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Cover picture: A peristaltic pump head with 12 rollers (see p15).

EDITORIAL COMMENT

I write this Editorial just after the General Assembly of the EIPG which was held in Milan and organised by the Italian Association for Industrial Pharmacy or Associazione Farmaceutici Industria (AFI). I would personally like to thank Piero Iamartino, our Italian representative, for his hard work and help in organising this stimulating and well received event.

I would also like to acknowledge the contribution of Professor Alessandro Rigamonti, the AFI President who sponsored the EIPG General Assembly and who is also celebrating the 50th birthday of the AFI as an organisation dedicated to the Pharmaceutical Industry. I have to say after reading the programme of the AFI symposium in Rimini, the AFI seems a very healthy Association with strong links to Academia and is an example of best practice for us all.

The discussion points and outcomes of the General Assembly have been summarised and are to be found on page 21 of the Journal. As the skill sets needed for staff in today's Pharmaceutical Industry are changing, so the career pathways for industrial pharmacists are evolving. Pharmacy remains as a most versatile qualification. However, whilst the industry consolidates and outsources into global markets, European pharmacists need the support of strong professional bodies.

The mantra of EIPG is always focussed on ensuring that pharmacists continue to play a pivotal role in the European Pharmaceutical Industry and as such we are keen champions of education, professional competencies and in particular the role of the Qualified Person. This year at the EIPG General Assembly we were pleased to have an industrial pharmacist, Martine Tratsaert from VAPI/UPIP, our Belgian member, who is also a Board Member of the European QP Association.

Our guests included Roberto Frontini who is President of the European Association of Hospital Pharmacists, Bart Rombaut representing the European education initiative PHARMINE and Jurate Svarcaite representing the community pharmacists of the Pharmaceutical Group of the European Union.

Also this year, we were pleased to welcome two observers from the Swiss pharmaceutical industry, Stephan Buchmann, President of GSIA, the Swiss Society of Industrial Pharmacists and Valter Gianesello, President of AFTI, the Associazione Farmaceutici Ticino. Dr Giorgio Bruno, Qualified Person for Corden Pharma, Italy, reported on the professional development of the Qualified Person in the Italian pharmaceutical industry. His overheads can be found on the website.

The education competencies needed by a pharmacist on Day 1 of graduation were agreed and are listed on our website. It was concluded that a general Advanced Masters in industrial pharmacy is not required by most of our members. However, specific diplomas or Masters courses in specialist subjects such as clinical trials management, regulatory affairs or quality assurance are needed for a successful career in the Pharmaceutical Industry. Prof Paola Minghetti, University of Milan joined the education working group and the overheads that she prepared for the meeting on the Italian education system can be found on the PHARMINE website, www.pharmine.org/pharmine.

As always, the EIPG Bureau and Committee are open to feedback, suggestions, areas for concern and any matters relating to Educational Policy and Standards. Any individual member can obtain a copy of the full minutes from me or from your country representative.

To contribute to the Journal or to contact the Bureau please use our website www.eipg.eu and contact the Bureau members direct.

With best wishes

Jane Nicholson,

Executive Director EIPG

THE PHARMINE PARADIGM –

MATCHING THE SUPPLY OF PHARMACY EDUCATION AND TRAINING TO DEMANDS

by Jeffrey Atkinson and Bart Rombaut

The roles and responsibilities of the modern-day pharmacist are evolving very quickly, and pharmacy education and training will have to adapt in order to provide the competences needed for the new roles and responsibilities (see Figure).

JEFFREY ATKINSON, Emeritus Professor Nancy University, Executive Director of Pharmacolor Consultants Nancy (PCN), 12 rue de Versigny, Villers, France.
jeffrey.atkinson@pharma.uhp-nancy.fr

BART ROMBAUT, Professor, Department of Microbiology and Hygiene, School of Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium.
brombaut@vub.ac.be

The first two demands on pharmacy education and training will have an impact mainly on duration and organisation of education and traineeship.

The first demand concerns the EU directive 2005/36/EC on the recognition of professional qualifications[1]. The abolition of obstacles to the free movement of persons and services is one of the objectives of the EU. For nationals of the member states, this includes their right to pursue a profession in a member state other than the one in which they have obtained their professional qualifications. Access in the member states to the profession of pharmacist is conditional upon the possession of a given qualification ensuring that the person concerned has undergone training which meets the minimum conditions laid down. The main factors involved are:

- "Evidence of formal qualifications as a pharmacist shall attest to training of at least five years' duration,…"
- "…four years of full-time theoretical and practical training at a university or at a higher institute of a level recognised as equivalent, or under the supervision of a university;"
- "…six-month traineeship in a pharmacy which is open to the public or in a hospital, under the supervision of that hospital's pharmaceutical department."
- "The balance between theoretical and practical training shall, in respect of each subject, give sufficient importance to theory to maintain the university character of the training."

The above factors impact mainly on duration and organisation of education and traineeship. In essence, they state that a pharmacy diploma should be given after a 5-year fully integrated course that incorporates a 6-month traineeship.

Directive 2005/36/EC also gives some indication of the subject areas to be taught: "Annex V.6. PHARMACIST 5.6.1. *Course of training for pharmacists*: Plant and animal biology/Physics/General and inorganic chemistry/Organic chemistry/Analytical chemistry/Pharmaceutical chemistry, including analysis of medicinal products/General and applied biochemistry (medical)/Anatomy and physiology; medical terminology/Microbiology/Pharmacology and pharmacotherapy/Pharmaceutical technology/Toxicology/Pharmacognosy/Legislation and, where appropriate, professional ethics."

Movement of pharmacists within EU

This directive is primarily concerned with the free movement of pharmacists within the EU. At the present time this probably does not involve a large number of pharmacists. For example, a survey published in 2009 by the French Council of Pharmacists found that there were 926 foreign pharmacists working in community pharmacy practice in France – out of a total of 55,523. Of the 926, 181 came from the EU, Monaco or Switzerland[2]. This may change in the future. The survey by the French Council

PHARMINE
(Pharmacy Education in Europe)

The Pharmine project will examine the opportunities for the introduction of the Bologna declaration into pharmacy education and training with ethe aim of tuning the latter to the future needs in the three areas of pharmaceutical expertise: community, hospital and industry pharmacy.

of Pharmacists reported that "10 countries (Belgium, Denmark, France, Iceland, Netherlands, Poland, Rumania, Slovakia, Slovenia, Switzerland) told us they already have a shortage of pharmacists, and 5 (Denmark, France, Latvia, Slovakia, Slovenia) today believe such will be the case 10 years from now." Furthermore, if one judges from the EU ERAMUS scheme[3], the (student) population of some countries shows more inclination to mobility than others. Comparing the 4 countries (Belgium, France, Italy, Netherlands) that founded the EU (together with Luxembourg not included as numbers are very small) in 1952, with the 8 countries (Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia) that joined (together with Malta not included as numbers are very small), the EU in 2004, the ratio of students going abroad to that of students coming in from elsewhere is 1.0 (range 0.7 through 1.2) for the old members and 2.2 (range 1.2 through 3.4) for the new members. Whilst more mobile pharmacy students do not necessarily turn into more mobile pharmacists, the difference in the numbers is striking.

The Bologna declaration

The second demand on pharmacy education and training is the *Bologna declaration*. It should be noted at the outset that the Bologna declaration is a collection of principles agreed upon by several European countries but – unlike directive 2005/36/EC – it is not EU law and thus not legally binding in the EU.

