different salt or other derivative, and the pharmaceutical form (at least for an immediate release product) need not be the same. Moreover, demonstration of pharmaceutical equivalence will often permit a bio waiver approach, negating the need for bioequivalence studies. Bio waivers are usually allowable for different product strengths. Mr Jones then summarised regulatory criteria for bioequivalence. The acceptance criteria are typically 80–125% for AUC (area under the curve) and Cmax (maximum plasma concentration); however, exceptions for highly variable and narrow therapeutic index drugs are allowable. Likewise, bioequivalence for other product types, eg, for locally acting, topical products, may require other approaches (for instance, a therapeutic or pharmacodynamic (PD) equivalence study is typically required for topical products). A concept paper for topically administered products is planned (a similar concept paper for orally administered products has recently been published). In addition, bi waivers are possible based on BCS (Biopharmaceutics Classification System) considerations, particularly for BCS class I and III drugs. However, Mr Jones showed how sugar excipients that affect gastrointestinal motility can impact on bioavailability (sucrose (enhanced) versus sorbitol solutions), and therefore formulation considerations are equally important. Mr Jones then detailed some examples of medicines where switching brands for a given patient is not recommended because of previously reported clinical consequences, eg, anti-psychotics. This strongly emphasised why bi waivers are not always possible, particularly for poorly soluble or narrow therapeutic index medicines. Therefore, the guidelines support a risk-based approach to determining if full bioequivalence studies are required for any given product. Mr Jones advocated prescriptability not switchability as the main driver for certain drugs, eg, anti-psychotics, where continuity of supply from the same supplier is very important, ie, brand prescribing of ciclosporin (Sandimmun versus Neoral), tacrolimus and Tazocin versus generic piperacillin/tazobactam.

Are all APIs equivalent? The drive for performance specification
Speaker: Dr Conrad Winters, Hovione, Portugal.

Dr Winters discussed the limitations of classical active pharmaceutical ingredient (API) specifications. These typically represent levels achievable by the manufacturing processes and testing methods, allowing for normal variability, rather than relating to limits that impact on product performance. There have been recent calls for improved understanding of the impact of API manufacturing changes and resultant particle properties on the performance of drug delivery systems. Dr Winters showed some examples of how the complexity of these formulation processes can result in significant inter- and intra-batch variability. He proposed that API particle “fingerprinting” that “fully” describes API particle characteristics can ensure consistent in vivo performance. Dr Winters claimed that generic API manufacturers are constrained from introducing
innovative quality or efficiency changes due to the convoluted regulatory process. However, defining critical quality attributes (CQAs) for therapeutic and manufacturing equivalence (over and above classical release specifications) could be a strategy to address this issue. Dr Winters exemplified the sources of variability and challenges in accurate particle size measurements using three case studies. The first example was that of a solvent change in an oral drug product resulting in API with the same median particle size but vastly different particle morphologies. The second example was an intramuscular suspension product that had a classical particle size specification, but testing of the originator product enabled the introduction of a more robust description of the particle size characteristics leading to a more detailed performance-based specification. The final example was for an inhalation product produced by a “wet polishing” particle formation approach, where the equivalence of the two different API materials was demonstrated using a wide range of advanced analytical characterisation techniques. Dr Winters suggested that these advanced analytical characterisation techniques can help highlight important differences in APIs that would otherwise appear identical. He summarised by indicating that all APIs are not equivalent (even when they appear the same they are often different). He advocated setting performance-based specifications to ensure consistency of API supply, with the caveat that we need to “measure only what is important and set meaningful limits”.

