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**Cover photo:** Oral drugs (see In a nutshell - improving biopharmaceutical performance of oral drug products on page 6).
In a departure from the norm, the President Jean-Pierre Paccioni has allowed me the honour to present this edition’s editorial. As immediate Past-President, I would like to acknowledge the hard work, commitment and resources that Jean-Pierre has injected into the EIPG. As I write this document, I can tell you that the General Assembly in Bulgaria is shaping up to be a great event with some first class speakers and, importantly, we are growing in number and in influence. One of the reasons for writing this editorial is to highlight one of the areas of interest for EIPG, and that is drug shortages, their causal factors and, more importantly, how we provide solutions to this problem.

Recently, I was asked to participate in a panel debate on the threat of anti-microbial resistance and what could be done to avert what seems to be an impending disaster to clinical health. Not wanting to dwell on the past and to propose solutions, I was, however, quite surprised to listen to how the global widespread use of antibiotics in veterinary and farming has been one of the major causes of resistance developing – in fact, the Lancet has quoted that antibiotic resistance has now been observed in the polar bear in Svalbard!

The debate focused on how the industry can generate new antibiotics when the climate of antibiotic stewardship and the restriction of usage mean that a viable reimbursement model does not exist, and are not conducive to stimulate research in this area. So what is happening in this area to help the discovery and development of new antibiotics?

Well, in the USA, the Food and Drug Administration (FDA), as part of the FDA Safety and Innovation Act, has introduced the Generating Antibiotics Incentives Now (GAIN) Act. Under GAIN, the Agency can designate an antibiotic as a qualified infectious disease product (QIDP). QIDP status provides priority review and a 5-year extension of market exclusivity if approved. To date, 30 QIDP designations have been granted. In addition, last year, the US Federal Government granted a $200 million fund to GlaxoSmithKline to develop new antibiotics.

In Europe, moves to deal with antibiotic resistance are afoot and are very visible with the Innovative Medicines Initiative (IMI) funded by the European Federation of Pharmaceutical Industries and Associations. IMI is the biggest public–private initiative in Europe. It is distinct from the EU framework programmes and aims to accelerate development and improve collaboration between industry and academia. It is estimated that circa 40 projects are in motion.

What was refreshing about the meeting and the intelligent discussions that resulted was that there were no recriminations but rather a collegiate spirit to do the right thing and solve this impending health crisis. As I keep telling my students, in order to predict the future look at the past. At King’s College London, we have access to the Gordon museum, and we certainly do not want to be treating infections like we used to in the pre-antibiotic era.

The EIPG will continue to play an active role in proposing solutions to drug shortages and to support the many initiatives to help with the discovery and development of new antibiotics, particularly the IMI programme.

If members would like to know more about this topic area, they are more than welcome to email me on luigi.martini@kcl.ac.uk

Let us hope that a viable solution to this global health issue is resolved sooner rather than later.

Best wishes
Professor Luigi Martini
Immediate Past President, EIPG
UNSTANDARD STANDARDS

by Michael Anisfeld

The need for a single worldwide accepted pharmacopoeia (compendium of drug quality standards) has been recognised for about 150 years when work first started in 1874 on developing the International Pharmacopoeia (IP). This harmonisation work, started over a century ago, ultimately resulted in the World Health Organization’s (WHO’s) publication “The International Pharmacopoeia”. It seems intuitively obvious that whether you are born in Albania, Canada, China, Mexico or Zimbabwe, you deserve drugs meeting the same high quality standards and this was the goal behind the establishment of the IP.

Deciding that they could not wait for the IP, which was first published in 1951, in the 1800s and early-mid 1900s, many countries developed their own pharmacopoeias with their own specifications, standards and test methods (see list of national pharmacopoeias in the appendix). This has resulted in a plethora of different drug standards. In the United Kingdom, walk into any pharmacy and the standard dosage of Acetaminophen Tablets (officially called Paracetamol in the UK) is a tablet containing 500mg of drug; while in the United States the standard dosage of Acetaminophen Tablets – the exact same chemical entity – is a tablet with 325mg of drug. Surely British headaches are not more severe than American headaches requiring higher dosages of the same drug to cure the same headache?

In 1989, the pharmacopoeias of Europe (the European Pharmacopoeia – Ph.Eur.), Japan (the Japanese Pharmacopoeia – JP) and the United States (the United States Pharmacopoeia – USP) concluded that by harmonising monographs and general test methods, tremendous savings could be achieved globally; a re-statement of what they had concluded 125 years previously. They determined that in the global marketplace of the 21st century, regulators could save dossier approval time, industry could save time and effort by the need to repeat the same test to meet different worldwide pharmacopoeial criteria, and patients could potentially receive cheaper drugs with faster regulatory approval – and perhaps the many different world’s pharmacopoeias would merge into a single Global Universal Pharmacopoeia (GUP*). Twenty-four years on after the current round of pharmacopoeial harmonisation started, what has been the progress towards this admirable goal of harmonisation between the Ph. Eur., the JP and the USP?

The current harmonisation process was performed under the collective leadership of the Pharmaceutical Discussion Group (PDG), which later associated with the International Conference on Harmonization (ICH) and published its deliberations under the ICH-Q4 Guidelines. As of September 2013, it was reported at the 3rd Global Summit on Pharmacopoeias1 that, of 35 general chapter test methods identified as candidates for harmonisation, 28 have been harmonised (80%). Of 62 excipient monographs identified for harmonisation, 43 have been harmonised (69%).

The USP lists 194 general chapter test methods while the USP National Formulary section lists about 250 excipient monographs, meaning that only about 14% of these USP general methods and 17% of the excipient monographs have been the subject of global harmonisation between pharmacopoeias. And, most strangely, the world’s most commonly used excipient – purified water – is not on the list of excipients whose monographs are to be harmonised. Clearly progress is painfully slow, but the question is why? Why have the world’s scientists and regulators not been able to speed the process of pharmacopoeial harmonisation?

How could it be that collectively hundreds or thousands of hours, or even more, of work by scientists globally has yielded such a paucity of results?

When discussing progress towards a single GUP, globally recognised by all the world’s regulators, it is generally conceded that two of the 46 pharmacopoeias currently published have the greatest impact on international commerce. These are the Ph.Eur. and the USP. Without in any way disparaging the value of the pharmacopoeias of Iran, Mexico and Ukraine (to name but 3 of the 44 other national pharmacopoeias with national legal standing but having little use outside their borders), three other pharmacopoeias also need to be taken into account in any globalisation effort – the British Pharmacopoeia widely used in over 100 countries, primarily in the British Commonwealth but an almost total clone of the Ph.Eur., the IP widely used in the developing countries of Africa, Asia and South America due to its less sophisticated cheaper test methodologies, and the Chinese Pharmacopoeia, a national pharmacopoeia but with impact on the quality of drugs used by a quarter of the world’s population.

* Author’s own terminology.
Scientifically, lack of progress towards a GUP can be attributed to three possible reasons.

a. Pharmacopoeial scientists and/or regulators cannot agree on which tests need to be performed for a specific pharmaceutical ingredient (active or excipient).

b. Pharmaceutical scientists and/or regulators cannot agree on the test parameter specifications that should be applied.

c. Pharmaceutical scientists and/or regulators cannot agree on the test methods to be used.