The purpose of the Bologna accords is to create a framework for the construction of the European higher education area (EHEA) by making degree and quality assurance standards comparable and compatible throughout Europe. It was signed in Bologna in 1999 by the ministers of education from 29 European countries[4]. The Bologna declaration concerns all university

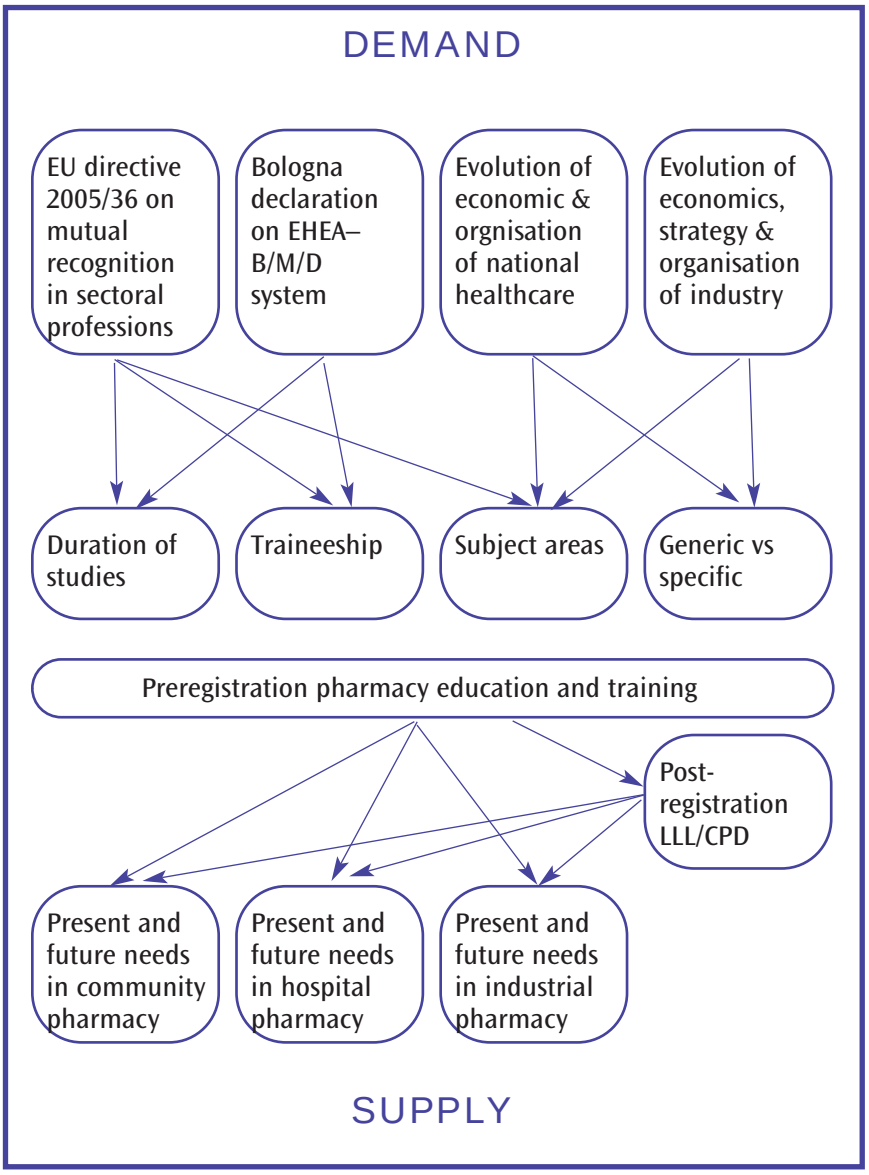

Figure. The PHARMINE paradigm – matching pharmacy education and training to demands.

EHEA: European Higher Education Area; B/M/D: bachelor/master/doctorate; LLL: lifelong learning; CPD: continuing professional development

degrees not only pharmacy. Albeit it could have a varying impact on pharmacy education.

Some principles such as "Adoption of a system of easily readable and comparable degrees" (implying that countries should adopt common terminology and standards) are relatively neutral in their impact.

Other principles such as the adoption of an ECTS (European Credit Transfer System) system of credits with links to LLL (lifelong learning) could have a positive impact on, for instance, the links between pre- and post-registration training.

Other principles are more problematic: "Adoption of a system essentially based on two main cycles, undergraduate and graduate. Access to the second cycle shall require successful completion of first cycle studies, lasting a minimum of three years. The

degree awarded after the first cycle shall also be relevant to the European labour market as an appropriate level of qualification."

Thus the Bologna principles divide university education into undergraduate (bachelor, 3 years) and postgraduate (master, 2 years. At a later stage doctorate, 3 years' duration was brought in). One of the objectives of the PHARMINE consortium is to evaluate whether and/or how this is relevant to the long (5 years) integrated course of pharmacy education and training, or whether there has to be an exception in the case of training for sectoral professions such as pharmacy.

The Bologna principles will have an impact mainly on the organisation of pharmacy courses. The two final demands on pharmacy education and training to be considered will have an impact mainly on the subject areas taught and the equilibrium between generic and specific subjects and skills.

Community and hospital pharmacists

The third demand on pharmacy education and training stems from the fact that several European countries are reflecting upon ways to develop the services offered by community and hospital pharmacies in order to strengthen the *roles and responsibilities of community and hospital pharmacists in the national healthcare system*. Such developments will inevitably have an impact on pharmacy education and training.

Some of the areas in which community and hospital pharmacists may play a greater role in a given national healthcare system[5,6] include:

- Provision of new pharmaceutical services in risk management, testing and/or management of chronic health problems such as: smoking, heart disease, hypertension, diabetes, obesity, chronic renal disease, asthma…
- Evaluation of and reporting on medicines and medical devices in areas such as: clinical research, pharmacovigilance, efficacy and adverse effects of medical devices…
- Evaluation of and reporting on issues of public health such as development of resistance to anti-microbial drugs…
- Advice to special groups such as: international travellers (vaccinations, disease prevention), young mothers (baby foods), athletes (nutrition)…
- Establishment of evidence-based medicines and therapy
- Development and running of systems of telemedicine
- Provision of basic first aid
- Interaction between community pharmacies and residential care homes

The ways in which the above changes in pharmacy practice may impact on pharmacy education and training include:

- Introduction of new subject areas such as pharmaceutical care. The latter can be defined as the responsible provision of therapy for the purpose of achieving definite outcomes that improve a patient's quality of life: cure of a disease, elimination of symptomatology, slowing of a disease process, prevention of a disease or symptomatology. It implies direct involvement of the pharmacist in the healthcare team responsible for the design, implementation, and monitoring of a therapeutic plan.
- A change in the importance of generic subjects and skills such as management and information technology, and in that of certain specific subjects such as statistics and experimental design, gerontology...
- Reflection on the possible introduction of a period (e.g. 1st year) of common studies with students in other healthcare professions (medicine, nursing…) in order to create ties between the different members of the healthcare system.

Hospital pharmacists are part of the medication management team in hospitals that is responsible for how medicines are selected, procured, delivered, prescribed, administered in order to optimise the contribution that medicines can make to producing desired outcomes. Albeit, the specific roles and responsibilities of hospital as opposed to community pharmacists need clarification in some countries. Once this is done pharmacy education and training will again have to adapt to the new situation.

As national healthcare systems differ in the EU, the ways in which the roles and responsibilities of community and hospital pharmacists are elaborated and defined will differ according to local conditions. So to some extent will the education and training judged necessary to obtain the competences required for such roles and responsibilities.

The pharmaceutical industry

The fourth demand on pharmacy education and training stems from the *rapid changes in the pharmaceutical industry*[7,8]. Change is dictated by several developments:

- As the population ages new medical needs emerge and generate a different disease burden (e.g. the growing need for treatment of neurodegenerative diseases like Alzheimer's). The so-called "grey factor" will also globally boost the need for new medicines as the elderly are often under poly-medication.
- As the E7 countries (Brazil, China, India, Indonesia, Mexico, Russia and Turkey) develop

economically, their disease burden changes (e.g. emergence of chronic cardiovascular conditions such as heart disease and hypertension) and thus so do their medical needs. Their increase in wealth also means that they play an increasingly important role in pharmaceutical marketing and economics.

- Global warning will have a major impact on disease patterns. It may bring previously eradicated diseases such as malaria and cholera back to countries in Southern Europe. It could boost the production of pollen and so aggravate respiratory illnesses. Small rises in temperature will modify bacterial growth and hence change microbial disease patterns. The examples are numerous.

In the face of these and other challenges, the pharmaceutical industry suffers from a lack of productivity in the lab. Costs in R&D soar but fewer and fewer innovative medicines are produced.

Furthermore, healthcare agenda and politics – no longer scientific advancement – have a major impact on the development of pharmaceuticals.

