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Cover photo: HIV virus (see Formulation technology enables the delivery of HIV medicines on page xx)

editorial

Dear Colleagues

Welcome to the December edition of the European Industrial Pharmacy journal.

Over the past 3 months, a number of actions have been undertaken by members of the Bureau and, in particular, I would like to emphasise the revamping of the website. This has been possible because of the tireless efforts of Dr Claude Farrugia, Vice-President, Communications, whom I would like to thank warmly for his dedication and support in this respect.

Rather than describing the new features and advantages of our website, I would like to invite you to pay it a visit at the following address: <http://eipg.eu>. The new website has been designed to raise the profile of the EIPG and its communications with its members and with pharmaceutical industry pharmacists in general, irrespective of whether they are employed within the European Union or outside it.

I consider it essential for the work of the EIPG – position papers, publications, presentations,

guides, codes, contributions to meetings with other European professional organisations and institutions – to be made rapidly available to all. By way of an example, I would like to invite you to check out our position papers: 'EIPG Feedback on Revision to Annex 16' and 'Joint call for actions on medicines shortages from European pharmacist organisations'.

I also consider it essential that visitors to our website become frequent visitors and would like to advise regular use of the site as a source of news and information for industrial pharmacists.

Lastly, in the context of strengthening the GPIE's partnerships with key stakeholders, I have the pleasure of announcing that GPIE has been accepted as an observer in the USP Convention, since several opportunities for close collaboration with the USP have been identified.

May I conclude by wishing you a very Merry Christmas and a Happy New Year.

Jean-Pierre Paccioni
GPIE President

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SCALE-UP OF SPRAY DRIED AMORPHOUS SOLID DISPERSIONS

by José Luís Santos, Paula Cordeiro, Márcio Temtem

With an increasing number of relatively insoluble drugs in development today, there is a need to develop and use platform technologies capable of addressing solubility issues. Among the different alternatives, the use of stabilised amorphous solid dispersions is becoming increasingly popular, with pharmaceutical spray drying being one of the key technologies used in their preparation. In spray dried dispersions (SDD), the active pharmaceutical ingredient (API) is molecularly dispersed in a polymeric matrix. The polymer is used to stabilise the amorphous, metastable form of the drug and sustain supersaturation of the API in solution/biological fluids, thereby increasing bioavailability.

José Luís Santos is a Drug Product Development Scientist at Hovione. He joined the company in 2011 and has worked on many projects involving development of spray dried dispersions, manufacture of micro and nanoparticles using integrated milling and membrane technologies, and implementation of scale-up and modelling methodologies. (email: jlsantos@hovione.com)

Paula Cordeiro is a Drug Product Development Scientist at Hovione. She joined the company in 2011 and has worked on many projects involving development of spray drying processes with the use of scale-up and modelling methodologies, spray congealing processes and milling technologies.

Márcio Temtem is Group Leader and Senior Scientist in the Drug Product Development team at Hovione. He joined the company in 2008 and has been technically involved in development of spray drying processes, amorphous solid dispersions, milling technologies, biodegradable release systems and oral final dosage forms.

Spray drying is a well-established unit operation, mostly owing to intense process optimisation in the food industry where profit margins are tighter. In pharmaceutical spray drying, powder properties (e.g. particle size and bulk density) are typically considered critical quality attributes and because of this a good process understanding is fundamental to enabling a seamless transfer between spray drying units/scales with the smallest number of trials and a minimal use of API.

Dobry *et al.*¹ proposed a scale-up methodology for developing SDD formulations with minimum API. Their approach is based on a

scientific understanding of the spray drying process and critical material attributes that need to be considered: amorphous stability, chemical stability to high temperatures, thermodynamic spaces of the different spray dryer units, atomisation assessment and droplet size measurement, drying kinetics in the drying chamber and experimental confirmatory runs. Such work, however, does not include detailed information on the impact of raw materials and process conditions on the SDD critical quality attributes.

In a review paper by Vehring², a theoretical framework was established for determining the

mechanisms of particle formation. Despite not considering local interactions with the drying gas flow, such simple approach can provide an understanding of what can be the structure and morphology of the spray dried particles. Nevertheless, due to the characteristics of the API, each formulation is unique, posing great challenges in the accurate prediction of final powder properties. A recent contribution by Paudel *et al.*³ reviews the state-of-the-art, from an academic perspective, including several examples of the impact of raw materials and process conditions on the SDD properties. This is, however, limited to laboratory- and pilot-scale equipment, and does not include industry-relevant case studies – the authors are clear in stating that the literature is scarce in that respect.

A recent work from Ullum *et al.* proposed the use of computational fluid dynamics (CFD) through the investigation of the flow profile of the drying gas in a spray dryer coupled with droplet drying⁴. Additionally, recent advances in the modelling of spray drying by CFD have been discussed⁵, including its use for pharmaceutical applications⁶. The complexity of the spray drying process, where phenomena occur on vastly different time and spatial scales, suggests that the computational power still needs to evolve substantially before the particle formation process can be adequately predicted within a plant-scale CFD simulation.

In this current paper, the authors aim to discuss the different challenges and perspectives of the scale-up of SDDs based on their experience with a large number of projects spanning from the laboratory up to the large pharmaceutical commercial scale. It is the authors' intention to share industry-relevant information and opinion on what needs to be considered in the scale-up of SDDs, hoping that it can contribute to improve the scientific and technical understanding of the relation of SDD quality attributes with both raw material attributes and process conditions.

Stability of amorphous solid dispersions

One of the most important attributes of an amorphous solid dispersion is its glass transition temperature (T_g), which is intrinsically related to the API molecular mobility and is one of the characteristics that dictates whether an SDD formulation is stable enough not to change significantly over the shelf-life of the product. To reduce the molecular mobility, a typical rule of thumb used during formulation development is to target a single T_g (true solid solution) of at least 50°C higher than room temperature⁷, i.e. a single T_g above 75°C is ideal from a product shelf-life perspective. Phase separation, as shown by multiple T_g s, is typically associated with the presence of clusters (API or polymer-rich phases) in the matrix and, therefore, the material presents a higher potential for recrystallisation. Both polymer/excipients and API contribute to the T_g of the formulation, which can be estimated by simple equations that weight the individual T_g s of the API, polymer and solvent, e.g. the Fox or Gordon–Taylor equations⁸.

Deviations to these predictions are typically attributed to interactions between the different ingredients and should be considered as positive events from a stability perspective. The inherent use of solvents in spray drying processes also contributes to lowering the T_g of the SDD through a plasticisation effect attributed to the solvent and this should be considered during process development and scale-up.

In addition to the supersaturation/bioavailability considerations that are not covered in this paper, laboratory-scale SDD development primarily focuses on achieving high and single glass transition materials, so that the formulation is stable and the process can be developed with a good yield. To prepare the scale-up and account for the operation in closed loop units (i.e. with nitrogen recycle), a few trials are executed with varying drying conditions to generate SDD materials with distinct residual solvent contents. The T_g of

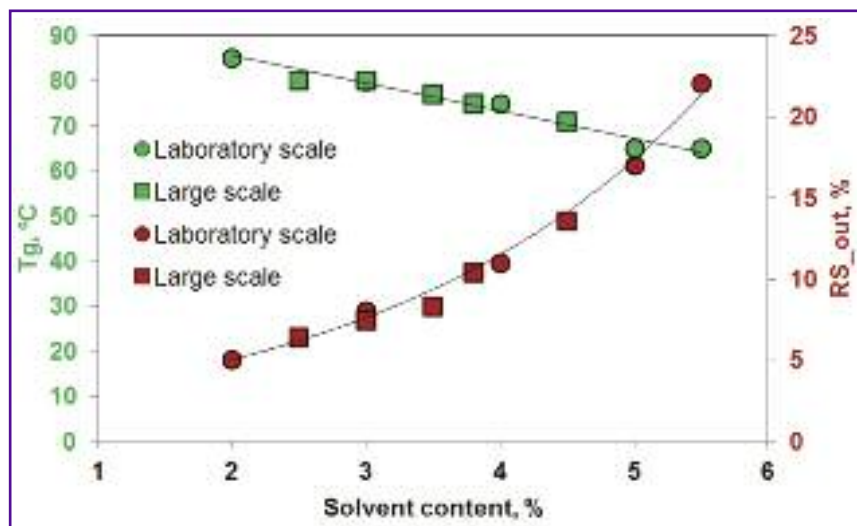


Figure 1: T_g and relative saturation of the solvent in the drying gas (RS_{out}) as a function of residual solvent content in the SDD (circles: laboratory scale spray dryer; squares: large scale spray dryer).

those materials is then assessed by modulated Differential Scanning Calorimetry (mDSC) in a closed pan to assess the plasticisation effect of the solvent. A useful illustration of these results is presented in **Figure 1**, where the drying conditions, expressed as the relative saturation of the solvent in the drying gas (RS_{out}), and T_g are plotted as a function of the residual solvent content in the SDD. The plasticisation effect is scale-independent and is used to support the selection of the most suitable drying condition. Included in **Figure 1** are laboratory and large-scale trials that can be taken as representative of the majority of SDD formulations. Conversely, the relation between relative saturation in the gas stream and powder solvent content is scale-dependent as it is related to residence time and droplet/particle size.

In particular cases, the trends of both spray drying scales are coincident as illustrated in **Figure 1**, which indicates that the data generated on amorphous stability in the laboratory with a small quantity of API can aid the preparation of the scale-up for commercially ready spray drying units. **Figure 2** illustrates one such case, where the material from the larger-scale spray dryer matched perfectly the T_g and X-ray powder diffraction (XRPD)

profile of the SDD produced in the laboratory. Furthermore, the data from laboratory-scale trials can generally be regarded as a worst-case scenario since the particles' residence time in the drying chamber is lower than in larger-scale spray dryers, causing the solvent content of laboratory-generated SDD to be typically higher.