Any or all of these reasons might be true; and perhaps others.

The concept of a pharmacopoeia is to be a list of quality standards for drugs that were known to be safe, however, this has not always proven to be true, and it is very difficult to remove a drug listed in a pharmacopoeia once its safety is doubted. Consider Aspirin (acetylsalicylic acid), known for hundreds of years as a folk medicine used by people with assorted pains who either suck on the bark of the willow or boil the bark and drink the infusion to achieve relief. It was first chemically synthesized by Felix Hoffman in 1897, and today is listed as an active pharmaceutical ingredient in most of the world’s pharmacopoeias. Aspirin is a drug that, if it had been discovered by Dr. Hoffman in 2013, would never have been approved by any of today’s regulatory agencies due to its plethora of life-threatening side effects (the risk of Reye’s syndrome in children, gastrointestinal ulcers, stomach bleeding and tinnitus), nor be listed in any of the world’s pharmacopoeias.

Cynics might cite the lack of progress in pharmacopoeial harmonisation as due to pharmacopoeias being big business; that there are vested interests in not harmonising pharmacopoeias. Consider the ultimate conclusion of international harmonisation. If pharmacopoeias were harmonised, then, instead of each pharmacopoeia needing their own dedicated staff, the GUP, wherever it might be located, would have a single staff and a single budget meeting the entire world’s pharmacopoeia and reference standard’s needs. As with any corporate merger, the synergies would bring tremendous cost savings – not having a need for the 717 staff at USP (in Rockville and USP’s other worldwide offices and laboratories) currently incurring USP a US$216 million annual budget; or not having a need for the 260 staff at the Ph.Eur.’s Strasbourg offices and their current €46 million (approximately US$60 million) annual budget. Or, if pharmacopoeias were harmonised, then there would not be a need for different references standards (RSs) for the same drug. Legally, to claim that a drug meets the specifications of the USP, it must be tested against a USP RS, purchased from the USP. For Acetaminophen RS purchased from the USP, this costs US$210 for 500mg2. Legally, to claim that a drug meets the specifications of the Ph. Eur., it must be tested against the Ph. Eur. Chemical Reference Standard (CRS) purchased from the European Directorate for the Quality of Medicines and Healthcare, the publisher of the Ph. Eur., or its agents, at a cost of €79 for 50mg3 (equivalent at US prices as US$1068 for 500mg). How different can these RSs be for the same molecule? Both RSs underwent the same characterisation studies to become RSs, so how different can they be? Why does pharmacopoeial harmonisation not start with having the pharmacopoeial RSs being interchangeable – scientifically and legally? Surely the reason for the non-interchangeability cannot be as simple a reason as these RSs being big money-making business for pharmacopoeial authorities?

The deeper one delves into the potential for a single GUP, the more one has to question whether national pharmacopoeias really want to harmonise into a single GUP. We’ve been harmonising for 139 years – surely it is time to rapidly finish the task for the benefit of all.

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Appendix 1. National and international (shown in bold) Pharmacopoeias.

African Pharmacopoeia
Argentine Pharmacopoeia
Belarus Pharmacopoeia
Brazilian Pharmacopoeia
British Pharmacopoeia
Chinese Pharmacopoeia
Croatian Pharmacopoeia
Danish Pharmacopoeia
Egyptian Pharmacopoeia
European Pharmacopoeia
French Pharmacopoeia
German Pharmacopoeia
Greek Pharmacopoeia
Hungarian Pharmacopoeia
Icelandic Pharmacopoeia
Indonesian Pharmacopoeia
International Pharmacopoeia
Irish Pharmacopoeia
Italian Pharmacopoeia
Japanese Pharmacopoeia
Kazakhstan Pharmacopoeia
Korean Pharmacopoeia
Lithuanian Pharmacopoeia
Mexican Pharmacopoeia
Montenegro Pharmacopoeia
Norwegian Pharmacopoeia
Philippines Pharmacopoeia
Polish Pharmacopoeia
Portuguese Pharmacopoeia
Romanian Pharmacopoeia
Russian Pharmacopoeia
Serbian Pharmacopoeia
Slovakian Pharmacopoeia
Slovenian Pharmacopoeia
Spanish Pharmacopoeia
Swedish Pharmacopoeia
Swiss Pharmacopoeia
Thai Pharmacopoeia
Turkish Pharmacopoeia
Ukrainian Pharmacopoeia
United States Pharmacopoeia
Vietnamese Pharmacopoeia
IN A NUTSHELL – IMPROVING BIOPHARMACEUTICAL PERFORMANCE OF ORAL DRUG PRODUCTS

by Uwe Muenster

An active pharmaceutical ingredient (API) needs to fulfil several criteria in order to be successfully brought to a patient in medical need. Besides clinical efficacy, an acceptable safety profile and desired pharmacokinetics, certain physicochemical properties as well as biopharmaceutical performance of the API and its formulation are required.

Certainly, the most frequent physicochemical challenge for the pharmaceutical scientist is poor aqueous solubility and/or dissolution of new chemical entities, and as a consequence solubility- and/or dissolution-limited absorption. Unfortunately, it lies in the nature of the interplay between physicochemical properties of an API and the human body’s (cell’s) biology that usually the more lipophilic a drug candidate is, the higher its affinity to the pharmacological target (e.g. a human cell receptor or an enzyme).

Thus, during recent decades, pharmaceutical companies’ research and development pipelines have become more and more populated with poorly water-soluble compounds. This was especially triggered by the beginning of the era of high-throughput screening in the early 1990s. Since then, ligand-binding assays are usually performed on an API by putting the API into screening wells as a dimethyl sulfoxide stock solution, not considering at all the dissolution process of a drug from crystalline API, and all-in-all promoting the selection of compounds with poor aqueous solubility. However, it is this very dissolution process starting from crystalline API that is relevant for a market product consisting of a standard immediate-release tablet containing the crystalline form of the API. Associated risks of poor drug dissolution in the human gastrointestinal (GI) tract include lack of efficacy and an increased absorption variability, the latter representing an increased risk of side effects for drugs with a small safety window. As a consequence, enabling formulation technologies are needed that correct for poor solubility properties of respective APIs.

What does poorly soluble mean? The term poor water solubility with respect to biopharmaceutical performance has evolved over the last 20 years. Within the biopharmaceutics classification system (BCS), originally designed as a regulatory tool to decide on biowaiver approval, and which evolved in 1995, low solubility is when the highest daily drug dose does not dissolve in 250mL of aqueous media of pH 1–7. However, applying this criterion as a biopharmaceutical performance predictor of drug development candidates, the majority of pharmaceutical pipeline compounds are BCS class 2 or 4, implying biopharmaceutical performance issues. However, in practice for many BCS 2 and 4 drugs, no enabling technologies are needed. This indicates that the BCS, for the sake of patient’s safety, is very conservative on the one hand, and on the other hand may not be very useful to make biopharmaceutical performance predictions of new chemical entities.

Therefore, in 2010, a refinement of the BCS, namely the developability classification system (DCS) was proposed, in which the low solubility criterion has been lifted from 250mL to 500mL for poorly permeable compounds, and up to several litres for highly permeable compounds. A further in vitro-in vivo correlation model established in 2011 reveals pH-dependent critical dose/solubility ratios, which, when exceeded, increase the probability of the need for enabling technologies (e.g. pH 4.5, >7L and pH 7, >35L).