All the above factors are modelling the face of the industry as it moves away from the "old" system of big pharma with innovation and production based on chemical synthesis, towards one of small and medium enterprises (contract research organisations and the likewise that are often developed by universities), with innovation and production based on biotechnology.

This will impact upon education and training for industrial pharmacists. Changes will be required in the generic subjects and skills behind the competences in fields such as management. New fields of expertise are emerging such as legislation on intellectual property – the latter being of prime importance in various biotechnological fields such as cell therapy, and allo- or xeno-transplantation. This could produce "double competence" study programmes such as pharmacy plus business management or pharmacy plus patent law.

There will also be a need for a change in subject areas. Here the strategy to be adopted is very hard to discern. Although the elucidation of the human genome revealed many opportunities for the industry (e.g. over 800 new drug targets in the form of G-protein coupled receptors), and the "*–omics*" thrived in higher education institutions and elsewhere, this did not produce the pharmaceutical revolution hoped for. With hindsight, perhaps too much time was spent in faculties on studies in genetics and genomics - before reality hit home. If in the future, education and training is to produce the right industrial pharmacist specialist at the right time, given the long-term nature of drug R&D, changes in curricula have to be made a decade before their fruits can be seen.

The PHARMINE consortium[9] is looking at how the pharmacy education and training supplied by European universities meets the above demands and how it will have to be modified in order to meet the challenging, future demands.

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THE IMPORTANCE OF THE INDUSTRIAL ACADEMIC INTERFACE FOR INNOVATION IN THE PHARMACEUTICAL SECTOR

by Mike Eaton

The pharmaceutical sector has, in recent years, suffered from a perceived lack of successful new drugs, especially blockbusters. There is much debate as to the causes of this, but the current regulatory and financial environment requires that the sector tackles new and innovative therapeutic targets that challenge its current science base. These new targets will continue the shift away from chemical entities (NCEs), to biologicals and in the longer term to explore all "drug space". "Drug space" that is not part of the current pharma repertoire includes higher molecular weight drugs eg. nanomedicines, nucleic acid-based drugs[1], and "non-Lipinski" inhibitors of protein-protein interactions (Figure 1). As a result the therapeutic sector is actively looking outside its walls, taking lessons from the biotech revolution, for new thinking from academics and SMEs.

MIKE EATON is head of antibody chemistry at UCB, Slough, UK
email: nanomedicine@btinternet.com

Examples from the past

Historically, industrial-academic contact in the NCE area has been, in general, limited to the education of new employees. This interface changed somewhat with the emergence of the biotech industry, largely based on the new and unexpected molecular and cell biology tools developed by the academic sector, especially in the US.

These opportunities were seized by visionary entrepreneurs and despite the conservatism and scepticism of large companies, new businesses, such as Genentech and Amgen were formed and were successful. Large companies can be slow to take on transforming technologies, having evolved processes which support incremental technical improvements, with a view that they can later buy in additional required technologies. Some enterprising companies are currently trying to avoid idea stagnation by encouraging clusters of start-ups businesses – research incubators where less conventional ideas can be evaluated, or through creating smaller, devolved research groups with greater independence and autonomy.

The whole pharma sector is being squeezed by generic companies, whose sales are predicted to have ~90% of the global market which was $820bn in 2009. Many companies no longer find "me toos" commercially viable and as a result are focusing on difficult drug targets with high unmet medical need, outside the traditional pharma comfort zone. Within the non-generic market, biologicals and antibodies are competing with NCEs for market share with the expectation that within ten years they will share the revenues equally[2]. We are now seeing the emergence of new therapeutics, occupying the last remaining untouched theoretical drug space (Figure 2).

Drug space can be defined by molecular size going from aspirin (picometre) to stem cells and regenerative medicine (micrometre or larger). Early examples of larger drugs are nanoparticulates but nucleic acid-based therapeutics and regenerative medicine are just around the corner. In parallel, there are steps to broaden the market for the major drug classes, such as NCEs inhibiting protein-protein interactions and antibodies that tackle intra-cellular targets, currently the exclusive providence of NCEs.

Therapeutics are set to become much more eclectic with the emergence of these new modalities. These are difficult challenges and the pharma and SME sector is once again looking for inspiration from academia. It has happened before – not so long ago – and gave rise to the biotech sector. Can history repeat itself?

The communications dilemma

A problem for both academia and industry is the lack of a common understanding of the technical issues facing drug discovery in the 21st century. Does academia, especially in Europe, have an understanding of what is required in the present pharma environment?

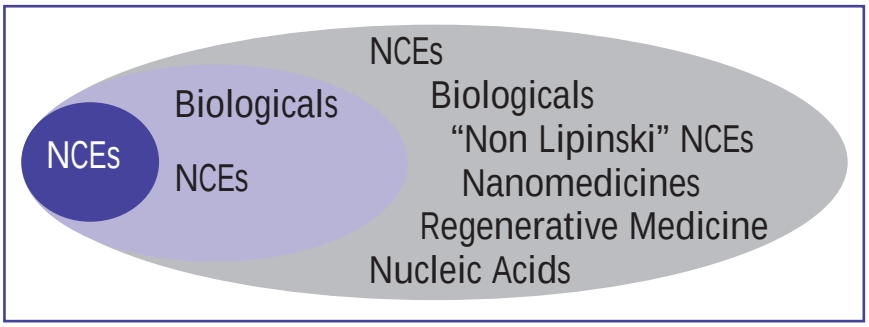


Figure 1. Diversification of "Drug Space" after the Biotech Revolution.

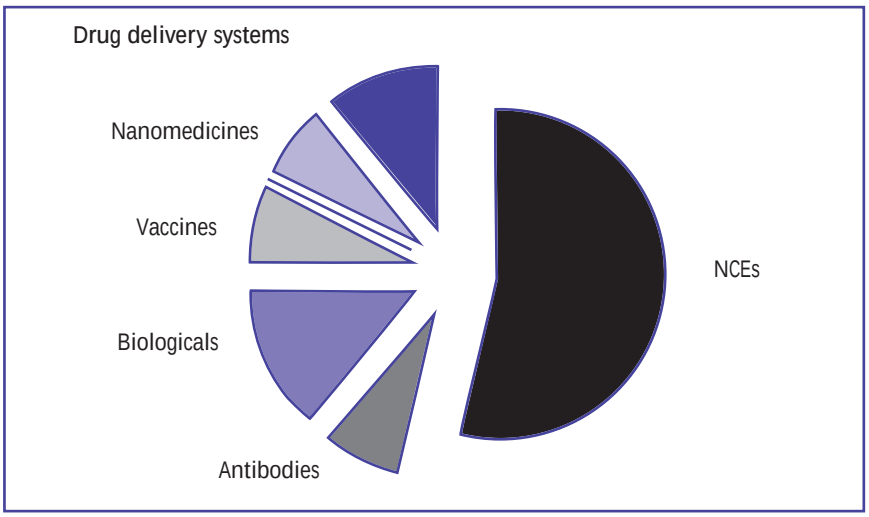


Figure 2. New molecules entities approved in 2008 by Class.

The sides have drifted apart, perhaps due to industrial arrogance, but there is also a perception that academic freedom may be adversely impacted by working on industrial applied research. Certainly "Blue Sky" research should be encouraged – national research councils and especially the peer review system probably do not do enough to support this type of activity. However there is within Europe a considerable body of funded research that purports to be therapeutic and hence is applied research by definition. Applied research, academic freedom and "Blue Sky" are totally compatible and these seemingly different and antagonistic approaches can and must be brought together to produce radical high value new products.

How is this publicly-funded applied research strategically guided? In general it is down to the individual and the reviewer to judge whether the project objective fits into an industrial wish list. European Technology Platforms (ETP) have been brought into being by the EC to advise, from an industrial perspective, how tax payers' research monies should be best spent.

The Commission's objective in the therapeutics sector is both to fund academic research into new treatments and diagnostics for diseases and to support European pharmaceutical industries efforts to be more competitive.

The author's experience with the ETP on nanomedicine[3] has shown that there is a significant need for more information flow from industry to academia. Without this information, much of Europe's funded research will be non-translatable to industry, the clinic and ultimately the patient; consequently much needed new ideas will not reach the pharma sector.