The secondary drying of wet SDD materials is another common operation in the manufacturing of amorphous solid dispersions. To achieve the International Conference on Harmonization limits for the residual solvents, tray dryers, double-cone dryers or static agitated dryers are most widely used. The same set of data shown in **Figure 1** can also be used in the optimisation and development of a secondary drying strategy. **Figure 3** shows secondary drying data, where the T_g of the powder is increasing with a decrease in residual solvent content. A conservative approach is to always use drying temperatures below the SDD T_g , which can be adjusted incrementally during the operation as illustrated in **Figure 3** to decrease the secondary drying cycle time.

SDD downstream processability and performance

The downstream performance of a spray dried material may be

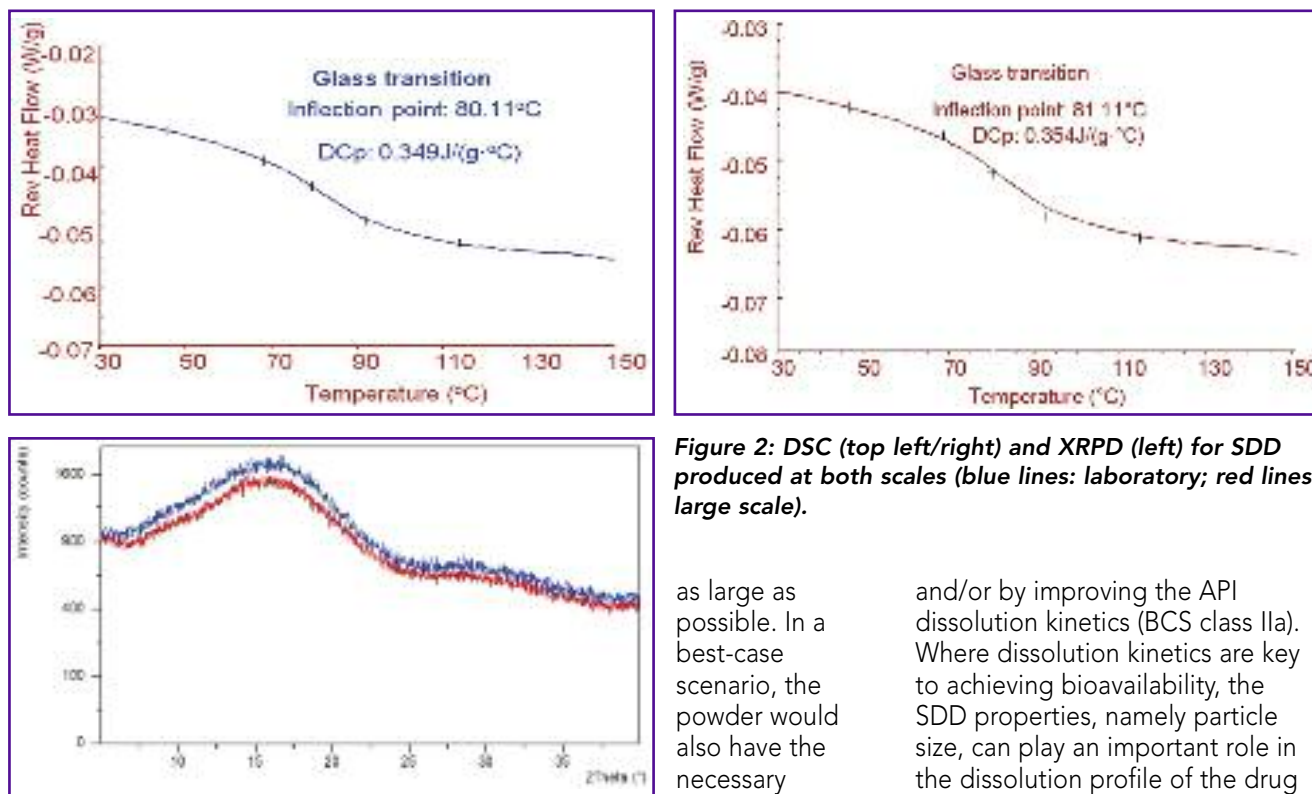


Figure 2: DSC (top left/right) and XRPD (left) for SDD produced at both scales (blue lines: laboratory; red lines: large scale).

discussed from two different perspectives: processability and product performance. Typical downstream operations include blending, roller compaction and tableting. The ability for an SDD material to flow and be processed in the downstream equipment with no major operational difficulties is closely related to powder properties, namely particle size, density and cohesive–adhesive balance between the ingredients⁹. Rule-of-thumb strategies for improving flow indicate that both particle size and density should be

as large as possible. In a best-case scenario, the powder would also have the necessary compressibility (indicated by the differences in bulk and tap density) to enable a direct compression approach⁹. The concern for product performance is that as SDDs are mostly developed with BCS class II APIs (good permeability, poor solubility), the drug product bioavailability challenge is more related to improving solubility. Solubility enhancement may be achieved by increasing the maximum API concentration in solution (BSC class IIb) – here the polymer used in an SDD may play an important role as it may promote supersaturation –

and/or by improving the API dissolution kinetics (BCS class IIa). Where dissolution kinetics are key to achieving bioavailability, the SDD properties, namely particle size, can play an important role in the dissolution profile of the drug product, in the same way as tablet disintegration due to the erosion of the small SDD granules. Particle size dictates the specific area available for mass transfer of the API in the dissolution medium (the smaller the particle size the larger the specific area).

Bioavailability can also be limited by the supersaturation potential of the amorphous solid dispersion rather than the dissolution kinetics, and in those cases particle size of the SDD is not as critical. Hence, a tight control over particle size should be on the list of priorities of every spray drying scientist when developing an SDD.

In the scale-up process from the laboratory to a commercial-scale spray dryer, distinct points should be considered. In the laboratory scale, the bottleneck is usually related to the powder properties that can be attained. Due to the reduced size of the drying chamber, laboratory-scale units typically use external mixing two-fluid nozzles. Such atomisation tends to produce particles with a Dv_{50} (mean particle size in volume) below 10 μ m and a bulk density below 0.15g/mL, which are not adequate for downstream processing, primarily due to very

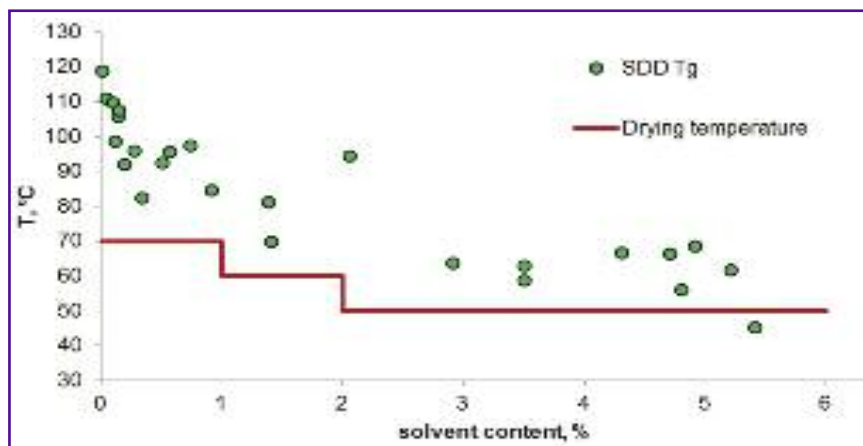


Figure 3: Secondary drying strategy for an SDD (green points: SDD Tg; red line: drying temperature).

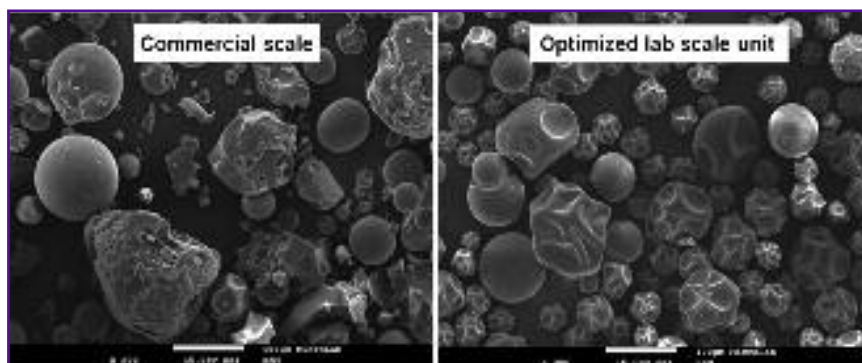


Figure 4: Scanning electron microscopy images comparing powders produced in a commercial scale pharmaceutical spray dryer and an optimised laboratory scale unit with an ultrasonic nozzle.

poor flow properties. Although a certain degree of flexibility exists in the blending step, and despite a judicious selection of the excipients and their relative amounts, it is very unlikely, particularly for large-dose drug products, that a good formulation candidate can be developed without an additional granulation step. In larger-scale spray dryers, an enhanced flexibility exists to improve the SDD properties since the range of atomisation mechanisms is broad, allowing the production of a large spectrum of droplet sizes and consequently products with particle size distributions more suited for downstream processing. During pre-clinical and formulation screening, with processes being developed on a smaller scale and clinical trials batches being produced with limited powder properties (e.g. small particle size and low bulk density), the advancing of the drug candidates to late-phase stages can pose significant challenges for the spray drying process development. One of these situations may be when an SDD process is locked with a small particle size.