The main strategies to overcome solubility- and/or dissolution-limited absorption include: i) prodrugs, ii) salts or co-crystals, iii) particle size reduction, iv) solid dispersions, v) lipid systems, vi) cyclodextrins, and vii) carrier-mediated dissolution enhancement (e.g. mesoporous silica).

Prodrugs

Prodrugs with increased solubility compared to their respective poorly soluble parent drugs are chemical derivatives of the API containing hydrophilic groups, such as amino acids or phosphate esters. Usually, prodrugs do not possess any pharmacological activity, rather during and/or after absorption, they are converted quickly into the pharmacologically active compound. The conversion may happen enzymatically, e.g. by esterases/amidases, or by non-
enzy\m\textbf{emic hydrolysis}. Several prodrugs have been launched to the market, however, they possess certain drawbacks requiring increased development efforts, including a more complex synthesis and bioanalytical profiling, as well as greater efforts to secure chemical stability throughout storage and handling (e.g. certain humidity control measures needed in case of non-enzymatic hydrolytic activation).

**Salts/co-crystals**

Salts usually consist of two partners which are held together by ion bonds. In the pharmaceutical field, one binding partner is the active drug molecule, the other may be an inorganic ion (e.g. Na\(^+\), K\(^+\), Cl\(^-\), Br\(^-\), PO\(_4^{3-}\), etc.) or an ion of an organic acid (e.g. maleate, citrate).

Generally, salts tend to form from saturated solutions if the difference in \(pK_a\) of the two partnering components is >3.\(^5\) It is hoped that due to the ionic character, a salt can interact with water molecules better and faster and thus form a solution faster than a salt’s corresponding free base or acid. However, it needs to be considered that salts may initially dissolve very fast, but once in solution may, depending on \(pH\) (which would be salt-specific), re-precipitate to form the respective poorly soluble free base or acid. Even then, a salt usually still improves bioavailability, since permeability of dissolved API may be faster than the speed of re-precipitation.

Co-crystals are being engineered aiming, like salts, at a better interaction with water molecules, thus at faster dissolution in the GI tract when compared to the free form of the API. Co-crystals usually consist of partners with \(pK_a\) differences of <3, otherwise a salt would form. The field of co-crystals is not as well-established in the pharmaceutical arena as salts. A major challenge is the limited physical stability during handling and storage of co-crystals. At the time of writing, no co-crystal-containing pharmaceutical drug product has been launched to the market (excluding hydrates, solvates, and racemates, which, in the literature, are sometimes also assigned to being co-crystals), but the ever increasing research being performed in this field may soon lead to respective drug approvals.

**Particle size reduction**

Reduction of particle size is associated with an increased contact surface area to surrounding GI fluids. This allows faster dissolution of the API and leads to an increased oral bioavailability if absorption is dissolution-limited. On the other hand, particle size reduction will not increase oral bioavailability if absorption is solubility or permeability-limited. Generally, particle size reduction might be a good strategy for so-called brick dust molecules. These are molecules that dissolve neither in aqueous media nor very well in organic solvents, making them very hard to formulate with other enabling formulation strategies discussed below (e.g. solid dispersions, lipid systems).

Technical options to achieve small particle sizes (submicron) can be either top-down or bottom-up. For both approaches numerous patents exist (e.g. >1000 patents/patent applications on top-down wet-milling procedures), and several marketed products containing nanoparticles manufactured by either wet-milling or high-pressure homogenisation have been launched since the late 1990s.

In bottom-up processes, mechanical forces are applied in order to break down larger particles into much smaller particles, e.g. by wet-milling or high-pressure homogenisation.\(^5\)

In bottom-up approaches, the starting point is usually an API solution, in which, at some point, a controlled precipitation event is induced. The type of precipitation trigger may differ, and numerous precipitation techniques to achieve nanoparticles have been described. One of the broader investigated bottom-up approaches is supercritical fluid (SCF) technology.\(^7\) SCF itself can be subdivided into several subtypes of precipitation principles, one of which is the “RESS” (rapid expansion of supercritical solutions) in which the API dissolved in, for example, supercritical carbon dioxide is released through a nozzle by which carbon dioxide instantly evaporates and API nanoparticles start to form from resulting precipitation. An advantage of the SCF technology is that a fairly narrow particle size range can be achieved.

Furthermore, it might be a good method for thermolabile APIs, and no organic solvents will reside in resulting nanoparticles. However, SCF is fairly high-maintenance and, to date, no drug product is on the market based on SCF or other bottom-up precipitation methods.

**Solid dispersions**

In solid dispersions, the metastable amorphous form of the API is embedded in a polymer,\(^8\) which together with other excipients can be pressed to a tablet. Ideally, the amorphous API is physically stabilised by the polymer in a way that prevents recrystallisation for at least the intended storage time at the established storage conditions of the drug product. Since the amorphous form is always more soluble than the respective crystalline phase of an API, an increase of dissolution and hence oral bioavailability can be observed with solid dispersions, compared to standard immediate-release formulations containing the crystalline API.

Two main manufacturing strategies are usually applied within the industrial setting, namely melt extrusion and solvent evaporation processes, both extensively described in the literature, and several solid dispersion drug products having been launched to market within recent years. Even though the basic principle has clearly proven that it does its job, certain physicochemical API properties are required to enable manufacturing of solid dispersion...
drug products. For example, for solvent evaporation-based processes, sufficient solubility of the API in organic solvents used for the manufacturing process is required. For hot melt extrusion, the API needs to be thermally stable, and for both processes a certain miscibility of the API with respective polymers is a prerequisite. If there is not a certain miscibility, recrystallisation of the API might occur at some point, leading to unreliable drug product performance.

Lipid systems

Lipid systems are usually capsule drug products which contain the API dissolved within liquid or semisolid excipients. Depending on the lipophilicity of the drug, the excipients used may be lipids only (e.g. triglycerides) or mixtures of lipids, co-solvents and surfactants, where the composition is optimised depending on the physicochemical nature of the API. After swallowing, the capsule opens within the GI tract, API plus excipients are released, and interaction with GI fluids takes place. With only triglycerides used as a carrier, a degradation of the lipid phase by lipase enzymes is required in order to release the API and make it available for absorption. If co-solvents and surfactants are present, a micro or nano-emulsion forms upon contact with GI fluids, ideally keeping the API dissolved for a long enough period of time in order to allow its absorption. Some of the excipients used for lipid systems may also influence drug permeability, thereby potentially promoting drug absorption not only of compounds with low solubility, but also of compounds with low permeability. However, it needs to be considered that a certain lipophilicity of the API is required to allow for sufficient drug loading. So far, only a few oral lipid system drug products are on the market, but with increasing knowledge on lipid system excipients, further launches can be expected in the future.

Cyclodextrins

Cyclodextrins can form inclusion complexes with the API at various ratios, with an inner hydrophobic cavity in which the lipophilic API is bound on the inside, and an outer hydrophilic surface allowing interaction with surrounding GI fluids. Various cyclodextrins are available for formulation design. Of these, mostly beta or gamma cyclodextrins, or derivatives thereof (e.g. hydroxypropyl- or sulfobutyl-beta cyclodextrin), are being used since they exhibit a high solubilisation potential of lipophilic API in aqueous media. Various drug products have been launched utilising the solubilising power of cyclodextrins (e.g. Pansporin T, Ono Sporanox, and other).