**Comparability of therapeutic protein products**

*Speaker: Dr Simon North, SGS, UK.*

Dr North introduced the concept of biosimilars, where similarity is assessed in terms of comprehensive comparability of physicochemical characteristics (efficacy and safety to a reference product also need to be demonstrated). The WHO guidelines indicate that for a biosimilar therapeutic product, it is not possible to simply demonstrate structural sameness and bioequivalence, due to the complexity of secondary and tertiary structures and the difficulty in characterising these products. However, comprehensive characterisation and comparison of the quality attributes may facilitate reduction in the extent of nonclinical and clinical data requirements. Dr North explained the extent of analytical testing required with reference to key guidance documents, emphasising the need for state-of-the-art analytical evaluation. Dr North then summarised the structural characterisation methods listed in ICH Topic Q6B: amino acid sequence, amino acid composition, terminal amino acid sequence, peptide map, sulphhydryl groups and disulphide bridges (and other related impurities) and carbohydrate structure. Dr North described some of the analytical methods that can be used for structural elucidation and some of the physicochemical properties that should be investigated. Thus, for example, the amino acid sequence is normally achieved using proteolytic digestion (Edman degradation) of the biomolecule followed by orthogonal analysis using pulse liquid or gas-phase sequencing together with mass spectrometric sequence analysis via MS/MS approaches. This is then compared to the defined sequence or versus reference comparison or it is defined de novo. He concluded by stating that product characterisation is essential for regulatory acceptance and that multiple synergistic methods, ie, orthogonality, are the key to successful characterisation.

**Characterisation of liposomal formulations**

*Speaker: Prof Daan Crommelin, Utrecht University, the Netherlands.*

Liposomes were first described by Gregoriadis in the late 1970s and several liposomal-based drug products have been approved since the early 1990s. The most recent of these was Marqibo, a liposomal injection of vincristine. Liposomes can carry a broad range of drug molecule types from hydrophilic to hydrophobic and charged nucleotides, and even drug combinations. The size of the liposomes (which may range from 0.03 to 20 µm), the morphological type (ie, whether they are uni- or multi-lamellar or multivesicular), the charge state, rigidity and drug delivery route will all affect the distribution and clearance rate of liposomes in the body. In developing liposomal drug products pharmaceutical issues often include low drug payload, short shelf-life, scale-up problems and difficulty in analytical characterisation. Payload can be increased by active loading of doxorubicin within liposomes using ammonium sulphate precipitation. Pegylation is an attractive means of extending half-life and non-target site uptake. Shelf-life may be limited by chemical degradation and physical instability, but these issues can be minimised by freeze-drying, selection of particular phospholipids and filling conditions. Liposome properties and chemical and physical stability can be characterised by numerous techniques. Liposomal size can be analysed by electron microscopic imaging methods and dynamic light scattering. Drug release rate, using an in vitro dialysis tube method, was described. There is added complexity when equivalence to an existing liposomal formulation needs to be demonstrated due to the myriad ways a liposomal formulation can be physicochemically characterised and the potential of these factors to influence in vivo efficacy. Similarity testing should involve encapsulation efficiency/free drug, impurities, residual solvents/reagents, excipients, turbidity, volume, drug characterisation, morphology, transition temperature, drug release and plasma stability. The need for this degree of characterisation is exemplified in the available regulatory guidance. Prof Crommelin stated that the diversity in physical properties means it is often impossible to fully define the liposome. He concluded by stating that a combination of long-term in vivo behavioural understanding together with addressing the pharmaceutical challenges is required for full commercialisation of liposomal drug products.

**Advances in dissolution testing and IVIVC of oral products**

*Speaker: Dr Maria Vertzoni, University of Athens, Greece.*

Dr Vertoni reflected that although intraluminal drug concentrations influence the rate of drug appearing in the plasma, direct measurement via sampling, or indirect measurement using imaging techniques, are technically challenging. This is due to sampling volumes, sampling reproducibility, high costs and the ethical constraints of sampling bio-fluids in man. This issue can potentially be addressed using in vitro dissolution testing in an appropriate bio-relevant medium, and the closer the test conditions reflect human physiology the better the chances of predicting product performance. However, she indicated that the gastrointestinal (GI) tract shows high intra- and inter-patient variability, high intra- and inter-dose variability and high transit time variability (disease dependent). The pH varies between 1 and 8. There
is a limited GI volume (~500 ml in total) and the GI media constituents are quite variable, ie, HCl and bicarbonate ions, bile salt micelles, mucous, enzymes, etc. The degree of physical agitation is highly variable, being dependent on both GI location and motility cycle. Finally, whether sink conditions are achievable is highly dependent on dose, drug solubility, permeability, wettability and formulation. In contrast, the classical pharmacopeial dissolution test uses fixed conditions; including media volume (500–900 ml), pH, agitation speeds and sink conditions are achieved by design.