The value of communication

Whilst academics are familiar with their departments being given a star rating by peer review, most will be unaware that industry often review departments and individuals independently. Industry will not only choose to work with the best scientists but also those most informed on what is needed to translate an idea to a product.

Breakthrough research requires a less conservative mentality on the part of grant reviewers. Traditionally, chemistry reviewers have strongly favoured extrapolations from the published literature. Equally it requires informed investigations to recognise where discoveries or serendipity can produce step changes for science and industry.

So we need to:

- Select fertile research areas (for industry)
- Explore good ideas or hypotheses
- Leave room for serendipity and most importantly its recognition
- Create more academic-based key opinion leaders with industrial knowledge.

What's in it for industry?

Providing information for academic scientists is a time-consuming activity that conflicts with mounting pressures on many Business Development departments and their industrial R&D colleagues. Academics need to know whether their idea is applicable, its manufacturability and why it has

not been done before. They need to understand the industrial requirements and their project's potential position in the industrial R&D process. Regrettably, much of this experience has not been published, neither is it academically accessible, and the commercial framework is changing all the time.

Fortunately the traditional secrecy barriers are slowly being pulled down, as the need to search globally for ideas takes root in forward looking companies. For academia the benefits are fiscal, highly-rated publications, being in the driving seat for new industrial sectors and the identification of new healthcare areas which can help patients.

What's in it for academics?

Whilst some individuals are perfectly happy to just publish their research, some departments are increasingly trying to build bridges with industry. Their aim is to increase potential funding – but also to solve real healthcare problems. There are perhaps two approaches to applied research:

- *Laissez faire* (default strategy)
- A more informed (but *not managed*) strategy

Given that academics by and large are not familiar with the patent literature or current industrial priorities the former approach is somewhat wasteful albeit it could produce a "Black Swan"[4], a serendipitous discovery that would produce a paradigm shift. Industrial experience is not well documented, but knowledge of it could reduce time spent on research with no possible commercial translatability. It is important that commercial information and experience is available to academics, but that no attempt should be made to impose industrial management processes. It is better to know and understand the perceived industrial roadblocks from the outset, rather than to travel hopefully.

The known obstacles to the market

Very often translatability of academic research is predictable from the outset, or if the route is not so clear then at least the roadblocks can be identified and strategies developed to overcome or bypass them. The author has come across many such predictable and manageable roadblocks, the following are purely illustrative!

Drug pharmacokinetics

The importance of *in vivo* DMPK studies is often not appreciated by academics, especially those of inorganic materials that have not commonly been into man, for example silica and gold particulates. Very significant work has been done on gold imaging and therapy, but unless there are appropriate clearance studies these will remain in academic laboratories and will not be translated to the clinic.

Another area requiring much more *in vivo* work is polymer therapeutics; polymer clearance being very difficult to monitor *in vivo* or in urine or faeces. Synthetic gene therapy vectors have also stagnated because of a reluctance to carry out *in vivo* studies.

Drug stability

In the drug delivery field much effort has been expended on drug release systems exploiting the lysosome's lower pH, following endocytosis of a delivery system. Such systems often use a stabilised Schiff's base, consequently they are inherently unstable to low pH.

To produce a marketed product from such a conjugate requires a simple reliable process and low exposure to water even at pH 7, to ensure that batches are analytically reproducible to regulatory requirements. The field of antibody drug conjugates has wrestled with this problem for a decade and has now adopted a manufacturable stable linkage approach – this industrial lesson has not transferred into related academic research, often with disastrous results on scale-up.

Polymer therapeutics

The use of polymers in therapeutics is part of a multi-billion dollar sector. Aggregation of some polymers could lead to anaphylactic shock or immune responses, but polymer self-association studies are often left until the pre-clinical stage. As although nature has evolved natural polymers not to aggregate at low concentrations, commercial products are formulated at high concentrations.

Industrial context

Often the answer as to why a concept has not been implemented before is there is no appreciation of what the advantages must be. An example here is molecular imprinting of polymers to a therapeutic target. This technology requires a substrate at a one-to-one ratio to imprint an expensive polymer. Such systems often compete with antibodies, which have much higher affinities and are cheaper and easier to scale up. Understanding the industrial context of your research is important if you are to make the most of your efforts.

Cost

DNA cages are an interesting way to entrap a drug, which potentially could be released by a particular mRNA relevant to a specific disease. Nucleic acids are, however, very expensive drug delivery materials when accessed by chemical synthesis. It is likely that the future of nucleic acid therapeutics lies in other directions where they are the agent rather than the formulant or drug delivery system.

Analytical challenges

The new types of drugs being

BIOPHARMACEUTICALS – FROM NICHE TO MAINSTREAM

by Gareth Williams

Introduction

Biopharmaceuticals are making an ever-increasing impact in the healthcare market. In recent years, biopharmaceutical medicines have successfully made the transition from niche players to multi-billion blockbuster drugs. Global sales rose from $75 billion in 2007 to $87 billion in 2008 and sales are forecast to continue to grow. For protein biopharmaceuticals, the main categories of products include monoclonal antibodies, erythropoietins, insulins and interferons.

Marks & Clerk's 2009 biotechnology survey focused on a number of key areas of particular relevance to stakeholders in the biotechnology industry – from entrepreneurs, to scientists, investors and academics. This short report covers the section on protein biopharmaceuticals.

Mergers and consolidation

Most pharma companies have sought to contribute protein biopharmaceuticals to their drug pipelines from bespoke in-house R&D departments, wholly-owned subsidiaries, or via significant partnership arrangements/investments with biotech companies.

For example, AstraZeneca has merged Cambridge Antibody Technologies (acquired 2006) with MedImmune (acquired 2007) to create a biopharmaceuticals division; Merck has established a biopharmaceuticals division, Merck BioVentures, to provide a pipeline of new and generic biopharmaceuticals; Novartis has strengthened its biopharmaceuticals capabilities by partnering with Lonxa and MorphoSys.

Yet the research shows that the view from the biotech community is somewhat divided. Only 59% of respondents assert that consolidation would be beneficial, meaning that a significant minority do not agree.

Thus, where consolidation leads to links between biotech and pharma was companies, the involvement of pharmaceuticals may be welcome in enabling biotech companies to become more commercial. Indeed, 89% of respondents assert that traditional pharmaceutical companies can assist with manufacturing and large-scale commercialisation.

Yet this enthusiasm for biotech to learn lessons from major pharma was tempered by the realisation that this could lead to a loss of independence for the industry. 83% of survey respondents consider that the combination of the current funding squeeze and the increased interest from pharma companies will shrink the independent biotech sector by the end of the recession.

Patents

As discussed later in this section, patents play a crucial role in securing funding for biotech companies to develop protein biopharmaceuticals. What may emerge is that the R&D, or the patents on that R&D, become the battleground for finance. Notably, 93% of respondents believe that in the current economic climate investors are increasingly securing their investment against IP rights or taking larger equity stakes.

However, it has to be remembered that patents are monopolistic – their justification is that they encourage innovation. Though the marketplace for therapeutics is vast and ever growing, a contraction in the number of biotech companies coupled with a shortfall in investor cash could mean that monopolistic patent rights are held by a small number of cash rich companies.

Will this scenario best serve society's needs for developing new therapeutics? We have already seen initiatives like the "orphan drug" provisions. When the current recession is over, schemes to encourage innovation in narrowly profitable markets could become more frequent.

GARETH WILLIAMS is an account executive of Marketforce Business Media email: gwilliams@marketforce.eu.com

Marketing approval and biosimilars

Protein biopharmaceuticals are highly complex molecules produced via manufacturing processes that often use living biopharmaceuticalal material. In view of the complexity of the products and the fact that the manufacturing process can lead to heterogenicity, specific regulatory mechanisms have been adopted to ensure protein biopharmaceuticals products meet necessary quality and safety criteria.

Striking the balance between safety and supporting drug development is essential. Notably, 89% of the respondents consider that greater certainty is needed for the approval of biopharmaceuticals, showing that regulatory mechanisms are not satisfying industry needs.