Mesoporous silica

Mesoporous silica (MS) consists of SiO\textsubscript{2} polymers manufactured on structure-directing templates, where pore size can be controlled in the nanometre range. The API is then layered into these pores, e.g. by stirring of MS polymer in a concentrated API solution. The high pore volume and surface area (e.g. 700m\textsuperscript{2}/g) allow rapid dissolution of the API. Advantages are high drug loading potential (up to 50% drug load without API crystallisation has been shown), little API–carrier interaction (thus might work for brick dust), as well as promising thermal and mechanical stability. However, MS is hygroscopic which might interfere with downstream processing. Thus far, there is no MS-containing pharmaceutical product on the market.

Summary

Altogether, in parallel to the steadily growing number of poorly soluble drug candidates, numerous strategies have evolved from chemical and pharmaceutical laboratories in order to overcome poor biopharmaceutical performance. As a consequence, attrition arising from lack of absorption caused by low-solubility/dissolution only accounts for a small proportion of all attrition reasons (only 5–10% of attrition is related to poor biopharmaceutical performance). However, with further exploration and expansion of chemical space during lead optimisation programs, innovation from formulation scientists is continuously required to support development and guarantee a reliable biopharmaceutical performance of complex new chemical entities.

References

THE YOUNG BIOPHARMACEUTICAL COMPANIES USE AND DEPENDENCE ON CMO/CRO

by Jan Gunnar Gustafsson

The big pharmaceutical companies were previously performing all steps from discovery research to commercialisation. Today the big pharmaceutical companies are organised to perform mainly phase III studies and commercialisation. Big pharma companies have a strong organisation for marketing and selling the products. They also have the resources and capital to perform manufacturing of the drugs, either in their own facilities or at a Contract Manufacturing Organisation (CMO).

Present situation

It has become difficult to obtain funding as venture capital is more interested in projects with short development time. In particular, it is especially difficult to obtain funding for the costly step of going from discovery phase to toxicology/phases I, when good manufacturing practice (GMP) is required. For phase III, big pharma can purchase or fund the project. The project has to fulfil the regulatory, clinical, market and chemistry, manufacturing and controls (CMC) requirements to have the possibility to be sold, meaning that the manufacturing process has to fulfil the requirements for scale up/commercial manufacturing (industrial), specification, GMP and regulatory requirements. The cost of goods sold (COGs) requirements can be a deal breaker; it is a critical issue for the profitability of the drug. That these criteria are fulfilled is crucial for the project to be interesting for sale.

However, many new products are originating from small young, start-up companies that are creative and fast moving. Being strong in medical research, they can generate ideas for new treatment and products. These small companies do not have these resources and know-how; they are dependent on support from CMC, a Contract Research Organisation (CRO) and consultants.

Requirement to be successful

Pharmaceutical development requires know-how in the scientific, regulatory, industrial and clinical/medical fields, as well as knowledge of the diseases and patient group the product will be registered for, total number of patients and the number that can be treated with the drug, meaning market size and potential income. There are not many industrial sectors where the requirements on the small/young companies are as high as on the pharmaceuticals companies, especially for a biopharmaceutical company. The companies are often started by physicians and/or scientists who, even if they have the medical know-how, do not necessarily know how to define a drug for the market and define the patient population the drug will be used to treat. The companies are developing a commercial drug; therefore, they also have to understand the business development requirements. Moreover, most companies have limited or no previous experience in the development of biopharmaceuticals concerning process development, manufacturing, and regulatory and competent authority requirements.

Business model, Virtual company

Those companies are operated as virtual companies, meaning that all operative activities are purchased, avoiding the cost for laboratories and manufacturing facilities which have to fulfil the GMP requirements. The company needs to have the know-how to define that to purchase, which they normally do not have, making them vulnerable to making the wrong decision and also increase the problems for getting funding for their projects. If their project fails, so does the company. This is also a risk for the CMO, for not getting paid for their service. The project has to be carefully evaluated before the decision to start the project. It is an all or nothing situation, either it is a viable project so perform it, or if the there are too many question marks, do not start. Medium-size companies, having their own R&D, have to have a number of projects in development. They cannot depend on one project.

All these companies need a management with experience and a strong drive for product development. For a company started by scientists, it is important to have a management that can take the company from science driven to product driven.

Medical need, market

The product under development...
has to fill a medical need. There has to be a market for the product and a market that can and will pay for the product when on the market. For the project to be interesting for purchase, it has to have good profit margin, no competition from similar/better products or products under development.

**Process development, QbD**

The traditional way to handle the process development for a drug project is to use the process that has been developed for creating the substance for Proof Of Concept (POC) in animals. The methods used during early development are not suited for market, so there are always huge demands for modifications. The process development is often driven by the accelerated quality demands and the development is performed stepwise without a proper plan and with no control of either the cost or the goals. It is an expensive way of conducting process development as it is reactive not proactive. It will not give an optimal process and will not take into account a low COGs and an industrial process.

The same tradition is also true for the analytical methods development. If the analytical methods have been of low quality, the new developments for phase III will probably show new/higher amount of impurities, meaning process development has to be done again. After POC in man (phase II), the focus should be on final tuning and validation of the process. If the analytical method development is done by the quality by design (QbD) concept, the knowledge of both accuracy and precision are much more secure than if one just uses an old method. By focusing on both methods and specifications early on in a development project, the knowledge about both methods as well as the substance are much more reliable than when trying to solve the problems/questions as they come by.

More reliable knowledge about both substance and impurities is an essential tool for process development. The process development could never be better than the analytical knowledge.

By knowing the substance early on, the chances for nasty surprises are reduced. Focusing on a well-designed process as early as possible during the project development is naturally a risk, investing both time and money in a project that may then fail at a later stage. However, the benefits for the project, should it be successful, motivates the risk. Therefore, one needs to be careful and critical in the choice of projects to develop further. After deciding to develop a project, plan for success and start all (assignment, investments, collaboration and so on) that is required for successful development of the project. However, if the required know-how is not available, seek professional help with the decisions on what to start.

Characterise the Master/Working Cell Bank, active pharmaceutical ingredients (API) and drug product (DP – final product) from each clinical phase to ensure that comparability is maintained during the clinical phases and different manufacturing sites if/when manufacturing has to be moved after POC. The characterisation should include potency measurements, preferably by a bioassay/cell line. Development, manufacturing and characterisation have to be well documented.

The process used to produce the drug for clinical phases I and II has to be designed in such a way that, after modification, a COGs level within the range that the product gives a good profit margin is obtained, by planning from project start.

The virtual company has to develop a manufacturing process fulfilling these requirements. This has to be done by the CMO, and understood by the purchasing company. They, therefore, have to choose a CMO that can deliver that service, understood from the start, without having the required know-how – a catch 22.

**QbD**

The developed process has to fulfil requirements for commercial manufacturing, in the scale required. Thus the quality of the product has to be planned and designed, namely QbD.