An ideal approach would be to have the exact same powder properties across scales, targeting those to be used in late-phase and commercial stages. One such approach involves the use of a laboratory unit with an ultrasonic nozzle atomisation and optimised drying gas flow rate and drying chamber configuration¹⁰. The use of ultrasonic atomisation enables the generation of droplets of similar dimensions to those in larger-scale

spray dryers, which coupled with the correct thermal and residence time conditions can meet the objective of matching the larger-scale powder properties in the laboratory. **Figure 4** illustrates the morphology of spray dried materials produced in the laboratory and in a larger-scale spray dryer, where particle size and density could be maintained across scales.

Droplet size

Experience shows that the most determinant parameter to adjust SDD particle size in spray drying is droplet size. Droplets can be generated through different atomisation mechanisms. The most widely used atomisation mechanisms in pharmaceutical spray drying applications are pressure nozzles and two-fluid nozzles. For the production of SDDs, pressure nozzles are typically preferred due to their flexibility in adjusting droplet size

(although two-fluid nozzles can be more efficient in this respect), and for enabling the production of powders with relatively larger bulk densities than with two-fluid nozzles. Droplet size can be estimated through the use of correlations available in the literature. These correlations are typically developed for water spraying, and conversion for specific solvents can be accomplished by considering their surface tension and viscosity¹¹. While such equations from the literature can be applied successfully for specific geometries (e.g. as for external mixture two-fluid nozzles which have a simpler geometry), their application for vendor-specific pressure nozzle geometries may be less adequate given the particularities of the different nozzles. For such cases, the development of droplet size empirical correlations is one of the most straightforward approaches, provided that droplet size measurements are available.

Figure 5 shows droplet size predictions for three different pressure nozzles for atomisation flow rate, using a correlation developed for one such vendor-specific nozzle geometries. This predicts the impact of changing the nozzle on droplet size for a fixed feed flow rate. One of the state-of-the-art methods for droplet size data generation is the use of Phase Doppler analysers. These, however, have limitations for

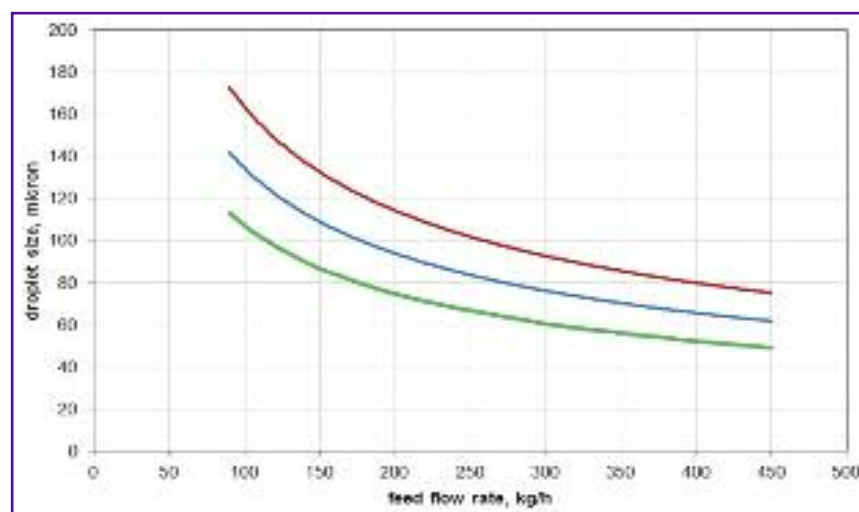


Figure 5: Droplet size estimation for three different pressure nozzles as a function of feed flow rate.

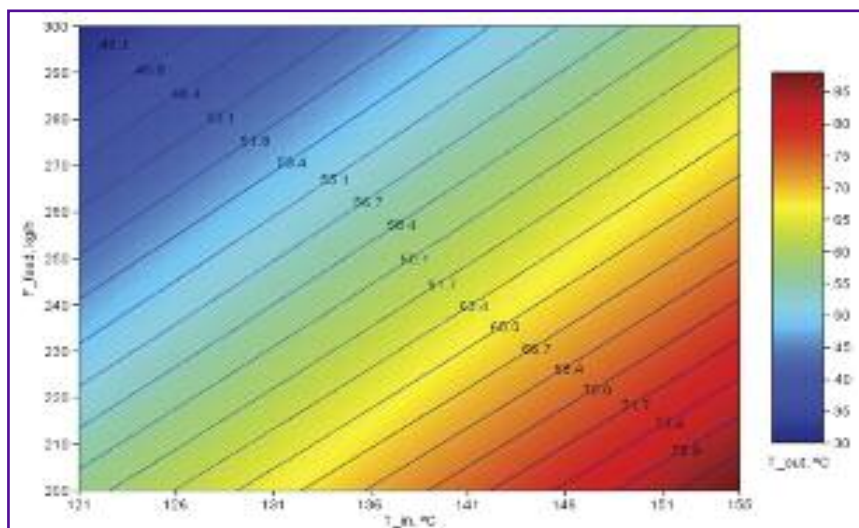


Figure 6: Thermodynamic space for a large scale spray dryer. The contour colours represent the temperature of the drying gas at the outlet of the drying chamber, while the contour lines are the simulated SDD Tg.

commercial-scale spray dryers due to the very high density of the spray plume (given the very high feed flow rates) which makes the penetration of the laser and adequate measurements of droplet size difficult. In these cases, extrapolation of available correlations may be the only option to make an estimation of droplet size.

Macroscopic heat and mass balance

In a macroscopic evaluation of a spray drying process, typically a combined heat and mass balance needs to be considered. In a spray drying process, a solution is fed to the top of a drying chamber where it is atomised into small droplets, being heated and vaporised upon contact with hot drying nitrogen. Solid particles are formed very rapidly, typically within seconds, and then separated from the gas in a cyclone and filter bag; the solvent within is later removed in a condenser, closing the mass balance in terms of solvents and solids. For heat balance closure, the only unknown is the heat transfer coefficient of the drying chamber walls that dictates the amount of heat lost to the surrounding room. As the walls are thermally insulated, the global heat transfer coefficient for the walls is a combination of that of stainless steel and of the

insulation material. As such, the global wall heat transfer coefficient for a spray dryer is not easily estimated and needs to be established using actual experimental data in a macroscopic heat and mass balance model. The use of such macroscopic models enables an accurate estimation of the drying conditions that are to be expected (e.g. in terms of relative saturation of the solvent in the drying gas), which coupled with the data generated in the laboratory in **Figure 1**, can provide an estimate of the SDD Tg in larger-scale spray dryers as illustrated in **Figure 6**.

Final remarks

The future strategies for the scaling-up of SDDs should include the use of advanced computational methods such as CFD that can better anticipate spray-related challenges, e.g. the sticking of materials with low Tg to the walls of the spray dryer. As for the impact of SDD powder properties downstream, key attributes that can affect powder flow (and consequently its processing by blending, roller compaction and tableting) and the SDD dissolution performance need to be better understood so that the spray drying process can be optimised to produce material that meets all downstream requirements. The use of advanced analytical

equipment, such as powder rheometers and compaction simulation apparatuses, should assist in meeting such objectives through the establishment of quantitative relationships between SDD properties (even with small quantities of powder) and downstream performance. Clearly, the possibility of producing SDD in the laboratory with comparable properties to that of larger-scale spray dryers can help to simplify and streamline the process development workflow (from the spray dried powder to the final tablet dissolution performance). The use of special atomisation mechanisms in laboratory-scale spray dryers (such as ultrasonic nozzles) needs to be further investigated to enable an improved match of particle size and density across scales, thereby reducing the time for an SDD formulation to reach the market.

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THE INNOVATIVE MEDICINES INITIATIVE OrBiTo PROJECT – DEVELOPING THE NEXT GENERATION OF PREDICTIVE TOOLS FOR ORAL BIOPHARMACEUTICS

by Mark McAllister, Bertil Abrahamsson, Hans Lennernäs

The Innovative Medicines Initiative (IMI) OrBiTo project is pre-competitive collaboration between pharma, academia and specialist technology companies which aims to enhance our understanding of how orally-administered drugs are absorbed from the gastrointestinal (GI) tract and apply this knowledge to develop new *in vitro* tests and *in silico* models that will better predict the performance of oral formulations in patients.

Dr Mark McAllister is a research fellow in the Drug Product Design Group, Pharmaceutical Sciences, Pfizer, located in Sandwich, UK. Mark currently leads the UK Academy of Pharmaceutical Scientists Biopharmaceutics focus group and is Deputy Scientific Coordinator for the Innovative Medicines Initiative 'OrBiTo' project.

Introduction

The IMI is a new model for public-private collaboration which aims to support open innovation in pre-competitive research and accelerate the development of safer and more effective medicines for patients. With a €2 billion budget, IMI is the world's largest public-private partnership in health research and development. IMI is a joint undertaking between the European Union (EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), who each contribute €1 billion to IMI in cash (EU) and by in-kind contribution (EFPIA; **Figure 1**). From the first three IMI calls for projects (spanning 2008–2010), 23 projects were approved for funding involving 221 R&D teams from EFPIA companies, 298 academic institutions, 47 small- and medium-

sized enterprises (SMEs), 11 patient organisations and 7 regulatory agencies.

The OrBiTo project was submitted as part of the IMI 4th call for projects in 2011 and, following approval of funding, started in

October 2012 and will run for a 5-year period with an overall budget of just over €24 million.

The OrBiTo project and consortium

Our understanding of the GI environment and prediction of formulation performance has advanced significantly over the last 15–20 years with the implementation of tools such as *in vitro* permeability models, biorelevant dissolution media, the biopharmaceutical classification scheme and *in silico* physiology-based pharmacokinetic (PBPK) models for the prediction of GI drug absorption. However, significant gaps in our understanding of oral biopharmaceutics still limit our ability to select drug molecules and/or formulation approaches which are truly optimised for the oral delivery route¹. The impact on preclinical and clinical drug development is often manifested in delays at key decision points due to the need to repeat *in vivo* trials to confirm formulation or drug product performance. The OrBiTo vision is to transform our ability to predict the *in vivo* performance of oral drug products across all stages of drug development. This will happen through partnership, collaboration and data sharing, developing our fundamental knowledge of the GI conditions to deliver innovative biopharmaceutics tools which will accurately predict product performance over a range of



Figure 1: Overview of the IMI.