Dr Vertoni then summarised the bio-relevance of fed/fasted state simulated gastric fluid (FeSSGF/FaSSGF), fed/fasted state simulated intestinal fluid (FeSSIF/FaSSIF) and fed/fasted state simulated colonic fluid (FeSSCoF/FaSSCoF) using a variety of different weak acids, bases and non-ionisable drugs. Dr Vertoni reviewed the usefulness of these bio-relevant dissolution tests for celecoxib in fed/fasted state in predicting in vivo dissolution rates. Her findings were that in the fastest state the profile is highly dependent on the dissolution rate and intestinal solubility whereas, in contrast, in the fed state the profiles were primarily dependent on gastric emptying. She then turned to the issue of prediction of supersaturation and drug precipitation when moving between different GI compartments. She indicated that this is complex and dependent on a multiplicity of factors and that it is difficult to predict based solely on simple physicochemical properties of the drug. Rather, bio-relevant dissolution allied with physiologically-based PK (PBPK) modelling is the optimal approach. She reflected that supersaturation typically occurs in the intestines with fasted doses of poorly soluble weak bases. Simple in vitro non-sink dissolution methods involving dynamic media transfer between two compartments (gastric to intestinal) or the more complex artificial gut models (ie, TNO intestinal model-1) can be used to explore intestinal precipitation. These phenomena had also been explored clinically using ketoconazole and dipyridamole. In conclusion, Dr Vertoni reflected that whereas many in vitro predictive models are available, the challenge is which tests to use, what degree of complexity is required and is it ever possible to convert these predictive yet complex tools into anything that is vaguely relevant or useful in a quality control (QC) and/or regulatory environment?

**Therapeutic equivalence in a quality by design world: Linking the patient to the quality target product profile (QTPP)**

*Speaker: Dr Paul Dickinson, AstraZeneca, UK.*

Dr Dickinson outlined some of the opportunities and challenges from a biopharmaceutics (BCS)/analytical perspectives in the quality-by-design (QbD) world. He based his overview on two recent, poor solubility, immediate release (IR) tablet products where there was supporting clinical data linking in vitro dissolution with in vivo performance. This helped to support QbD decision-making and importantly, current regulatory feedback on these approaches was available. Dr Dickinson summarised the QbD paradigm, particularly the Design Space and QTPP concepts, linking ICH Q8 (pharmaceutical development) with ICH Q9 (quality risk management). Using these approaches the QTPP can drive patient-aligned clinically relevant specifications based on the desired performance (in this case, ensuring rapid and complete release and ensuring bioequivalence between different product batches). He reflected that this did not necessarily require an IVIVC (in vitro in vivo correlation) as typically other processes, eg, gastric emptying or permeation, are absorption rate limiting. This ensures that dissolution could guarantee in vivo performance in the absence of an IVIVC across a constrained dissolution range (safe space), where dissolution is never the rate limiting process. He noted that the US FDA's views were that industry should produce tablet variants with differing release characteristics, define an "optimal" dissolution method with adequate discriminatory power, determine relative bioavailability for these products, and then define an appropriate design space that ensures similar (ie, bioequivalent) product performance.

Dr Dickinson presented the first case study (BCS II compound with low solubility above pH 6, standard wet granulated IR tablet with doses in the range 100–300 mg). Based on a quality risk assessment, tablet variants with differing release characteristics were manufactured. These included modifications to API particle size, an over-granulated product and thirdly a product with increased levels of binder and decreased levels of disintegrant in the formulation. Then, four different in vitro dissolution methods were assessed (pH 1.2, pH 4.5, pH 6.8 and surfactant). The latter method was selected as providing the most discrimination, with the optimal recovery and least analytical variability. An in vivo comparative bioavailability study was performed that interestingly showed no in vivo differences, indicating that the highest risk product and process variables do not impact on bioavailability. The clinically relevant in vitro dissolution limits were established based on the worst performing in vitro batch using the surfactant method. This necessitated a balance between over-discriminating methodology (producer risk) and under-discrimination (patient risk). Finally, a design space was established encompassing input material quality (API particle size), formulation composition and manufacturing process.