Moreover, in recent years several major protein biopharmaceuticals have gone off-patent, opening the door to generic manufacturers to gain a share in the market. Biosimilars (or "follow-on biopharmaceuticals") are copycat biopharmaceuticals drugs. The market for biosimilars is rapidly growing as a consequence of the lapse of patents rights, and also public policy in encouraging the development of cheaper alternatives to branded products.

Encouragingly, the survey reveals that on balance 75% of industry consider the emergence of biosimilars as a commercial opportunity, yet 71% recognise in a climate already dogged by funding and regulatory woes, as well as increased political pressure, the emergence of generic competition is a growing challenge for originators. Notably, nearly three-quarters (72%) argue that insufficient incentives are given to reward the R&D of innovator firms.

While the research shows huge optimism among the industry, with 81% believing the rise of generics will result in more affordable healthcare, adequately compensating innovator companies emerges as a concern. 68% believe the legislation should provide greater reward for protein biopharmaceuticals products than for traditional drug products, due to the longer time and greater expense in bringing these products to market.

Patenting of protein biopharmaceuticals

Current patent system

As a result of the considerable delay and expense of developing new biopharmaceutical medicines, in many cases the IP portfolios of biopharmaceuticals companies are often their main means of attracting investment , and indeed their main asset. Hence a strong patent systems and a clear IP strategy are of key importance, particularly in the current climate.

Yet the research shows that respondents lack confidence in the IP systems in Europe and the US – the very frameworks used to reward innovation. Only 57% describe themselves as confident in the patent system at a European level, rising to 64% at the US level.

Against this background, when asked about the establishment of a European Community patent system, a clear majority of 80% of respondents indicate that the reaction of a common patent would be beneficial for the biotech industry. Certainly, a European Community patent system should offer considerable costs savings over the presently fragmented (in some respects) route to obtaining patent protection throughout Europe. Were such a system coupled with a centralised European Patents Court, then the cost of litigation would likely be reduced, though any benefit of "doubt and delay" for patents would be minimised. Notably, little over a third (37%) expect the common patent to become a reality, likely indicating a frustration between what the industry feels would be beneficial and achievable, and the level of development it expects at a co-ordinated European level.

Protein biopharmaceuticals offer great hope in the development of highly-specific therapeutics, as well as gaining importance as major revenue sources for the large pharmaceutical companies, but the needs of both generics and originators will need to be met in what is a very fragile market. Ultimately, it may be the case that pharma companies may play a key role here in bringing new protein biopharmaceuticals to market, to the benefit of all.

IP strategies for protein biopharmaceuticals

Over two-thirds (68%) of the survey respondents think that the IP system should more generously reward the biotech industry to compensate for the greater expense of bringing biotech products to market when compared to traditional drugs.

Indeed, given the very large delay in bringing new medicines to market, often a "first generation" patent covering a protein biopharmaceutical will be heading for expiry not long after the product has established a firm market presence. Against this background, what strategies can be used to secure further IP protection?

A starting point is obtaining a patent term extension. In Europe, the Supplementary Protection Certificate scheme can give up to an additional five years of patent-like protection to compensate for delay in obtaining marketing authorisation for medicinal and veterinary products. In the USA patent term extensions are also available.

By implementing an IP strategy to continuously monitor the research

required to bring the protein biopharmaceutical from the laboratory to the marketplace, it will usually be possible to obtain further patents that protect innovative modifications. These are sometimes referred to as "patent thickets", although the title can provoke unwelcome reaction (see section 4 on the EU commission enquiry).

For example, optimising protein function, enhancing MAb binding, or reducing immunogenicity may be covered by later filings. Also, cell lines used to produce the protein biopharmaceuticals could be patented, as could methods of manufacturing the protein. Any one of these subsequent patents could provide an invaluable further extension to patent protection, often when the protein biopharmaceutical is in the marketplace and sales are close to peaking.

Finally, it is important not to overlook the protection afforded by regulatory bodies, referred to as data or marketing exclusivity. In certain countries, regulatory authorities are not permitted to reference data submitted by the original marketing authorisation holder for a prescribed period of time. This is relevant if a generic or biosimilar manufacturer applies for abridged marketing authorisation. In certain countries, there may be further period of marketing exclusivity as well.

This annual survey was made by Marks & Clerk, one of the world's leading intellectual property consultants. Over 360 executives, scientists, academics and investors responded to an international online survey concluded in May 2009. The 2009 report brings together key findings of the survey and the role of intellectual property – most significantly patents, to the biotech sector.

For a copy of the research findings, contact Joanne Colton on jcolton@marks-clerk.com

PERISTALTIC PUMPS – AN ANSWER TO INCREASING DEMANDS WITHIN THE BIOPHARMA INDUSTRY

by Henrik Ejsing

Peristaltic pumps have proved superior to other pumps in many respects especially in the biopharma industry and the implementation of peristaltic pumps is a growing market in the industry. Augmented needs for safety precautions and flexibility are causing increased focus on the peristaltic pump as a viable alternative to traditional pump technologies.

HENRIK EJSING is managing director of Watson-Marlow Flexicon, Copenhagen, Denmark.
email: hej@flexicon.dk

The peristaltic principle

The human intestine is in fact a peristaltic pump as muscle contractions push the food forward through the bowels. The corresponding technical solution consists of a tube, which is squeezed flat by a roller and then the content of the tube is pushed forward – see Figure 1.

Behind the roller the tube will acquire its normal shape because of the plastic memory. In this way a vacuum is created and hence the tube is refilled and ready for the next squeezing.

As you can see the tube is actually the pump. This fact constitutes the very special qualities of the peristaltic pump resulting in unique advantages in relation to production in the biopharma industry:

- No cleaning of the pump – the tube is discarded
- Reduced cleaning validation
- No risk of cross-contamination
- Change over time less than five minutes. Load new tube, purge and calibrate.

The modern peristaltic pump is moreover designed with the built-in possibility of using different sizes of tubes. This means that the same pump as an example can fill volumes from 0.1 ml to 250 ml simply by changing the tube size.

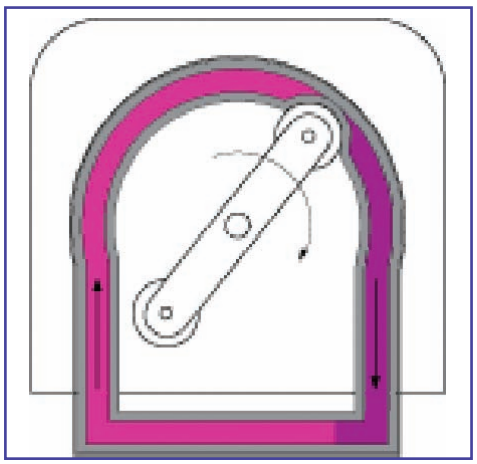


Figure 1. The principle of the peristaltic pump.

The filling capacity depends on the size of the pump and with that the range of tubes to select from – see Figure 2. In high speed filling applications several pumps are installed on the same line co-working in parallel or serial mode. A big pump would in theory be able to carry out the task, but small pumps have proved more accurate.

The filling speed can easily be adjusted by varying pump speed. This can be necessary if the product has a tendency to foam or in order to avoid splashing, which causes unwanted stains on the inside of the vials after freeze drying. Foaming and aeration can also be reduced by changing the acceleration for ramping up and down while maintaining a high flow rate.

Accuracy

Figure 1 shows a peristaltic pump with two rollers, which is the standard configuration often used for flow operations. For applications for dispensing biopharmaceuticals accuracy will be of vital importance and in this case more complex configurations of the peristaltic pump will usually be chosen.