QbD is often seen as an expensive way to develop an early project. However, in the long run, it is quite the opposite. The smart design of the process for the API and DP secures the quality of the product. The quality is not created by analysing the final product. Thus, QbD is a structured way of doing process development, gives a required understanding of the process chemistry, and creates the control strategy. It can also reduce the timeline for authorities’ handling of your applications, and help to possibly achieve a low COGs.

**CMO deliverables**

If the assignment is based on activities, it is probable that new activities will have to be added to achieve the goal. This will add costs and burn rate during performance of the added activities. It will require that the purchasing company have the capital for the added costs. Increased costs can also create problems with funding of the project. Deliverables, and not activities, should be defined. If the assignment is goal driven, there will be no added costs and no added activities as long as the scope of the project is not changed. This makes it easier to get funding, as investors know what they will get for their investment.

**COGs**

The COGs for commercial manufacturing is one of the critical success factors. They should be calculated in such a manner that, once the product is on the market, it will generate a reasonable profit. One should also bear in mind the risk of potential competition. Thus, COGs should be set at the start of the project or, even better, as part of the evaluation of the project before the decision to start. The COGs figure should be a
requirement for the process development goals. The COGs figures should be verified for the current and upcoming phases, including commercialisation, once a year or if new competition arises. For commercial manufacturing, it is of utmost importance and can be a deal breaker.

**Regulatory**
The regulatory requirements must be part of the project from the start. It should be ensured that the project under development will fulfil all authority requirements, making the process for approval for clinical trials and registration as fast as possible. The company should have a regulatory person/department with up-to-date know-how, including process know-how. Alternatively, the company should use a consultant.

It is also a requirement to understand the process chemistry and describe this in the applications. If QbD has not been used, the data that would have been generated by the QbD approach must be in the application, as specified in FDA requirements. The companies do not have to understand the process chemistry described in the applications, but they are responsible for the content as the project/product owner.

**Manufacturing**
The chosen CMO for the commercial manufacturing should be inspected by the authority and approved by the countries in which the product will be marketed. The CMO should also have an organisation, experience and interest in commercial manufacturing, and have the required capacity and scale for long-term manufacturing according to the product requirements. All handling, from purchase of raw material to API/DP should be performed according to specifications and GMP. The CMO should also be able to perform the analytical methods and characterisations as required, and have the scientific and industrial know-how needed to manufacture the product.

**IPR**
For the project to be of interest and be purchased at a reasonable price, there must be some form of patent protection. A strong patent portfolio will increase the value of the project and generate commercial interest. Therefore, it is important to protect the patent right, not giving royalty rights as part of payment for development cost. When working with a CMO, Intellectual Property Rights (IPR) must be regulated in the assignment. Generally, no IPR should pass over to the other company as a result of the assignment.

**Patent issues**
The API process can be difficult to protect by a patent. It is better to avoid publication of the process in the form of a patent application, since it can be difficult to protect a process patent from infringement. It would probably require prosecution of the company accused of the infringement to be able to prove that this is the case, which is risky and expensive if you are unable to prove it or are wrong.

The formulation can, in many cases, be protected by a patent. The product has to be described in the drug description, therefore, there is no difference to have the formulation described in the patent application. Furthermore, it is easier to prove that patent infringement has occurred.

**Assignment**
The contract should be evaluated from a scientific point of view to ensure that it covers your needs, and should be based on deliverables, not activities. Take professional help with the drafting of the assignment and the assignment negotiation. If the CMO's assignment draft is used, ensure that it clearly states the CMO responsibilities. In case of failure, how will it be handled? Cost, payment schedule, deliverables, project plan, IPR, specification, audit rights, termination rights and quality agreement should be included in the assignment.

The quality agreement should be added to the contract, as an attachment, approved by the involved legal persons who have the legal responsibility for the main agreement, therefore, ensuring the two documents are in agreement. Termination rights are difficult; spend time on getting it right for both parties. The legal, scientific and specification parts are of utmost importance for success. They require knowledge from the customer, something that the smaller/younger company seldom has, and, therefore, the assignment is then based on deliverables.

Clearly define the responsibilities and the next step if one part fails. Refund? New batch? When? Can a booked time slot for manufacturing or a study be moved? Make a plan for handling these situations. The assignment should reflect and take into account the situation where the parties disagree. It is the only time the contract is needed. Take professional help with evaluation and negotiation.

**Collaboration, win-win**
For a successful collaboration, the involved companies must understand each other and what is of importance to each company. The CMO should understand what the customer needs, and the customer should understand what they need and what they will get. If there is any doubt, get help from external consultants. Both parties must receive what they need from the assignment to regard it as a success.

**Conclusions**
Young small biopharmaceutical companies are required for generating new pharmaceutical projects for big pharma to license for commercialisation. It requires a CMO/CRO that can develop, manufacture, regulate and conduct clinical trials for these companies. Since the CMO/CROs have the required know-how and the
purchasing companies do not have such know-how, the CMO/CRO must deliver defined goals, not activities. The CMO/CRO has to take on the risk of delivering a defined process and manufacturing of API/DP, not activities, at a fixed price and to a predetermined timeline. The pharmaceutical industry and investors rely on such collaboration. If such collaborations do not exist, there is a risk of a reduction in the development of new drugs, leading to increased costs for healthcare. However, there seems to be moves by CMO/CROs in the right direction. To support small biotechs is important for the CMO, big pharma, the whole pharmaceutical industry and society. With this, there is the opportunity to reduce medical costs and satisfy patients’ needs. The pharmaceutical industry must take care of their babies, the small biopharmaceutical companies, and ensure that they can grow up.

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DIVISION OF LIABILITY BETWEEN PHARMACEUTICAL COMPANIES AND SUPPLIERS USING THE EXAMPLE OF THE LAW IN THE FEDERAL REPUBLIC OF GERMANY

by Martin Wesch

Liability systems

German law distinguishes between liability and warranty. Liability deals with statutory entitlements that may exist between any parties. Warranty laws are only possible between parties to a contract. Pharmaceutical companies and suppliers are, on a regular basis, parties to a contract. Accordingly, questions as to both liability and warranty may arise between them.

Warranty laws exist in cases of defective products which are delivered in violation of the obligations under the contract. A product is defective if it does not contain the characteristics as agreed upon in the contract, or if it does not comply with the contractual purpose. Warranty laws provide the right of conversion, abatement or compensation for damages as a result of non-performance.

Statutory liability has two pillars: tortious liability and strict liability. Tortious liability is based on the violation of an obligation incumbent upon every person to ensure safety. This is the case, for example, if one slips on a banana skin or on a freshly cleaned and subsequently slippery floor. In such cases, the defective cleaning could – in the case of the banana skin or the lacking notice of danger – constitute a violation of an obligation to ensure safety.

The violation of law would have to have taken place illegally. The violation of law is given in the lack of grounds of justification. Let us assume that someone had thrown another person into the river Thames. This would, in fact, constitute bodily injury and consequently a violation of law. If, however, the affected person had previously taken away the wallet of the other with the support of Smith & Wesson, the violation of law could be justified.

Moreover, the behaviour has to be at least negligent. An individual parameter always applies in such cases. Organisations as well as companies can be executed by disclosing the careful selection, instruction and monitoring of their personnel. It is often the case that negligence – from the injured party’s point of view – cannot be proven in a court room. Not least as a consequence of this, the member states of the European Union (EU) agreed upon the Directive for product liability¹. Consequently, it is envisaged that consumers who have suffered damage be granted entitlements irrespective of negligence in cases of defective products.