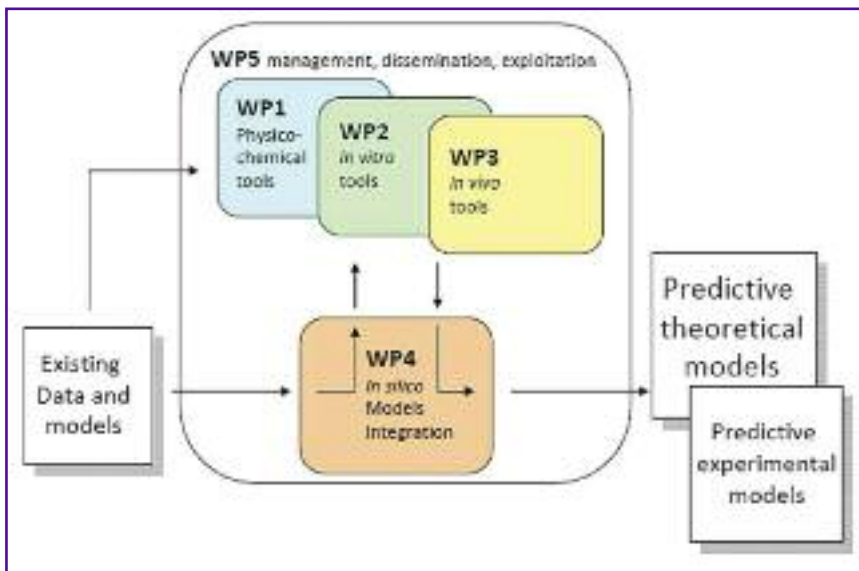


Figure 2: Overview of the OrBiTo work packages.

clinically relevant conditions. The integration of *in vitro* and *in silico* approaches will provide a biopharmaceutics toolkit, validated using clinical data, to accelerate drug development. The main objectives of the OrBiTo project are as follows.

- To increase the understanding of the GI drug absorption process as a prerequisite for improved biopharmaceutical predictions.
- To create new or refined *in vitro* and *in silico* methods contributing to improved *in vivo* predictions.
- To develop a framework for the optimal use of predictive tools and preclinical models.

OrBiTo is structured in four research work packages (WPs) focusing on physico-chemical tools (WP1)², *in vitro* tools (WP2)³ and *in vivo* understanding and tools (WP3), with the integration of results and data across all WPs being achieved through the application of *in silico* models of drug absorption in WP4 (Figure 2)⁴.

WP1 seeks to improve the understanding of the physico-chemical and biopharmaceutical properties, which affect the *in vivo* performance of poorly soluble active pharmaceutical ingredients (APIs; BCS class II and IV drugs). The data generated by the new

models and characterisation tests developed through WP1 will inform the selection of candidate molecules during preclinical testing and guide appropriate formulation selection for first use in human studies. Characterisation data describing biopharmaceutical

properties will also be used as a key input for the integrated *in silico* models being developed as part of WP4. WP2 will focus on *in vitro* development tools in the dissolution and permeability area that provide high quality quantitative predictions for late stage/market formulation development. WP3 will focus on generating *in vivo* understanding in areas where remaining gaps hamper the development of predictive methods. This will include regional permeability studies, enhanced system characterisation of the GI physiological conditions as well as studies of model drugs to elucidate specific biopharmaceutical processes, providing a basis for improved *in vitro* and *in silico* tools. In addition to integrating the results from WP 1–3 within PBPK models of the GI absorption process, WP 4 will also seek to build on and improve existing prediction algorithms to improve the accuracy of simulation and

Table 1: OrBiTo project consortium

EFPIA member companies	Universities, research organisations, public bodies, non-profit groups	SMEs
AstraZeneca AB, Sweden	Uppsala Universitet, Uppsala, Sweden	Simcyp Limited, Sheffield, UK
Abbvie GmbH & CoKG, Germany	Copenhagen University, Denmark	Sirius Analytical Ltd, Forest Row, UK
Bayer Pharma AG, Germany	Ernst Moritz Arndt University Greifswald, Germany	Simulations Plus, Inc., Lancaster, USA
Boehringer Ingelheim International GmbH, Germany	Johann Wolfgang Goethe-Universität Frankfurt am Main, Germany	
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prediction of *in vivo* performance.

Much of the work described in WP 1-4 will be underpinned by the development of a novel and unique database containing *in vivo* data of well-characterised novel APIs and diverse oral pharmaceutical products. It will mainly consist of novel material from the EFPIA partners and the first version of this database is expected to include data from more than 100 clinical studies. EFPIA partners will also supply APIs or formulated drug product for additional experimental characterisation. An important aspect of the research concept is to use this material and database resource across the different WPs in the project to generate common data which can be integrated throughout the programme to identify a generally applicable framework for use of predictive tools. The database will be supplemented by literature data and it will also be open for additions with novel EFPIA compounds during the project. However, it is emphasised that the vast majority of work will be done on novel APIs with the exception of the prospective human clinical studies to be performed within

OrBiTo which will use well-characterised marketed APIs as model drugs.

The OrBiTo Project consortium comprises 12 EFPIA companies and an academic-SME group with 14 members as shown in **Table 1**.

Conclusions

Over the 5-year duration of the project, it is hoped that the combination of industrial biopharmaceutics expertise, specialist technology providers and academic centres of excellence will create the next generation of tools for oral biopharmaceutics and transform our ability to predict oral formulation performance. The IMI principles and framework for pre-competitive collaboration are central to OrBiTo's research strategy. This is clearly illustrated by the development of a cross-company physicochemical and pharmacokinetic database containing extensive and diverse data-sets which will be used to develop and validate new *in vitro* and *in silico* tools. In conclusion, the OrBiTo project provides a tremendous opportunity to advance our understanding of oral biopharmaceutics and offers a

template for collaborative efforts in other areas of pharmaceutical science.

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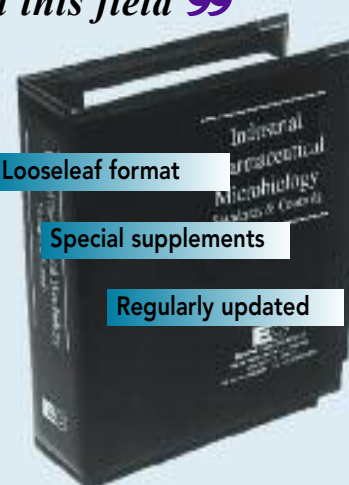
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FORMULATION TECHNOLOGY ENABLES THE DELIVERY OF HIV MEDICINES

by Peter Timmins, Jonathan Brown

The most recent entrants into clinical practice for the treatment of human immunodeficiency virus (HIV) infection include a number of compounds with drug delivery challenges. Innovative formulation technologies have been developed and applied to overcome these challenges and provide medicines suitable for the clinical need. Problems of solubility, pharmacokinetics and physical material properties are described along with their resolution in a series of case examples that are illustrative not only of HIV medicines but are applicable solutions to similar problems in other therapeutic classes.

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Jonathan Brown is a Principal Scientist within the Portfolio Enabling Technology group. He has research interests in oral modified release formulation technologies and physiologically-based pharmacokinetic modelling.

Introduction

Significant advances in the treatment of HIV infection have occurred since its identification around three decades ago, leading to a reduction in its incidence and longer life expectancy of infected individuals¹. Although a cure still remains an aspiration, anti-retroviral drugs have been an important factor in managing the infection and the need for new therapies and improved versions of existing drugs remains important to assure effective viral suppression, to enable patient compliance with medication regimens, and to deal with the development of drug resistance^{1,2}.

The efforts of drug discovery scientists have generated a number of new anti-HIV agents³ but, as is the case for many emerging drug candidates across all therapeutic

areas, the physicochemical and pharmacokinetic properties of a number of the new entities have provided challenges to formulation scientists to assure that the finished medicine delivers the desired clinical profile to realise therapeutic success. This challenge may be further emphasised if doses in the hundreds of milligrams are required, as is the case for a number of HIV therapies. With the emergence of the highly active antiretroviral therapy (HAART) approach in the late 1990s, as newer agents that targeted different stages of viral replication life cycle⁴ appeared and made this possible, combination drug therapy advanced and eventually provided for simplified treatment regimens with co-formulated drugs⁵.

Assuring the performance of the

newer drugs with their inherent challenges, as well as supporting simplified dosing of multiple medicines therefore defines an important role for pharmaceutical formulation. This review focuses on how formulation science has effectively enabled the utility of some newer, as well as some more established, treatments for HIV infection and illustrates examples that inform how to deal with formulation challenges of today's medicines irrespective of therapeutic class.

Formulation of HIV medicines – case histories

Efavirenz

Efavirenz (*Sustiva*, Bristol-Myers Squibb, and a component of *Atripla*, Bristol-Myers Squibb/Gilead) is a poorly soluble, non-nucleoside reverse transcriptase inhibitor (NNRTI) reported as showing sensitivity of bioavailability to tablet disintegration time. Therefore, the original single entity formulations⁶ employed optimised disintegrant choices and levels, along with a careful distribution of disintegrant between intragranular and extragranular phases of the tablet, to assure very rapid disintegration. Tablets formulated in this way were bioequivalent to earlier marketed capsule formulations (200mg efavirenz per capsule) and as they contained a higher dose of drug per unit dose form (600mg) in an acceptably sized tablet, offer greater convenience to patients where a dose of 600mg is prescribed.