There is a natural connection between accuracy and pulsation and the more rollers the lesser the pulsation. Of course the size of the rotor imposes a limitation on the number of rollers, there is room for. However this can be solved by using a double rotor with six rollers each – offset with respect to one another. The two tubes are connected on the pressure-side with a Y-piece and the solution is in

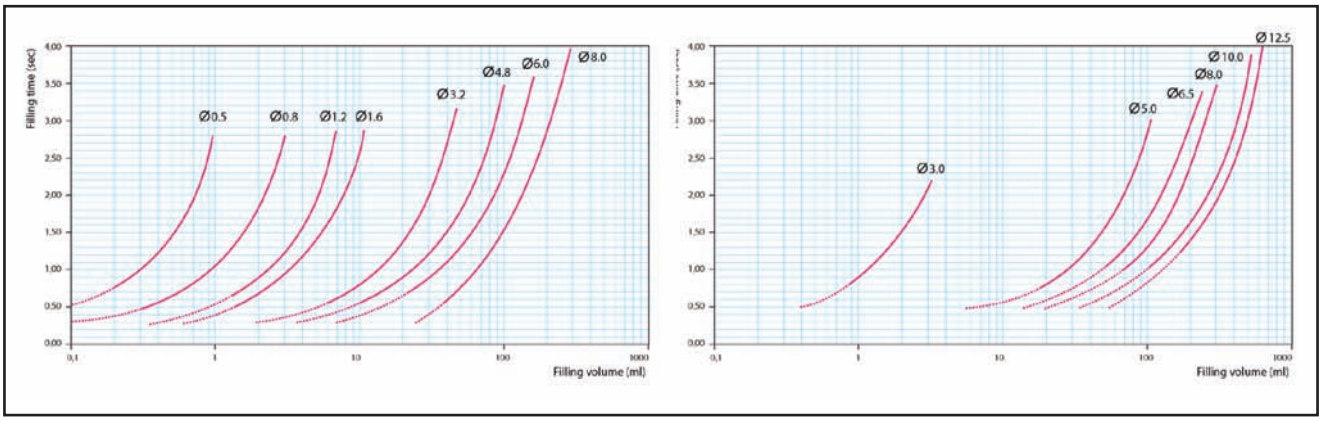


Figure 2. Filling capacity by type size for two different pump sizes.

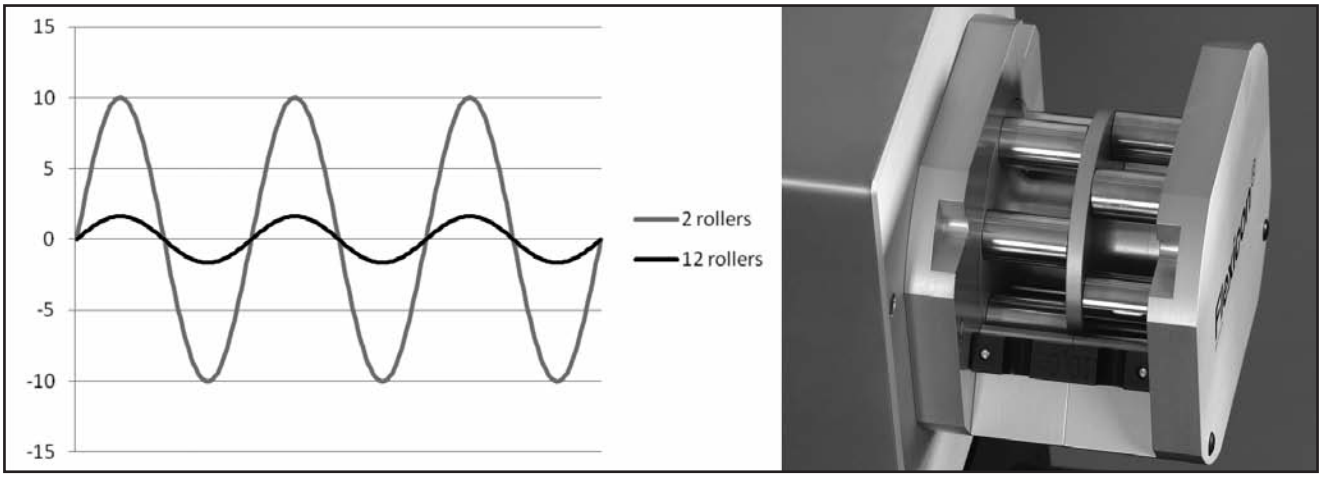


Figure 3. Pulsation as function of number of rollers. To the right a pump head with 12 rollers.

practice working like a rotor with 12 rollers resulting in a pump with practically no pulsation, see Figure 3.

Combined with precision motors and specially developed dispensing systems the peristaltic pump meets fill volume accuracy at +/- 0.5% for fill volumes as small as 0.5 ml. A particular feature on many peristaltic pumps is the possibility to reverse the rotor slightly after the filling sequence in order to avoid dripping from the filling needle.

Peristaltic pumps for filling applications generally operate at low pressure and micro fills are executed i.e. down to approx. 1.3 bar of pressure. That is why peristaltic pumps are ideal for handling shear sensitive products.

For filling applications requiring high accuracy, validation of the filling accuracy is of vital importance and there are different ways to go. Most companies do a process qualification where based on filling tests it is decided how to control the process in terms of set up procedures, initial tests and on going process control.

For instance it is always important to run a new tube dry for approx. 1 minute to warm up the tube and to activate the mechanical abilities. If this task is not performed, changes in flow rate will be seen over the first 20 minutes of filling and without a 100 % check weighing you would consider the process “out of control”.

Process control is normally done based on sample checking, but it is becoming increasingly normal to do in line check weighing, where the measures feedback directly to the pump for recalibration. This results in a very high level of control and accuracy in the process of filling.

The tube

It goes without saying that choosing the tube is of the outmost importance for the performance of the pump. First of all, the choice of tube material is critical as mechanical as well as chemical characteristics are inherent in the material. The product-resistance of the tube is meant to prevent contamination of the product and damaging of the tube, while the

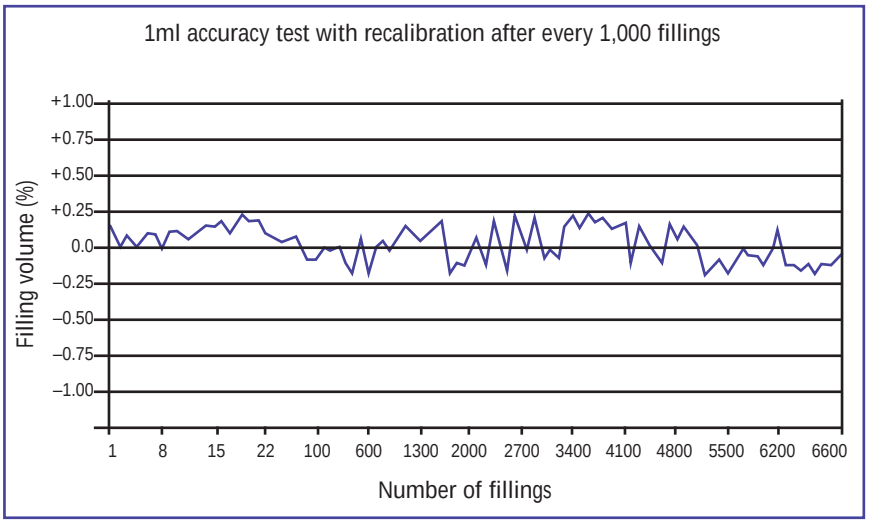


Figure 4. Filling accuracy with fixed calibration procedures.

shore and the plastic memory of the material ensure homogenous and precise dispensing. The most common tube is the peroxide- or platinum cured silicone tube which combines a relatively low cost with good mechanical abilities.

For some applications it is crucial to choose a tube that has been baked to get rid of residuals from extruding and curing the tube.

The lifespan of the tube varies with the application. Most suppliers of silicone tubes would guarantee a lifespan of 40 hours when requirements for filling accuracy are high. The tube can within the lifespan be autoclaved 4 to 5 times without problems but most users of peristaltic pumps in biopharma industry normally use a tube only once to avoid cleaning and risk of cross contamination. In many cases single use will also be the most cost effective solution.

Ease of use

Most peristaltic pumps are easy to use. Typically they are part of filling systems with built-in in-line weighing and auto calibration, and the operator can concentrate on loading and off loading of vials, bottles or syringes.

In productions with many different operators and multiple-shift production peristaltic pumps are preferable because the pumps are easy to use and the principle is manageable and easily understood.