On the basis of the above, the EU Product Liability Directive was adopted in the Federal Republic of Germany in 1989. This grants legal claims which provide a link to endangering elements of an offence. The endangering element as such is accepted by the company in the case of so-called typical social behaviour. Such cases are, for example, the operation of a rail or airline company, the participation in road traffic, the operation of an atomic power plant, the putting into circulation of products and, in particular, drugs. The latter is provided for in the Federal Republic of Germany by the Medicinal Products Act.

Consequently, the strict liability system in accordance with the Product Liability Act or in accordance with the Medicinal Products Act merely provides a link to the putting into circulation of a defective product. This results in liability claims, which have an upper limit in individual cases up to €600,000 or an annual pension in the sum of €36,000². In the case of damage suffered by several parties, the upper liability limit is set at €120 million or pension payments of €7.2 million annually. The companies subject to strict liability must take out insurance coverage against these risks³. In contrast to tortious liability, the liability is not subject to contrary agreement⁴.

Allocation of risks

This raises the question of how the liability between the pharmaceutical company and the supplier can, if at all, be divided. Is the pharmaceutical company liable in any case irrespective of whether the negligence applies to the company or not? It is also the case that this liability cannot be limited or
excluded by way of contractual agreements. However, the statutory regulations of strict liability merely provide for the claims of third parties, in particular consumers. This is the liability in an external relationship which cannot be amended. In the case of an internal relationship between a pharmaceutical company and its supplier, the liability can well be divided. Negligence aspects also play a role here. With regard to liability of the participating parties among themselves, liability division applies according to the law whether the damage was largely caused by one or the other party.

However, the causal contributions are usually disputed. In such cases, quality assurance agreements have the effect of clearly distinguishing between the responsibilities of the participating manufacturers. Consequently, it serves as a division of liability. Pharmaceutical companies may transfer the overall responsibility for a product for the bought-in outside services, which is incumbent upon them in the capacity of manufacturers of finished products, to the supplier. In such cases, regulations pertaining to the burden of proof frequently play a role. Following the delivery of a product, it is often unclear whether a product defect has occurred on the premises of the manufacturer of the finished product or on the supplier’s premises. In quality assurance agreements, the burden of proof can be turned around. The supplier is then required to furnish proof of a flawless production if he intends to ward off product liability within an internal relationship.

The scope and limits of such liability agreements arise on the basis of the transferability of the obligations to ensure safety. The liability precedes the assumption of obligations by the supplier. Strict and tortious liability are the same in such cases. Insofar as it is possible to transfer tortious obligations to ensure safety to the supplier, the same can also assume strict liability within an internal relationship. The transferability of obligations to ensure safety is limited in the law pertaining to the regulation of General Conditions and Terms of Business. According to the same, no agreements may be made which constitute an unreasonable disadvantage to the contracting party. An unreasonable disadvantage is given if an agreement with a considerable basic idea of a statutory regulation cannot be reached. This would be the case, for example, if a supplier is held responsible for the risks of his product even if he cannot exert an influence upon such products.

Mistaking a package for another or damage caused to such a package can also occur at the drug company. A regulation that did not take this into account would, insofar, be invalid.

It is also the case that the transfer of obligations to ensure safety may not itself take place contrary to the duty under the contract. Obligations to ensure safety may impede this. These call for the drug companies to select their suppliers initially according to their ability to perform a quality service. Otherwise, the manufacturer of the finished product must completely monitor the supplier or the supplied products. Only in dealings with a company known to be reliable and professional, can a special supervision by the manufacturer of the finished product be dispensed with. The release from one’s own responsibility is conditional on the fact that the supplier offers a guarantee for the adherence to the required safety precautions. Consequently, it is not sufficient to select a supplier on the basis of price and schedule criteria. A supplier’s capability to provide a quality performance is crucial. The manufacturer of the finished product must verify this capability and should not be satisfied with the supplier merely giving the assurance that he shall perform the work professionally.

In addition, obligations to ensure safety must be described in detail. The pharmaceutical company is, insofar, under the obligation to provide the packaging manufacturer with precise details of the type of quality assurance measures. The obligations to ensure safety must, therefore, be agreed upon in detail. Of course, it is possible in the field of drug production that the procedural provisions of good manufacturing practice (GMP) which applies to drug manufacturers also be stipulated for suppliers.

Ultimately, the supplier must be willing and in a position to perform the tasks assigned to him. This requires that insurance coverage be taken out regarding the product liability risks. An internal exemption from liability only applies to the extent to which the assuming party can actually cover risks resulting from the same.

Economic purpose

The transfer of obligations to take care to the supplier produces pecuniary advantages. On the one hand, recourse is made available to the supplier. These rights of recourse can also be asserted. Furthermore, the tortious liability extends beyond that of strict liability in accordance with the Medicinal Products Act. The liability is not subject to an upper limit. Claims for damages for non-material damage, in particular compensation for pain and suffering, are also included. Insofar as the tortious liability extends beyond the strict liability, the supplier is solely liable; in other respects secondary, but he is ultimately liable. The drug company can find relief in this respect from the risks of the bought-in partial products.

The transfer of obligations to ensure safety also simplifies the movement of goods. The drug company can restrict its inspection of incoming goods to a minimum. This merely requires that incoming goods deliveries be inspected regarding easily detectable variations from the contractual agreements. This includes obvious defects, shortages and wrong shipments. The superficial inspection of a sample of a batch...
can, therefore, be sufficient. However, less should not be carried out. Otherwise, the drug company could be charged with the violation of an obligation to which it is subject in accordance with the law at least as regards the incoming goods. Consequently, the flat-rate elimination by way of an agreement of any kind of incoming goods inspection is not permissible\textsuperscript{17}. In such a case, the drug company would jeopardise the entire purpose of a quality assurance agreement of keeping its warranty laws and transferring liability risks to the supplier. In this respect, not too much is expected of the drug company – as is the case with any other manufacturer of finished products. It is not required to carry out a 100% check. Furthermore, it need not perform representative random checks. Merely that what is easy to detect is to be verified. In the case of the inspection, for example, of a collapsible cardboard box, it will establish whether it is a wrong shipment, whether the printing ink is dry and not smeared and whether easily detectable wrong prints can be recognised.

The reduction of the inspection of incoming goods is, on the other hand, conditional on the transfer of obligations to ensure safety. The manufacturer of the finished product carries the overall responsibility for the product, including the bought-in parts. In the case of key supplier parts whose faultiness may jeopardise life and limb, this call for incoming goods to be subject to a 100% check\textsuperscript{18}. The reduction of the inspection of incoming goods in the manner described is only permissible if the obligations to ensure safety regarding the supplies are transferred to the suppliers in a legally valid manner. Fewer checks regarding incoming goods require greater checks on the part of the supplier\textsuperscript{19}. Both are linked like water levels in communicating pipes. If the water level on the one side is reduced by ram force, it will be increased on the other side by the same amount. The link between the inspection of incoming goods and the verification of suppliers is no different.

However, the drug company is not under an obligation to carry out the verification of suppliers itself (by Audits). It may transfer this to third parties\textsuperscript{20}. There are institutions which perform such tests. However, the pharmaceutical company has to check the compliance of the quality management system of the supplier with the needs of its own quality management system\textsuperscript{21}.