A globally approvable method and specification limits were a key challenge. Unfortunately, this was not forthcoming. The FDA indicated that the preferred surfactant method was over-discriminating and mandated the adoption of the pH 1.2 method with a conventional Q-based release limit. In contrast, the European Medicines Agency (EMA) accepted the surfactant method but mandated tightening the specification (even though this had no clinical relevance). Dr Dickinson ruefully reflected that the company had ended up in the worst possible scenario, with two different methods for key markets and the imposition of clinically irrelevant, tighter specification limits.

Dr Dickinson presented the second case study (BCS IV compound with reasonable permeability and solubility). In a similar fashion, several variants with different formulation (increased binder and no disintegrant) and processing (over-granulated and over-compressed) variants were manufactured, tested and taken into a comparative in vivo bioavailability study. The findings were very similar and the exposure was the same for all tablet variants. Four in vitro methods were assessed (FaSSIF and three surfactant methods). They selected the fastest and easiest to use method (but not the most discriminating) as there were no clinically relevant consequences of the different in vitro profiles. The company had similar regulatory experiences to the first case study. The FDA did not accept the method as it was not discriminating enough ("less rapid dissolution profiles would be expected for a BCS class IV compound"). Based on limited EMA feedback this method was likely acceptable, but the company had already proposed a new method. For the new method, both regulatory agencies wanted tighter specification limits, but again their expectations were not aligned. The FDA wanted a higher and later...
Q-value, whereas the EMA wanted a higher Q-value based on process capability arguments.

In conclusion, Dr Dickinson noted that the FDA places a greater focus on clinical relevance, using standard methodology with complete release. In contrast, the EMA places a higher emphasis on discriminatory QC methodology and Q-values reflecting process capability, not clinical experience. This ensures that different specifications for different regions are a probable outcome.

The challenges of IVIVC for oral inhaled products
Speaker: Dr Dave Prime, GSK.

Dr Prime outlined the differences between the three most common types of inhaled product, ie, nebulisers, pressurised metered dose inhalers (pMDI), and dry powder inhalers (DPI). Dr Prime then reflected that the difference between the metered dose and the emitted dose was due to the fact that a proportion of the metered dose always remains within the device, container or spacer (if used). The emitted dose is typically between 50–60% for various rotahaler and diskhaler products and tellingly the lung dose is generally lower still; ie, metered dose > emitted dose > lung dose. A key determinant of lung dose is particle size (DPI) or droplet (pMDI) size. Dr Prime described the various efforts to analytically determine the particle size within the emitted dose and the key differences between the various impactor methods, ie, Andersen and new generation impactor (NGI). He then reviewed the various IVIVCs that had been published using particle size distribution and concluded it was often difficult to demonstrate a realistic correlation. He reflected that the intrinsic design of the impactors and in particular the sharp 90° bend that all impactors use to mimic the throat was a significant hurdle. This is because this produces a characteristic “square flow profile” when flow is plotted versus time, whereas, in contrast, patient profiles are much more skewed and highly variable (both within and between patients). Thus the standard QC impactor tests do not simulate patient use as deposition is by impaction only (no sedimentation or diffusion), unrealistic “throat” geometry, unrealistic inhalation profiles, there are no humidity or temperature effects, it does not discriminate dose emission timing effects nor that variations can occur in entry angle of the device. He stressed that impaction tools are sizing techniques, not accurate models of human airway deposition. Dr Prime discussed some of the more complex ex-throat dose measurements, for example the Electronic Lung device™. In these cases there does appear to be a reasonable correlation between ex-throat dose and lung deposition.

In conclusion, Dr Prime indicated that the dose reaching the lungs is very different to the metered dose. Currently, the best Q measure of potential lung dose is the particle size distribution. Although, aerodynamic particle size is a key influence on lung deposition, there are a number of other factors. In vivo outcomes are typically derived from PK, PD or lung scintigraphic deposition studies. IVIVCs based on particle size distribution have been variable and conclusions based on different in vivo measures don’t always agree. He noted that ex-throat studies using anatomically correct throats and breathing models are potentially more useful, but are very complex and may still not address the large intra- and inter-subject variability. Therefore, until IVIVCs can be confidently established and reproduced, inhaled products will continue to require multiple in vitro and in vivo supporting studies.

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