STABILITY PROGRAMS NEED TO BE RE-INVENTED

By Patrick Crowley

One has to sympathize with Johnson & Johnson. A volatile residue on wooden storage pallets, purportedly tribromoanisole, a breakdown product of a chemical used to treat wood, was adsorbed on to Tylenol Caplets and other OTC products, leading to complaints of a moldy odor, nausea/pain and product recalls in the US. www.reuters.com/article/idUSTRE5BS2L820091229

This seems to be the "one-in-a-million" incident that conventional stability programs would rarely, if ever detect! J&J's announcements and recall seem to have been exemplary, in the light of the single-digit level of complaints of GI disturbance. A "when to recall" decision is notoriously difficult if the volume of complaints is around "noise level", particularly as low levels of complaints of "nausea and stomach pain" are not unusual with many products. If organizations recalled product following each such report (many of which can be outlandish) there would be few medicines left to treat patients.

The incident may raise wider issues. Pallets, like those at the J&J facility are probably used by many other organizations to stack food, nutritional products, beverages, etc. Can the same volatile residues contaminate such products? Foods contain carbohydrates and other components that are also used as excipients. These probably have similar adsorptive capability for volatiles as materials in medicinal products. Packaging may be equally, if not more permeable to vapors. Nutritionals utilise the same excipients, containers, packaging accessories as Ethical Drugs. It would be good if a collaborative program were to consider the implications for such products. J&J have probably now accumulated expertise in detecting and quantitating such contaminants, as well as acumen in associated "root cause" investigations. Co-operation and sharing such expertise could be initiated and spearheaded by the organization whose mission is to improve the health of all Americans, viz the FDA.

But that has not happened. Instead, the Agency quickly defaulted to "blame game" mode and issued the usual "warning letter". www.fda.gov/ICECI/EnforcementAction/WarningLetters/ucm 197811.htm.

Investigations to establish the cause of the contamination were probably long and arduous. Scientists and other personnel must have spent many long days establishing root cause. The reward? – a warning letter ! One can be cynical and think that earlier notification by J&J would have elicited similar castigation that "root cause had not been established". Will there now be a knee-jerk "pallet stability" requirement for future filings? Don't bet against it.

What are the take-home messages?

Drug product stability and component interactions never fail to surprise and require constant diligence, awareness and excellent science to predict and control.

Mandated stability requirements, being large tabulations of data, generated over many months and years rarely if ever mitigate the risk of such surprises.

It is time to redefine what constitutes good stability practices. Good stability studies should be designed to get to know the drug in terms of its chemical and physical propensities for degradation and interaction (particularly in the state it takes in the dosage form: not just mechanistic and kinetic evaluations in solution). Knowledge of the materials with which the drug is compounded is also vital (numbers of excipients are relatively small). We also need to "know" the packaging materials (and yes, even the pallets, the volatiles that may emanate from lacquers and coatings in warehouses, etc.). For too long the focus on packaging materials has concerned capability to protect (with meaningless WVTR requirements in pharmacopoeias): too little attention is paid to capability to "contaminate" due to their being a source of agents that can interact with

PATRICK CROWLEY is Head of Callum Consultancy – Pharmaceutical Industry Consulting & Services, based in Devon, Pennsylvania, USA. email: info@callumconsulting.com; tel: +1 610 999 2434.

components or residues in the dosage form or delivery device.

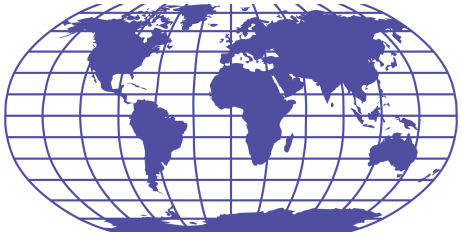
"Stability" evokes images of multiple tables of "all the same data" among Regulatory Affairs professionals and of testing that most probably will produce "the same" results among laboratory scientists. In a word "boring" and no prizes for guessing who mandates the generation of such data. Paradoxically, stability is seen by many analytical scientists as only becoming interesting when an incident mandates in-depth studies and creative chemistry.

It's time to re-assign "good science" status to stability studies so that organizations (and academic institutions) can once again study behaviors in depth and use the accumulated knowledge to creatively assign use periods, storage cautions and appropriate packaging to safeguard the quality of medicinal products.

Allocating blame post-the-event is all very well but at times we need to see the mote in our own eye. It's time to re-think approaches to stability and incorporate genuine "QbD" in our stability programs!

Are you listening ICH?

REGULATORY REVIEW



Review of major developments in GMP in the EU and USA, February to May 2010

by Malcolm Holmes

Introduction

The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in both the USA and in the EU. The most significant of these would appear to be changes to the EU GMP guide and standards for securing the drug supply chain (FDA). MHRA requirements relating to risk based inspections and returns of non-defective refrigerated product are also of significance.

United States of America

New and Updated Regulatory Guidance

The FDA has issued new and updated guidance covering the following topics:

- Standards for Securing the Drug Supply Chain—Standardized Numerical Identification for Prescription Drug Packages.
- Guidance for Industry, Q4B evaluation and recommendation of pharmacopoeial texts, general chapters for use in the ICH Regions – Dissolution/Tablet friability/ Polyacrylamide gel electrophoresis.

FDA has announced

- A new programme known as FDA-TRACK (Transparency / Results / Accountability /Credibility / Knowledge). A new system for measuring performance at FDA.
- The tightening of controls on overseas manufacturers of medicines and on global supply chains.

Europe

EU GMP Guide

The European Commission has proposed the following updates:

- Revision of Annex 6 to Part I of the EU GMP Guide – Manufacture of Medicinal Gases – effective 31 July 2010.
- Revision of Annex 13 to Part I of the EU GMP Guide – the Manufacture of Investigational Medicinal Products (IMP) – effective 31 July 2010.
- A draft revision to Annex 2 (Manufacture of Biological Medicinal Substances and Products for Human Use) as a consequence of the restructuring of the GMP guide and the increased breadth of biological products such as transgenic derived products and the Advanced Therapy Medicinal Products (ATMPs).
- A draft guideline on Real Time Release Testing which is intended to replace the current guideline on parametric release.
- A draft guideline on the requirements for Quality Documentation concerning biological IMPs used in clinical trials.

Products

The European Pharmacopoeial Commission has:

- Conducted a survey on the potential use of reverse osmosis for the production of Water for Injection. Results are not yet available
- Issued a proposal for a new expression of acceptance criteria in the test for related substances which allows for a quantitative determination to be made in line with ICH guideline Q3A (R2).
- Issued revised monographs for heparin under the rapid implementation procedure. These will come into force on August 1 2010.

MHRA

The MHRA has issued:

- A requirement to communicate significant changes between inspections in its risk-based inspection programme.
- An updated policy on returns of non-defective refrigerated products.
- Frequently asked questions (FAQ) on the importation of medicines.

International

API

EMA/FDA/TGA have agreed to hold regular teleconferences to maintain progress on the topic of strategies to enhance assurance of the quality of active pharmaceutical ingredient (API) manufacture and distribution.

PIC/S

The PIC/S has created an example of Quality Risk Management implementation.

PIC/S has also issued a notice of a possible application from Hong Kong's Department of Health for PIC/S membership.

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 publisher@euromedcommunications.com

NEWS FROM THE EIPG

2010 General Assembly of EIPG in Milan, Italy

The 2010 General Assembly of the EIPG was held in Milan on the 15-16th May. During the meeting, the Association for Industrial Pharmacists of Bulgaria was welcomed as a new member of the EIPG subject to receipt of the necessary documentation. This will become available after their inaugural meeting later in the year. Valentina Belcheva was congratulated on her hard work in establishing a national association.

Election of the Bureau

The member from Great Britain, represented by Gino Martini was re-elected as President and the member from France, in the name of Jean-Pierre Paccioni, was re-elected Vice-President Finance (Treasury) . The Belgian member, represented by Kristina Bindus, was elected as Vice-President European Affairs (External affairs delegate) for the next 2 years. The Swedish member, represented by Par Tellner was co-opted to the Bureau for one year as Vice-President Education and Careers.

Representatives from sister European Associations, PGEU (community pharmacists), AEHP (hospital pharmacists) and EAFP (colleges of pharmacy) attended our meeting as observers.

Contact with the EMA

A report of the EMA meeting with "interested parties" by Piero Iamartino demonstrated the continuing large number of pending GMP related issues. Jane Nicholson reported that submissions had been made by EIPG on the EMA concept paper for the revision of Chapter 7 of the GMP Guide and on Part III proposals for the Site Master Files. Some concern was expressed as to whether the costs that are being absorbed by industry with all the revisions to GMP in Europe are really justified.