Other work suggested that the visually observed tablet disintegration alone is not the key factor that determines bioavailability for efavirenz, but what is most important is the completion of disintegration down to primary particles and dispersion of the active ingredient⁷. For two tablet formulations, *in vitro* disintegration and the time to complete disintegration *in vivo* as measured by gamma scintigraphy were different, but the one that exhibited slower disintegration both *in vitro* and *in vivo* had slower *in vitro* dissolution but had the highest bioavailability, with higher area

under the plasma concentration-time curve, higher maximum plasma concentration and an earlier time to maximum plasma concentration. It was suggested that the reason for the delay in absorption for the apparently faster disintegrating formulation was that it was disintegrating to larger aggregates *in vivo* relative to the better performing formulation but this difference is not discernible in visual observation of disintegration. From these larger particles, resulting perhaps from poorer effectiveness in this specific formulation of the included sodium starch glycolate disintegrant, drug release was slower. Also it was suggested that *in vivo* gelation of the sodium starch glycolate also acted as a further barrier for drug release⁷.

Translating this learning to a fixed combination dosage form, containing efavirenz with emtricitabine and tenofovir disoproxil fumarate, led to choice of a bilayer tablet to mitigate compatibility problems and to assure the efavirenz layer could disintegrate readily and disperse the poorly wetting efavirenz particles *in vivo* to assure bioavailability^{8,9}. A non-bilayer formulation based on wet granulation led to instability, attributed to high water levels needed for efavirenz granulation that allowed a eutectic formation between emtricitabine and tenofovir disoproxil fumarate which dried as a

glassy or amorphous unstable form¹⁰. Additionally, interaction with the surfactant included to help wet and disperse the efavirenz was implicated, but its removal led to impaired bioavailability⁸. A bilayer tablet that separated the efavirenz component showed good stability and bioequivalence of its components to the single entity formulations⁹. It combines three medicines useful together to treat HIV infection as they come from more than one therapeutic target class, that have pharmacokinetics suited to once daily dosing and all have the same lack of restriction regarding dosing with food. As such, formulation science has provided for a fixed combination, one tablet, once daily dosing treatment for HIV infection, offering an opportunity to improve the patient adherence to therapy that is critical to maintaining disease control¹¹.

Etravirine

Etravirine (*Intelence*, Janssen-Cilag), a second generation NNRTI, is a very insoluble weak base. Conventional and nanosized drug formulation approaches resulted in negligible blood levels on oral dosing. It was necessary to dose amorphous drug, where the barrier of crystal lattice breakdown as a first step in dissolution was absent in order to achieve an acceptable degree of absorption¹². However, preparing amorphous drug required

cryomilling of crystalline drug for 3 hours at -196°C and the amorphous drug had poor physical stability, being prone to partial recrystallization¹³. Due to its low solubility and its low to moderate permeability (Biopharmaceutics Classification System Class IV compound)¹², effective drug delivery requires consideration of not only optimising the etravirine physical form, but also to assure very rapid disintegration and *in vivo* drug release from the dosage form. This is to minimize any impact of variability in gastrointestinal transit time on presentation of the poorly permeable drug to the sites where drug has highest absorption potential (the very high surface area proximal small intestine).

An initial formulation for clinical trials that attempted to resolve these drug delivery problems, referred to as a granulo-layered formulation¹⁴, required a dose of drug of 800mg twice daily to achieve desired pharmacokinetics. Layering amorphous drug as dispersion in hydroxypropylmethylcellulose (HPMC) from organic solvent solution onto excipient beads¹⁵ was used to improve etravirine dissolution rate, a technology approach previously applied to commercial formulations of the antifungal itraconazole¹⁶. This formulation strategy is one of the oral drug delivery approaches

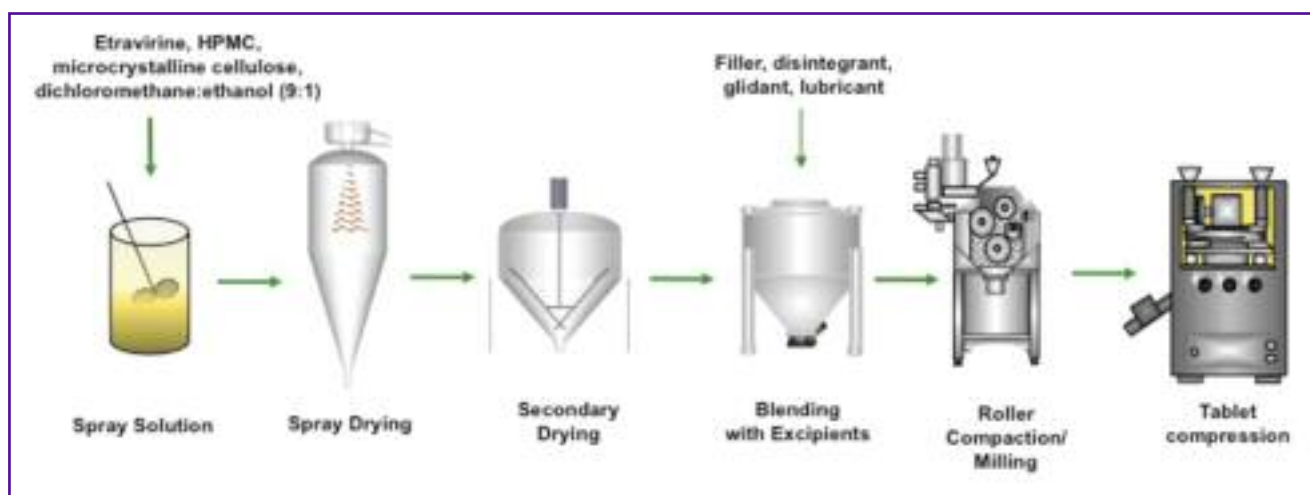


Figure 1: Process train for manufacture of etravirine tablets based on spray-dried amorphous dispersion based on description in innovator patent application¹⁸.

described for etravirine in a drug synthesis patent¹⁷.

Spray drying drug from organic solution together with a polymer was subsequently pursued as an approach to further improve drug dissolution and hence bioavailability, but initial dispersions of drug in HPMC yielded particles on spray drying that were of low bulk density and gave problems with tableting. Co-spray drying etravirine, HPMC and microcrystalline cellulose, with drug and polymer in solution and with microcrystalline cellulose suspended in the spray drying feed, led to denser particles highly suited to processing into tablets (Figure 1)¹⁸. This formulation technology provided for significantly improved bioavailability of etravirine in HIV-infected subjects, as indicated by area under the plasma concentration-time curve over the period to 12 hours post-dosing, and allowed for smaller and a reduced number of tablets to achieve the clinically effective dose. The range of exposure seen with 200mg of the spray dried formulation given twice

daily was comparable to that yielded by 800mg of the granulo-layered formulation dosed twice daily and with reduced interpatient variability¹⁹.

Novel HIV attachment inhibitors

Novel HIV attachment inhibitors interfering with the binding of the viral gp120 glycoprotein to the host cell CD4 have been identified by Bristol-Myers Squibb²⁰. One such compound, BMS-626529, is a potent inhibitor of viral replication *in vitro* but exhibits low oral bioavailability and a very short apparent half-life *in vivo*. To overcome the low bioavailability of the compound associated with its poor water solubility, a prodrug strategy was pursued in which the chemical structure was modified by the addition of hydrophilic cleavable substituent groups to improve solubility. Enzymatic hydrolysis *in vivo* enabled effective delivery of the parent molecule. Based upon animal and human *in vivo* screening experiments, BMS-

663068, a phosphonoxymethyl prodrug of BMS-626529, was selected for evaluation in the clinic²¹.

The highly soluble prodrug, when delivered orally, is converted locally via intestinal brush border alkaline phosphatase to the poorly soluble parent, BMS-626529, immediately prior to/during absorption. Maintaining a threshold minimum plasma concentration (C_{min}) prior to administration of the next dose is considered important to efficacy, whilst the minimisation of maximum plasma concentration (C_{max}) may mitigate peak-related adverse events. Sustained absorption of parent throughout the gastrointestinal tract via slow release of prodrug from a formulation is required to achieve this and overcome the short half-life of the compound.

The achievement of target pharmacokinetics was enabled through the design of a novel extended-release (ER) tablet²². Tablet development was based on *in silico* modelling and built upon