**Quality assurance agreements**

The economic success of the transfer of obligations can be secured by way of quality assurance agreements. Primarily, the quality requirements placed on the product, and the product and material specifications are to be stipulated therein. Furthermore, the quality assurance measures which the supplier is to carry out need to be determined. These are the obligations to ensure safety which are transferred from the manufacturer of a finished product to the supplier. The consequence of the agreement results in the exemption of liability which the supplier declares as regards dealings with the drug company. The supplier assumes the product liability for the supplies up to an upper liability limit. The supplier takes out insurance coverage against the liability risk. In addition, the supplier enables the drug company to reduce the inspection of incoming goods and undertakes to have his capability of performing a quality service verified by a professional and independent third party.

To cut a long story short, this type of quality assurance agreement results in a series of advantages for drug manufacturers\textsuperscript{22}. First of all, the quality assurance measures adopted by suppliers reduce the risk of product defects. Drug companies find themselves in a situation similar to that of airline companies. Damage which becomes public results in a considerable loss of trust. This frequently by far exceeds the material damage that is suffered. Consequently, situations like these should, ideally, not occur. Quality assurance agreements are, therefore, primarily geared towards the prevention of damage.

In addition, the capability of a supplier to provide a quality performance, which is subject to reviews, creates the precondition for a permanently reliable supplier relationship. As a result of the coordination of quality assurance measures via the preventive avoidance of errors during the verification of production processes – and even during product development – both companies move closer towards each other. This promotes trust. Both companies can build on this.

The third advantage is that the division of liability enables the drug company to largely unburden itself of the dangers of the bought-in products. This creates real cost advantages.

A further advantage is the fact that drug companies can reduce their scope of verification. This applies not only to the inspection of incoming goods but also to the verification of suppliers, which can be outsourced.

Everything is consequently in favour of transferring the implemented procedures of GMP, to which drug companies are subject by law, to suppliers, and securing this by way of quality assurance agreements. In this respect, it is envisaged that suppliers do not wait until they are approached by the drug companies. Rather, they should take the initiative to approach the drug companies and offer such agreements. Consequently, they can secure market advantages over rival companies. They should make use of this opportunity.

**References**


2. § 88 AMG, the German Medicinal Products Act. www.gesetze-im-internet.de/englisch_amg/index.html
DIVISION OF LIABILITY BETWEEN PHARMACEUTICAL COMPANIES AND SUPPLIERS continued

3. § 94 AMG, the German Medicinal Products Act. www.gesetze-im-internet.de/englisch_amg/index.html

4. § 92 AMG, the German Medicinal Products Act. www.gesetze-im-internet.de/englisch_amg/index.html


7. § 93 AMG, the German Medicinal Products Act. www.gesetze-im-internet.de/englisch_amg/index.html


9. § 3 AMG, the German Medicinal Products Act. www.gesetze-im-internet.de/englisch_amg/index.html


regulatory review

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

USA
Permanent discontinuance or interruption in manufacturing of certain drug or biological products
This proposed rule requires all applicants of covered approved drugs or biological products, including certain applicants of blood or blood components and all manufacturers of covered drugs marketed without an approved application, to notify the Food and Drug Administration (FDA) electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply of the product in the USA.

FDA and EMA launch generic drug application inspections initiative
This is a joint FDA and European Medicines Agency (EMA) initiative to share information on inspections of bioequivalence studies submitted in support of generic drug approvals. It provides a mechanism to conduct joint facility inspections for applications submitted to both agencies.

Draft guidance for industry on size, shape, and other physical attributes of generic tablets and capsules
FDA is concerned that these characteristics of generic drugs are too varied compared to the originator drug and could affect patient outcomes.

Europe
Q&A on Design Space Verification
Following the EMA and FDA joint evaluation pilot, there are agreements on a wide range of quality by design (QbD) elements. The joint Q&A document reflects harmonisation on some QbD aspects. Of the 9 Q&As, the first 6 cover common expectations. Two separate EU expectations are covered by questions 7 and 8 and those for the FDA by question 9.

Report on personalised medicine
This addresses the progress made in personalised medicine and the opportunities and challenges it presents for healthcare systems. It recognises the potential for personalised medicine to offer new treatment opportunities, better targeted treatment, avoiding medical errors and reducing adverse reactions. It recognises the challenges to its successful incorporation into healthcare systems.

AEDs: changing products
Concerns about switching between different manufacturers’ products of antiepileptic drugs (AEDs) have been raised by patients and prescribers. These include switching between branded original and generic products, and between different generic products of a particular drug.
The UK Commission on Human Medicines advised that AEDs could be classified into three categories, based on therapeutic index, solubility and absorption, to help prescribers and patients decide whether it is necessary to keep using a supply of a specific manufacturer’s product.

Statements of non-compliance with GMP now publicly available in EudraGMDP
These statements of non-compliance with good manufacturing practice (GMP) contain information on the nature of the non-compliance and the actions taken or proposed by the issuing authority in order to protect public health.

EU GMP Guide
Responses to proposed changes in the EU GMP
The European Commission (EC) has published comments from interested parties regarding the following proposed changes to the EU GMP:
- EC Medicinal Products GMP Guidelines Part I, Chapters 3, 5, 6 and 8.
- The formalised risk assessment for ascertaining the appropriate GMP for excipients of medicinal products for human use.
- The draft guidelines on the principles of good distribution practice (GDP) for active substances for medicinal products for human use.
- The revision of Annex 16: Certification by a Qualified Person and Batch Release.

Revised Guidelines on GDP for Medicinal Products
This 5 November 2013 version replaces that of March 2013 and corrects factual mistakes identified in subchapters 5.5 and 6.3. It also gives more explanations on the rationale for the revision. Both take into account recent advances in practices for appropriate storage and distribution of medicinal products in the EU, as well as new requirements introduced by Directive 2011/62/EU.

MHRA
Self-inspection and data integrity
The Medicines and Healthcare products Regulatory Agency (MHRA) requires pharmaceutical manufacturers, importers and contract laboratories to review the effectiveness of their governance systems to ensure data integrity and traceability and will check this during 2014 inspections.

Voluntary parallel scientific advice with NICE and the MHRA
Licence applicants may request a joint scientific advice meeting with National Institute for Health and Care Excellence (NICE) to discuss their...
development plans for medicinal products. This process offers:
- a guaranteed face-to-face meeting with both organisations together,
- discussion of clinical study(s) design that will be used to satisfy regulatory and NICE requirements,
- optional advisory input from Clinical Practice Research Datalink.

International Revised PIC/S GMP Guides
Revisions of these two Pharmaceutical Inspection Cooperation Scheme (PIC/S) Guides to Good Practices for the Industrial Manufacture of Distributed Medicinal Products and Preparation of Medicinal Products in Healthcare Establishments will enter into force on 1 March 2014.

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news from the EIPG

Bureau meeting
During their January meeting, the Bureau discussed education and financial matters, and the final draft of the Domestic Rules, which will be voted on by delegates in April. As well as the Bureau members, the meeting was attended by the Bulgarian Industrial Pharmacy Association (BIPA) representative Evgeni Grigorov. The format and agenda for the 2014 General Assembly to be held on 12–13 April in Sofia were agreed. BIPA announced the arrangements for a Scientific Symposium on Clinical Trials Research to be held on Friday 11 April.