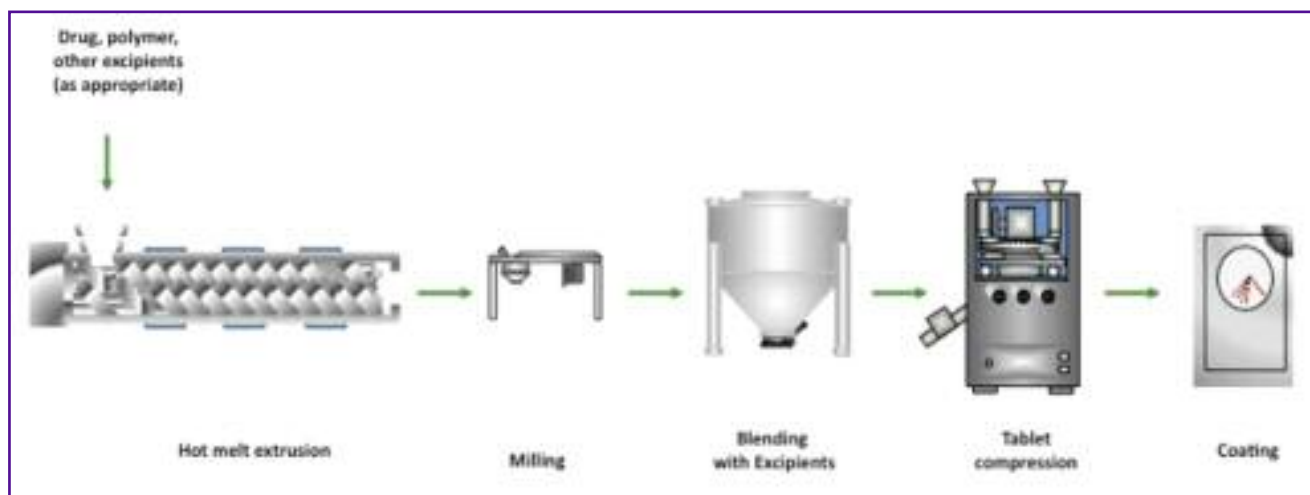


Figure 2: HME process to make amorphous dispersion formulations (e.g. lopinavir with ritonavir). The HME approach involves dispersing the drug within a pharmaceutically-acceptable polymer in an extruder with the application of heat. If it is done by raising the drug and the polymer in admixture to above the melting point of the drug and the glass transition temperature of the polymer and then cooling without allowing the drug to recrystallize, then the resultant solid dispersion is amorphous. The physical stability of such a formulation might be dependent on the miscibility of the drug and polymer, i.e. the amount of drug dispersed in the polymer, temperature and humidity at which the solid dispersion is stored, and whether there are molecular level interactions between drug and polymer that impair its propensity to recrystallise. Commercial equipment is usually a twin screw extruder which enables feeding of drug and polymer (and other excipients if needed) into the extruder where specifically-designed motor driven screws convey the materials along the heated barrel, mix them, allow them to melt and soften as appropriate, knead and densify them, shear and cut the formed mass and allow it to cool as it leaves the extruder barrel. The resultant material can be further processed into granules and, if needed, blended with other excipients to make it suitable for tableting.

Careful evaluation of bioavailability in specific areas of the intestine and colon to gain an understanding of how gastrointestinal physiology and luminal fluid volume and composition could influence prodrug conversion and absorption of the parent²³. The formulation was developed as a non-disintegrating monolithic, matrix tablet utilising hydrophilic swellable cellulose ether polymer technology. Although unbound alkaline phosphatase was shown to penetrate the hydrating gel layer of the tablet and represent an *in vivo* risk from luminal alkaline phosphatase, conversion of prodrug to parent within the hydrated dosage form was shown to be inhibited²⁴. This is essential to maintaining the required release rate and pharmacokinetics as premature conversion to parent within the dosage form would lead to reduced bioavailability. The optimised, *in vivo* stabilised ER formulation was found to be suitable for once to twice daily dosing.

Lopinavir with ritonavir

Lopinavir with ritonavir (Kaletra, AbbVie) commercial formulation employs hot melt extrusion (HME), resulting in an amorphous drug dispersion in the finished product. Amorphous dispersions have been progressed as a solution to overcome poor drug-like properties, solubility and dissolution rate, and mitigate poor bioavailability relating to those properties²⁵. HME represents a commercialisable approach to manufacturing such dispersions²⁶ (Figure 2). It has long been used in other industries where a thermoplastic material is softened under temperature and shear force, usually admixed with other materials (fillers, pigments, stabilisers, etc), then extruded to form granules/pellets, tubes, rods or sheets. HME was first described for creating pharmaceutical dosage forms over 40 years ago²⁷ but only

became of demonstrated potential for creation of commercialisable products in the last 15–20 years²⁸.

The commercial lopinavir 200mg with ritonavir 50mg combination tablet employs copovidone and sorbitan laurate as the polymeric components to provide the material for tableting. The amount of copovidone in the product was higher than previously used according to the US FDA Inactive Ingredient Listing and required the submission of a package of toxicity studies to support the higher level, including data on repeat dose toxicity, genotoxicity and carcinogenicity²⁹.

As well as reducing the number of dosage forms the patient has to take in transferring to the HME formulation from the prior available liquid-filled capsule formulation, the HME formulation avoids the requirement to store the medicine in a refrigerator. The tablet shows lower variability in pharmacokinetic parameters relative to the capsule and has a much diminished food effect, allowing for the possibility of not restricting to dosing with food^{30,31}. These are valuable improvements in terms of supporting patient compliance with this medicine resulting from the application of modern formulation science.

Cobicistat

Cobicistat (Tybost, and component of Stribild, Gilead) is a novel cytochrome P450 (CYP) enzyme (CYP3A4) inhibitor used as a “booster” in combination with some HIV treatments e.g. protease inhibitors, to reduce their metabolism during absorption and so increase the amount of unchanged drug reaching the systemic circulation. Ritonavir is also used as such a boosting agent but cobicistat differs in that it has no anti-viral activity of its own and is purely used to modify pharmacokinetics.

Cobicistat drug substance does not occur in crystalline form and is isolated as an amorphous,

hygroscopic solid foam of low glass transition temperature which readily transforms under ambient conditions via a moisture- and temperature-driven phase transformation into a rubber-like material that is difficult to process into dosage forms. The removal of the absorbed moisture and reversion to the original solid form does not occur³².

Initial approaches to making solid dosage forms involved handling the drug substance in solution in an appropriate organic solvent, such as ethanol³³. This solution is added to silica and then excipients and water in a high shear mixer to wet granulate. Fluid bed drying achieves removal of the organic solvent as well as the water. The challenges of handling large volumes of flammable solvent in a drug product processing facility, whilst not insurmountable, can be avoided if the drug is loaded on to a suitable carrier material that impart superior handling properties to the drug substance prior to introduction into a dosage form manufacturing area.

By adsorbing onto silica by evaporation from a dichloromethane solution of drug as part of the isolation of the cobicistat³³, a free-flowing powder is produced. Although still hygroscopic, moisture uptake is now reversible and the cobicistat no longer undergoes phase transformation. The drug adsorbate is highly suited to further processing into pharmaceutical dosage forms. The finished dosage form using the adsorbate showed bioequivalence for cobicistat with dosage forms prepared by the ethanol/water high shear granulation process. For cobicistat, formulation technology has dealt with challenging physical properties of an active pharmaceutical ingredient and provided an approach to improved handling and manufacturing of dosage forms.

Nevirapine

Nevirapine, a well-established NNRTI, has recently become available as an ER formulation (Viramune Prolonged-Release,

Boehringer Ingelheim). Although it is inherently a long half-life drug, $t_{1/2} > 45$ hours³⁴, there are advantages in offering patients an ER nevirapine formulation. Despite the long half-life, immediate-release nevirapine is typically dosed in treatment-stabilised patients at 200mg twice daily³⁵. A concern with using a 400mg once daily immediate-release dose is that it results in high mean peak and low mean trough plasma concentrations of drug relative to using a dose of 200mg twice daily, although the exposure to drug as measured by the area under the plasma concentration–time curve was equivalent for once and twice daily dosing regimens. Higher peak concentrations give concern as to an increased risk of liver toxicity and lower trough concentrations raise concern as to risk of emergence of viral resistance³⁵. Also, twice daily dosing is less convenient for HIV patients taking multiple medications where many of their other medicines have once daily dosing. Hence, there is good clinical relevance to creating the ER formulation. Predicting or demonstrating that there is effective drug absorption from the colon is essential to determining the viability of developing an oral ER formulation³⁶. Nevirapine delivered to the ascending and descending colon had 82 and 58% bioavailability, respectively, relative to an orally-administered suspension of nevirapine³⁷, exceeding the value of $\geq 40\%$ suggested as an indicator of likely success³⁸, and supported the development of the ER product.

The commercial formulation was selected on the basis of pharmacokinetic evaluation of a series of hydrophilic matrix tablets that employed different amounts and grades of HPMC as a release rate controlling polymer. Tablets contained 20, 25, 30 or 40% w/w of HPMC 2208 4000 cps grade or alternatively 20 or 25% w/w HPMC 2910 4000 cps grade and the amount and grade of polymer used yielded a range of *in vitro* release

rates that translated to a range of *in vivo* pharmacokinetic profiles³⁹ with the lower amount of polymer leading to a faster release rate, and with the 2910 polymer leading to faster release rates than the 2208 polymer. The marked change in release rate with polymer amount, given similar tablet sizes across the range studied, suggests a degree of dependency on erosion as a key rate controlling mechanism from the hydrated polymer matrix *in vitro* and *in vivo*. It was possible to build a correlation between the *in vitro* release profile and the *in vivo* performance enabling prediction of the pharmacokinetic behaviour of dosage forms as *in vitro* release rate was changed, which would enable further formulation development studies to be prosecuted using *in vitro* drug release rate for decision making⁴⁰. Contrary to what was seen in the single-dose human study used to establish the *in vitro*–*in vivo* correlation, in a steady state human bioavailability study of the 20 and 25% w/w polymer ER formulations, the (more slowly releasing) 25% w/w polymer formulation showed higher bioavailability compared to the 20% w/w polymer formulation⁴¹. As metabolism of nevirapine is impacted by induction of CYP enzymes, which include CYP3A4⁴² (which is more extensively expressed in the upper gastrointestinal tract), a more slowly releasing formulation might deliver more drug to the regions where the enzyme is not expressed compared to the faster releasing formulation, and result in increased exposure that is more obvious in a steady state study. This observation offers the caution that the performance of an enabled formulation has to be considered in light not only of its fabrication technology, but the physiological environment in which it has to operate, including gastrointestinal transit, absorption sites, metabolising enzymes, etc.

Summary

The development of modern medicines for the treatment of HIV infection has benefitted from

formulation technology to accommodate the inherent properties of the active pharmaceutical ingredient and assure that pharmacokinetic and physicochemical challenges are managed. HIV medicine formulations offer examples of extended release technologies, managing *in vivo* disintegration and dispersion, adsorption on to a carrier, spray drying and melt extrusion. All of these technologies are in place for commercialized products and demonstrate how formulation technology in general may be deployed to deal with the challenges inherent in contemporary potential therapeutic agents of any disease class.

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TAKING STEPS TO IMPLEMENT THE FALSIFIED MEDICINES DIRECTIVE AND COMBAT COUNTERFEITING IN EUROPE – THE EUROPEAN STAKEHOLDER MODEL

by Richard Bergström

Falsified medicines present a public health threat at global level, with counterfeit goods threatening the health of patients in countries around the world. With the increased prevalence of unlicensed online “pharmacies” and points-of-sale, the problem is attracting growing attention – inspiring governments, security officials and the pharmaceutical industry to take action. The pharmaceutical industry has a vested interest in fighting counterfeiting: developing new medicines is only one part of providing healthcare treatments for patients – we also have to ensure that people benefit from those medicines. Part of that involves making sure that any medicine we produce reaches the patient in the same condition as when it leaves the manufacturing site.

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Falsified Medicines Directive: fighting a growing problem

Counterfeiting is a crime with very real consequences: it presents a major threat to patient safety and we have seen the devastating evidence of this. Just this past October, customs agents seized 1 million fake Xanax pills at Zurich airport¹. In May of this year, French customs officers seized 1.2 million doses of counterfeit aspirin – an over-the-counter medicine that could have reached patients even more easily than the fake anti-anxiety pills seized in Switzerland². Germany, meanwhile, experienced one of its most significant counterfeiting scares in March, when it was discovered

that a common heartburn counterfeit or sub-standard medication had made it onto the market³. In 2011 alone, approximately 30 million fake medicines were seized at EU borders⁴. What makes these statistics even more troubling is the fact that it is impossible to know what the real numbers are – but we can be sure they are much higher than what is reported. The people behind counterfeiting are criminals – they aren't reporting earnings and sales, they aren't releasing quarterly reports. It is impossible to gauge just how big the problem is. And that is cause for serious concern. All we can know is that we need to act – and quickly.

In an attempt to fight back against counterfeiters and the dangerous goods they bring into the markets, the European Union (EU) put forth the Falsified Medicines Directive (FMD; 2011/62/EU) first published in the EU Official Journal on 1 July 2011. The FMD sets out steps to secure the supply chain of medicines in Europe. It asserts that all prescription-only medicines will have to bear safety features (i.e. a unique serial number placed on each pack, together with tamper-evident packaging)*. The FMD also requires the establishment and management of a repositories system that will store the unique identifiers of the serial packs, and contain information on the safety features. The European Commission will determine the specifications of the serial number to be placed on packs when it sets out the rules for implementation in the “Delegated Acts”. Once the Delegated Acts are published – anticipated in the second half of 2014 – EU Member States and pharmaceutical companies supplying the EU market will have 3 years to take the necessary steps and ensure they are in compliance.

A solution in the European Stakeholder Model

In Europe, the FMD is an important step in better protecting patients from counterfeit medicines. The European Federation of Pharmaceutical Industries and Associations (EFPIA) sees the need to move as quickly as possible to ensure the legitimate supply chain is as safe as possible. One of the FMD's key elements is the onus it places on pharmacists to be able to verify that the medicine they dispense to patients is genuine. Towards this end, EFPIA has joined together with the Pharmaceutical Group of the European Union (PGEU), the Groupement International de la Repartition Pharmaceutique (GIRP) and the European Association of the Euro-Pharmaceutical Companies (EAEPC) to develop the European Stakeholder Model (ESM) Medicines Verification System. These organisations – representing

* Certain products or product categories of prescription-only medicines might be exempted according to a risk assessment. Over-the-counter medicines, for instance, are excluded – unless there is a risk of falsification.

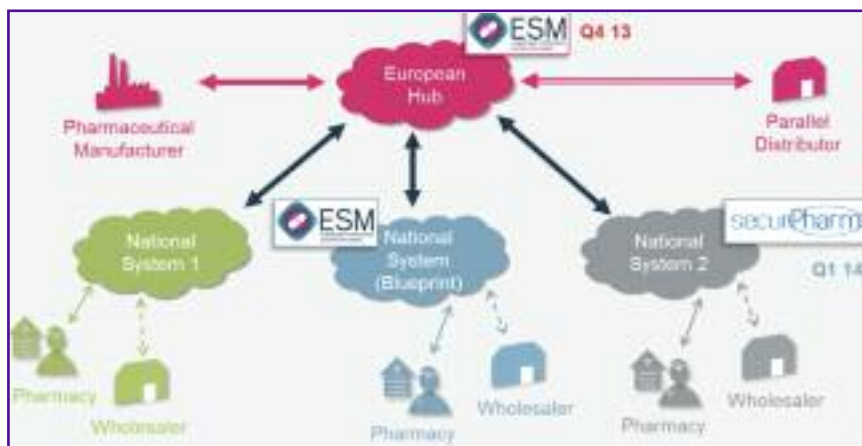


Figure 1: The European Medicines Verification System (EMVS)[†].

pharmacists, wholesalers, and parallel traders, respectively – came together with the aim of developing a system that will provide a high level of security for patients while being cost-effective, pan-European and interoperable, and capable of being effectively integrated into existing structures and practices in the distribution chain. The result is the European Medicines Verification System (EMVS; Figure 1), a system designed to ensure the medicines are making it safely from the point of manufacture to the point of sale – to the patient.

The EMVS proposed by EFPIA, EAEP, PGEU and GIRP is comprised of the European Hub and the National Blueprint Systems (nBPS). The European central hub is connected to a series of single-country or multi-country data repositories that serve as verification platforms; pharmacies and other registered parties can use these to check a product's authenticity. The system will be interoperable between EU countries and will allow for the reconciliation of products traded between EU member states (known as parallel traded products) through the European central hub. It will also offer those countries that do not want to set up their own national system the opportunity to join an existing product verification infrastructure. These components are to be managed by the European Medicines Verification Organisation

(EMVO), which is to be founded in the course of 2014 and foresees participation of authorities and other relevant stakeholders in the overall governance.

The EMVS was successfully tested in a pilot project in Sweden from 2009–2010. Stakeholders in Denmark, Finland, Norway and Sweden have already expressed their commitment to the Blueprint System. Meanwhile, development and implementation of the European Hub is well under way. By the first quarter of 2014, results are expected from user-accepted testing in Germany, in which the Hub was connected to the German securPharm system[†], demonstrating the first scenario covering the full information chain at European level – from manufacturer to pharmacy.

Fighting counterfeiting in a collaborative and comprehensive way

The measures set forth by the FMD, and the systems being developed to help implement its provisions are a major step forward in the EU against counterfeiting. But fighting counterfeiting requires a collaborative, multi-faceted effort. Part of this simply involves education: when it comes to the dangers of counterfeit medicines sold on the Internet, for instance, patients need to be aware that the vast majority of medicines they come across on the Internet are

either counterfeit or unsafe.

The pharmaceutical industry invests huge amounts of time and money into developing medicines to treat a huge variety of illnesses – but this work is irrelevant if we can't ensure that patients are safely receiving these medicines. Any medicine that reaches the patient should be in the same condition as when it leaves the manufacturing site. That is the goal of initiatives like the ESM and the FMD. The sooner we can implement such measures, the sooner we will be making patients that much safer.

References

- 1 BBC. Fake Xanax anxiety pills from China seized in Zurich; 18 October 2013. www.bbc.co.uk/news/world-europe-24585099
- 2 EUbusiness. Million doses of fake aspirin from China seized in France; 25 May 2013. www.eubusiness.com/news-eu/france-china.or/9/
- 3 Die Welt. Razzia wegen eines gefälschten Medikaments; 7 March 2013. www.welt.de/newsticker/news3/article114240342/Razzia-wegen-eines-gefaelschten-Medikaments.html
- 4 European Commission. Report on EU customs enforcement of intellectual property rights. Results at the EU border – 2011; July 2012. http://ec.europa.eu/taxation_customs/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/2012_ipr_statistics_en.pdf

Editor's comment:

EIPG, a stakeholder organisation representing the industrial pharmacists responsible for ensuring, under Art. 51 of the Directive, that the safety features have been affixed to the packaging of medicinal products, commented on the EMVS during a symposium at the University of Lisbon in 2012. In particular, EIPG expressed its concern that the model proposed voluntary verification at the wholesaler dealer level, given that Art. 80(ca) of the Directive stipulates that "Wholesale distributors must verify that the medicinal products received are not falsified by checking the safety features on the outer packaging".

[†] securPharm is a national anti-counterfeiting initiative. Launched by German pharmaceutical manufacturing, pharmacist and wholesaler associations, it is designed to test whether medicinal products are genuine or not and is intended to comply with the EU FMD.

regulatory review

The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, USA and, International markets.

USA

Proposed regulation – administrative detention authority during inspection of drugs intended for human or animal use

Under this proposed regulation, the Food and Drug Administration (FDA) will be able to administratively detain drugs encountered during an inspection that an officer or employee conducting the inspection has reason to believe are adulterated or misbranded until FDA has had time to consider what action it should take concerning the drugs, and to initiate legal action, if appropriate.

Draft Guidance for Industry – Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration

FDA's preferred UFI for a drug establishment is the Data Universal Numbering System (DUNS) number. The DUNS number is available free of charge to all drug establishments. Alternative identifiers may only be used after consultation with FDA.

Unique Device Identification (UDI)

FDA has released a final rule requiring that most medical devices and certain combination products that contain devices that are distributed in the USA carry a UDI.

Secure Supply Chain Pilot Program (SSCPP)

Qualified firms will be enabled to expedite the importation of active pharmaceutical ingredients and finished drug products into the USA. Participating firms in this voluntary programme must meet certain criteria. The pilot program will run from February 2014 through February 2016.