European Commission
The European Commission has launched the public consultation on the revision of European Commission Guidelines on GMP, Annex 15: Qualification and Validation. The consultation document is available on the Commission’s website. Industrial pharmacists belonging to Member Associations should provide feedback to their representative by 1 April in order for EIPG to consolidate its response to the Commission.

EMA’s meeting with interested parties
As mentioned in the last issue, Claude Farrugia represented EIPG at the meeting of the European Medicines Agency (EMA) Inspectorate with “interested parties” on 28 November and the following is a summary of his report.

David Cockburn, Chairman of the Inspectors Working Group opened the meeting. The main topics of discussion were the burdens on the industry in terms of auditing and the applications of the latest good distribution principles for active pharmaceutical ingredients (APIs) and finished products alike.

The EMA update on their work plan provided a summary of the present position on GMP and GDP guidance.

Final and upcoming final guidelines
GMP Guide Chapter 2
GDP Guide for Finished Products
GMP Guide Chapters 3, 5, 6 and 8
GMP Guide Annex 16
GDP Guide for Active Substances

Upcoming public consultations
GMP Guide Chapters 3, 5, 6 and 8
GMP Guide Annexes 15 and 17
GMP for excipients

EXCI-PACT delivered a presentation on a proposed Certification Scheme to help reduce the audit burden for pharmaceutical excipient users and suppliers. This was followed by a presentation by Rx-360, who outlined their proposals for a role in supply chain security and audit burden sharing. Two presentations on GDP were then delivered; the Active Pharmaceutical Ingredients Committee first presented an update on their draft guideline on GDP for APIs, followed by a presentation by the European Federation of Pharmaceutical Industries and Associations (EFPIA) on implementation questions on the latest GDP guidelines for medicinal products.

In the course of the latter presentation, Claude Farrugia supported the EFPIA call for clarity and common understanding. In particular, he referred to the EFPIA call for science and risk-based approaches in the determination of temperature control and the establishment of qualification of transport routes, and stressed that, whilst such approaches were acceptable in terms of the supplier’s obligation with regards to storage conditions during transportation, one also had to be cognisant of the need for Responsible Persons to be able to verify such storage conditions prior to release to saleable stock. In this regard, common interpretations by players in the pharmaceutical supply chain and by inspectors, especially where cross-border movement of medicinal products was concerned, were crucial. He also called on EMA to clarify the GDP guidelines with regards to the conditions under which returns of medicinal products to wholesale dealers could be released to saleable stock, and was informed that such a clarification had indeed been addressed in an update to the GDP guidelines that was published in the same period.

Education PHAR-IN
The kick-off meeting of PHAR-IN, the project looking at competencies and coursework in the field of biotechnology, was held on 20 December 2013. Vitor Sousa (Areta International, representing an SME) Gunther Pauwels (Genzyme, representing a large company) and Jane Nicholson (EIPG) attended the meeting with a number of academics, including Professor Bart Rombaut (Belgium) and Professor Jeffrey Atkinson (France). Competencies in biotechnology which are needed by both undergraduate pharmacy students and postgraduate scientists are being prepared.

Anyone working in a biotech company who is interested in providing their opinions on staff training in biotechnology is welcome to contact Jane Nicholson at jane@nicholj.plus.com

Jane Nicholson, Executive Director EIPG, jane@nicholj.plus.com

Death of Professor Bart Rombaut, Head of School of Pharmacy at the Vrije University in Brussels
In January, Bart Rombaut, President of the European Association of Faculties of Pharmacy (EAFP) died suddenly. He had a vision for the development of pharmacy education to prepare students both for professional and scientific activities for the future new demands and technologies. He was a driver for EAFP to take a leadership role in the developments of pharmacy education and the profession at an international level. He was successful in leading applications for EU-funded projects, namely PHARMINE, PHAR-QA and PHAR-IN, and attended several EIPG General Assemblies to champion these projects. Our condolences go to his family and many friends in EAFP.
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<tr>
<th>Date</th>
<th>Event</th>
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<tr>
<td>MARCH</td>
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<tr>
<td>24–26 Mar</td>
<td>ICH Q7 Compliance for APIs Manu-factured by Chemical Synthesis</td>
<td>Heidelberg, Germany</td>
<td><a href="http://www.gmp-compliance.org">www.gmp-compliance.org</a></td>
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<tr>
<td>25–26 Mar</td>
<td>Modern Biopharmaceutical Manufacturing</td>
<td>Lyon, France</td>
<td><a href="http://www.pda.org">www.pda.org</a></td>
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<td>31 Mar</td>
<td>9th Pharmaceuticals, Biopharmaceutics and Pharmaceutical Technology World Meeting</td>
<td>Lisbon, Portugal</td>
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<td>APRIL</td>
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<td>1–4 Apr</td>
<td>World Generic Medicines Congress Europe 2014</td>
<td>Barcelona, Spain</td>
<td><a href="http://www.healthnetworkcommunications.com">www.healthnetworkcommunications.com</a></td>
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<td>1–4 Apr</td>
<td>Biosimilar Drug Development World Europe</td>
<td>Barcelona, Spain</td>
<td><a href="http://www.healthnetworkcommunications.com">www.healthnetworkcommunications.com</a></td>
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<td>2–3 Apr</td>
<td>Compliant Handling and Recall Management</td>
<td>Berlin, Germany</td>
<td><a href="http://www.gmp-compliance.org">www.gmp-compliance.org</a></td>
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<td>2–3 Apr</td>
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<td><a href="http://www.terrapinn.com">www.terrapinn.com</a></td>
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<td>2–4 Apr</td>
<td>4th Annual Pharmaceutical</td>
<td>Vienna, Austria</td>
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<td>MAY</td>
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<td>4–8 May</td>
<td>Respiratory Drug Delivery 2014</td>
<td>Fajardo, Puerto Rico</td>
<td><a href="http://www.rddonline.com">www.rddonline.com</a></td>
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<td>13–14 May</td>
<td>Risk Management in Sterile Manufacturing</td>
<td>Copenhagen, Denmark</td>
<td><a href="http://www.gmp-compliance.org">www.gmp-compliance.org</a></td>
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<td>17–18 May</td>
<td>3rd World Health Professions Regulation Conference</td>
<td>Geneva, Switzerland</td>
<td><a href="http://www.fip.org">www.fip.org</a></td>
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<td>JUNE</td>
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<td>2–5 Jun</td>
<td>Pharmaceutical Quality Week</td>
<td>Baltimore, MD, USA</td>
<td><a href="http://www.ispe.org">www.ispe.org</a></td>
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<td>4–5 Jun</td>
<td>Document Management – GMP Requirements and Best Practice</td>
<td>Berlin, Germany</td>
<td><a href="http://www.gmp-compliance.org">www.gmp-compliance.org</a></td>
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<td>18–19 Jun</td>
<td>Pharmaceutical Packaging and Labelling</td>
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<td>24–26 Jun</td>
<td>5th World Conference on Drug Absorption Transport and Delivery</td>
<td>Uppsala, Sweden</td>
<td><a href="http://www.eufeps.org">www.eufeps.org</a></td>
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