Draft Guidance for Industry – Refuse-to-Receive Standards

This guidance is intended to assist sponsors preparing to submit abbreviated new drug applications (ANDAs) and prior approval supplements to ANDAs for which the applicant is seeking approval of a new strength of the drug product. The guidance describes what should be included and highlights serious deficiencies that may cause refusal to receive an ANDA.

Europe

Q&A – Practical implementation guidelines on variations

Procedural elements in relation to the implementation of the revised guidelines are clarified.

Improving the safety of medical devices

Following the Poly Implant Prothèse breast implants and other scandals the European Commission has adopted two measures for immediate implementation. The new rules are:

- a Commission Implementation Regulation clarifying the criteria to be met by notified bodies;
- a Recommendation clarifying the tasks these bodies have to undertake when they perform audits and assessments.

Reflection paper – coated nanomedicines general issues for consideration

The reflection paper describes general issues to consider during the development of nanomedicines that have a coating

MHRA

Can a single system simplify reporting of incidents to the MHRA?

The MHRA currently runs five reporting systems to collect reports of different types of incidents involving medicines, medical devices and blood. MHRA is considering whether bringing all

five systems together under the Yellow Card Scheme brand (currently used for reporting side effects to medicines) could help increase incident reporting and reduce confusion of reporters.

Proposed introduction of Tell-and-Do variations for a specific subset of parallel import licenses

Parallel Importers (PIs) must notify MHRA if they observe certain changes to the imported products (e.g. changed appearance of dosage forms). While MHRA is investigating the changes, there is a 'stop-processing' requirement on the importing companies which prohibits them from processing, repackaging or releasing the product onto the market until given approval. This can be an unexpected disruption of several months and affect the importer's business negatively.

The new proposal abolishes the 'stop-processing' requirement if imported products are part of European Mutual Recognition or De-Centralised procedures. PIs will notify the Agency of the changes and release the products onto the UK market. This notification principle is known as 'Tell-and-Do'.

Falsified Medicines Directive (FMD)

The UK MHRA has published on its website an overview of the medicines regulation and guidance in relation to the FMD as it applies to the UK.

Nicotine-containing products

The European parliament did not support The Commission's proposal to regulate electronic cigarettes as medicines. MHRA, however, will continue to encourage companies voluntarily to seek a licence for their products.

Q&A for Specials manufacturers

Q&As have been used in this guidance to promote easy updates

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US Pharmacopoeial Convention

EIPG has received a formal invitation to be an observer organisation at the US Pharmacopoeial Convention. The organisation is looking for European candidates for the USP Council of Experts and Expert Committees to serve for the period of 2015–2020. Anyone wanting to impact public health, share expertise and collaborate with colleagues worldwide and add to their career experiences can apply online during the coming year (www.usp.org/) Please let us know if you are a member of your National Association within EIPG and are applying to become an expert for the USP.

Future training opportunities

Discussions are underway between EIPG and representatives of a training company which covers Qualified Persons (QP)/quality, Quality by Design and biopharmaceuticals aimed, in particular, at professionals who are working in companies operating in niche areas. The aim is to offer on-demand training for the members of EIPG Associations and those who visit our EIPG website.

October EIPG Bureau Meeting

The President and Treasurer's visit to Bulgaria was reported and practical aspects of the General Assembly 2014 were considered. A series of points on medicines shortages were drafted including the working of Article 126A. The European

Medicines Agency's (EMA's) dedicated facilities workshop attended by Piero Iamartino (VP, Italy) was discussed.

European Commission

Representatives of EIPG and the community and hospital pharmacists (PGEU and EAHP) attended a meeting with Dr Patrizia Tosetti, DG SANCO, to discuss medicines shortages. Various EIPG concerns were raised and some suggestions were made to her.

EMA

a. Comments on the Revision of the GMP guidelines

EIPG submitted comments on the Revision of the GMP guidelines (Annex 16) on certification by a QP and batch release.

b. Interested Parties Meeting

Claude Farrugia (VP, Malta) attended on behalf of EIPG. The EMA Workplan was discussed and David Cockburn, chair of the meeting, confirmed that cooperation and collaboration with industry is one of their fixed topics for consideration.

Presentations were made by representatives from Rx-360 and EXCiPACT on their auditing programmes, supply chain security and certification scheme for active pharmaceutical ingredients (APIs) and excipients.

APIC, the APIs Committee presented on their development of a "how to do" document to help industry to comply with Good Distribution Practice for APIs. A representative from EFPIA requested clarity on the

interpretation of several requirements for Good Distribution Practice. Further information will be published on the discussions held during this meeting.

c. Dedicated Facilities Workshop

A report from Piero Iamartino (VP, Italy) who participated on behalf of EIPG is as follows.

The revised versions of EU GMP Chapters 3 and 5, together with the EMA-proposed guidance about a toxicological tool in evaluating dedicated manufacturing facilities, were discussed between EMA, its regulatory partners and the representatives of industry coordinated by EFPIA. The need to set health-based limits and to adopt Quality Risk Management principles were agreed among all participants. However, industrial representatives requested a more flexible approach, though always being adequately justified. Amendments of the text were requested for IMPs (low toxicological data available), APIs (specific guidance to be added), genotoxic materials (threshold limit to be in line with ICH M7).

According to industry, a suitable implementation period is necessary for existing products, while the application to "new products" (definition still to be clarified) could start with usual timeframes after the guidance has been finalised. Authorities will provide a revision of the three documents and a second public consultation is expected to be held in 2014.

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Regulatory Review

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when further clarification on specific good manufacturing practice topics is required relating to the manufacture of unlicensed medicines. It does not replace any of the requirements already contained in Guidance Note 14.

International WHO

Good trade and distribution practices for pharmaceutical starting materials (revision)

A number of recent incidents have created awareness of the need for further improvement of the present guidelines. A new draft has been issued to a restricted audience for comment.

For further information on these and other topics we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications. To subscribe to this monthly news service contact info@euromedcommunications.com

events

JANUARY

21-23 January 2014 – Frankfurt, Germany

Clinical Supply Chain
www.pharma-iq.com

22-24 January 2014 – London, UK
Understanding and Preparing the Quality and Pharmaceutical Module

www.pti-global.co.uk

28-29 January 2014 – Berlin, Germany

Protective Packaging Solutions for Pharmaceutical Product Stability

www.gmp-compliance.org

28-29 January 2014 – London, UK
Joint Regulators/Industry Q&D Workshop

www.pda.org

28-29 January 2014 – Washington, Dc USA

11th Annual Pharmaceutical Compliance Congress

www.cbnet.com

FEBRUARY

4-5 February 2014 – London, UK
EU Biosimilar Registration and Marketing Requirements

www.pti-global.co.uk

6 February 2014 – London, UK
Developments in Analysis of Orally Inhaled and Nasal Drug Products

www.jpag.org

11 February 2014 – Manchester, UK

Good Clinical Practice Symposium

www.mhra.gov.uk

18-19 February 2014 – Brussels, Belgium

6th Annual Disposable Solutions for Biomanufacturing

www.pharma-iq.com

18-19 February 2014 – Berlin, Germany

Pharmaceutical Microbiology

www.pda.org

18-20 February 2014 – Munich, Germany

6th Disposable Solutions for Biomanufacturing Summit

www.disposablebiomanufacturing.com

24-25 February 2014 – Washington Dc, USA

2014 Aseptic Annual Conference

www.ispe.org

24-27 February 2014 – Montreal, Quebec, Canada

12th Annual Cold Chain GDP & Temperature Management Logistics Summit

www.coldchainpharm.com

25-26 February 2014 – Barnard Castle, UK

Cleaning Validation

www.honeyman.co.uk

27-28 February 2014 – London, UK

Process Validation for Pharmaceutical Products Regulated by EMA & FDA – Balancing Science and Risk during the Product Lifecycle

www.management-forum.co.uk

MARCH

4-5 March 2014 – London, UK

Clinical Outsourcing & Partnership World 2014

www.healthnetworkcommunications.com

11-12 March – Brussels, Belgium

Parenteral Packaging

www.pda.org

13 March 2014 – London, UK

The Pharma Summit 2014 – Reinventing Business Models and Markets

www.economistconferences.co.uk

17-18 March 2014 – London, UK
Distribution of Medicines – The New EU Good Distribution Practice Guide...Are You Prepared?

www.management-forum.co.uk

14 March 2014 – London, UK

Good Clinical Practice Symposium 2014

www.mhra.gov.uk

24-26 March 2014 – Heidelberg, Germany

ICH Q7 Compliance for APIs Manufactured by Chemical Synthesis

www.gmp-compliance.org

25-26 March 2014 – Lyon, France
Modern Biopharmaceutical Manufacturing

www.pda.org

26-27 March 2014 – Frankfurt, Germany

4th Annual Pharma Packaging & Labeling Forum

www.flemingeurope.com

26-28 March 2014 – Barcelona, Spain

19th Congress of the EAHP: The Innovative Hospital Pharmacist – Imagination, Skills and Organisation

www.eahp.eu

31 March-3 April 2014 – Lisbon, Portugal

9th Pharmaceuticals, Biopharmaceutics and Pharmaceutical Technology World Meeting

www.apv-mainz.de

APRIL

1-4 April 2014 – Barcelona, Spain
World Generic Medicines Congress Europe 2014

www.healthnetworkcommunications.com

1-4 April 2014 – Barcelona, Spain
Biosimilar Drug Development World Europe

www.healthnetworkcommunications.com

2-3 April 2014 – Prague, Czech Republic

10th Annual BioProcess International European Summit

www.informa-ls.com

2-3 April 2014 – Barcelona, Spain
World Generic Medicines Congress Europe 2014

www.terrapinn.com