Supply chain security

A working group considered the latest proposals for amendments to Directive 2001/83/EC to prevent entry of counterfeit medicines into the supply chain. Claude Farrugia considered the latest proposals are an attempt to juggle the need to raise standards whilst trying to mitigate the cost of implementing these standards. Half measures will be worse than no measures because they will give a false sense of security he warned. Conclusions were that legislation and its implementation will be a major challenge that must be undertaken to protect public health.

Proposals for the future of the clinical trial supply chain were presented by Philippe van der Hofstadt.

Consultation on the European Commission's Review of Directive 2005/36/EC (recognition of professional qualifications directive)

Two meetings have been held with the Head of Unit 4 and staff at the Directorate General for the Internal Market and Services. The Bologna declaration and the place of the Bachelor of Pharmacy were raised by the Commission and a presentation on the need for Masters level education for all pharmacists was made on behalf of EIPG by our Belgium Association, VAPI/UPIP.

EIPG is a partner in the education consortium, PHARMINE, which is preparing competency based curricula that will inform the European Commission's update to the Directive. The project coordinator, Professor Bart Rombaut from Vrije University attended our General Assembly and acted as rapporteur for a working group reviewing industrial pharmacy competencies and the need for Advanced Masters and Diploma courses.

Country reports

Price reductions on pharmaceuticals resulting in lower margins and cuts in the number of employees in the pharmaceutical industry were recurring reports from delegations.

Industrial Pharmacy in Italy

Dr Giorgio Bruno, Qualified Person for Corden Pharma reported on the professional development of the Qualified Person in the Italian pharmaceutical industry. His overheads can be found on the EIPG website: http://www.eipg.eu/

European Pharmacy Students Association (EPSA) Annual Congress

On behalf of EIPG, Claude Farrugia made a presentation on the amendments to Directive 2001/83/EC to combat counterfeit medicines during the EPSA Annual Congress held in Krakow, Poland on 27th April. An interesting debate took place among speakers who included representatives from EFPIA (the European Federation of Pharmaceutical Industries and Associations), GIRP (the organisation of pharmaceutical full-line wholesalers in Europe), and PGEU (Pharmaceutical Group of the European Union, representing community pharmacists).

Jane Nicholson,
Executive Director EIPG

PHARMACEUTICAL FORUM

The following questions and responses are a selection of those published on an open online discussion group www.pharmweb.net/gmp.html. The Forum serves as a means of exchanging views on international regulations affecting the pharmaceutical industry. Readers are invited to contribute to the Forum.

Leak testing of BFS/FFS

Q I would like to learn from your experience in performing leak tests of BFS/FFS bottles. What procedure is required to perform such tests? Is there any equipment/instrument available for leak testing of bottles? Is there a guidance document on this?

Response 1 – Vacuum leak test apparatus can be used for leak testing BFS/FFS bottles. Once your filling and sealing is complete, you have to keep those bottles in the VLT apparatus under high vacuum for a particular time period and once the process is complete you have to check the volume by visual inspection or by weighing them.

Leaked vials will show a low volume level or less weight than the standard one.

Response 2 – I am afraid that the "vacuum leak test" as described here will be only appropriate for important leaks. The same for the "pressure test" which consist in firmly pressing the bottles (mechanically or by hand) and to inspect them for traces of liquid.

When it comes to microleaks, and because of the plasticity of the BFS/FFS bottles (PE or PP), the chances of detecting a failing bottle by "emptying" it are not optimised. Detection of leaks by measurement of gas (air or helium) entry/output is much more effective but also much more expensive. You can also detect microleaks through the perturbation of an electro-magnetic field in which the container is placed (the method was first developed by Nikkai Densok but you can now find other manufacturers).

Change control

Q I have revised our MPCR (Master Process and Control record). I need to know whether it is absolutely necessary to file a change control even though the changes that have been incorporated are not process related and are purely for the sake of simplifying the document content?

Response 1 – Yes, all changes must be documented by change control. Among other things, this allows readers in the future to follow the evolution of the document.

Response 2 – Absolutely yes. You need to record the change through your change control system.

If you don't you could be on a very slippery slope – today you have just simplified the document (no change control), tomorrow someone else makes what they think is a minor change (no change control). And pretty soon your entire documentation system is corrupted and useless.

Response 3 – I believe that to use or not to use change control depends on what the Validation Master Plan requires you to do. After all, any auditor would expect you to follow what *you have* stated to be your site policy. Any departures from those "promises" would be regarded with concern.

If in your VMP you have documented satisfactorily *how* you intend to deal with any GMP document revision/change and you carry out that stated procedure, then I see nothing that suggests any breach of GMP has occurred.

In my experience of well over 30 years in the pharmaceutical industry such intended physical changes *must* undergo representative and structured debate within the business groups that are planning to make such changes *and be approved by* the QA group that will be called at audit to defend/explain them.

However, it is also important to recognise that auditors are also human and may have interpretations of the GMP requirements which are perhaps different from your own. It isn't sufficient to simply assume they will approve of all your VMP detail (and therefore of any change you may conduct under the details you have documented).

The site must be fully prepared in advance of any audit to defend the decisions it decided to take in order to delivery GMP compliance.

Finally, successful GMP delivery is not something to be learned by rote. Its achievement is always predicated upon the assumption that common sense will be applied.

Equipment usage log

Q A usage log of major equipment shall be maintained. How can we categorise major/minor equipment? For example, do we need to maintain a usage log for pH meters used in production?

Response 1 – Industry practice is to maintain usage logs for all equipment that must be calibrated or otherwise maintained. Impact on the product, rather than cost or size of the equipment, determines whether the equipment is "major".

Yes, there must be a usage log for a pH meter and probe used in production. The log must record in GMP fashion what batches the equipment was used for. It should also record, or reference another recording document, each standardisation of the pH meter, including the batch identification of each standardisation buffer solutions used. (Your SOP should guide on the pHs of the buffers used, which generally should bracket the target pH range. Your SOP should also guide on what the acceptable performance of the pH probe is, which is usually the slope of the response.) The actual performance of the probe during standardisation, and that it passed or did not, are also to be recorded in the usage log.

Response 2 – Generally people identify equipment as critical (may be termed major) and non-critical (may be termed minor). Then obviously you should maintain a log book of all critical instruments as those are instruments which have a direct impact on your processes. For non-critical equipment, only a maintenance and calibration log my be sufficient.

Response 3 – Your question comes at a good moment for me. I am currently auditing a company and every piece of equipment requires the staff to record the time started to use and the time of completion. This includes pH meters and even analytical balances. This seems to be completely ridiculous (particularly as they also then need multiple signatures for this).

In other words they have converted simple things like pH and weighing into a user log.

Response 4 – I agree with the previous responder that some companies manage to interpret GMP as "Great Mounds of Paper". The silly situation is reached where the process holds up the smooth flow of paper.

However, I'm not in complete agreement with not having log books for pH meters and balances.

If the procedure is to buffer (standardise) the pH meter daily and not before each pH check, there should be a record that this has been carried out – a simple log book. If there is more than one pH meter in the lab, noting which measurements have been carried out on which meter can make life easy should there be a problem.

A similar argument can be made for balances.

Most importantly, keep it simple and the information can be recorded in a few seconds. All that is required is date and either standardisation (daily check) or Lot Number.

Sterile powder injection in polypropylene containers

Q I would like to know whether lyophilised sterile powder injection materials can be packed in polypropylene containers under sterile conditions and sterilised by ethylene oxide?

Response 1 – There are two issues for consideration:

1. EtO is a surface sterilant. How would you validate the process for the material inside the container?
2. The levels of residual EtO/EtCH, etc. remaining from the processing will need to be very closely monitored and controlled.

Response 2 – Wow! Your project is risky. Certainly polypropylene containers could be filled with a powder but this powder should be sterilized beforehand (ideally with gamma-irradiation). This is because ethylene oxide is a gaseous sterilant agent known to exert its action mainly on surfaces. If you read Annex 1 of the EU-GMP guide you'll see that point No. 105 discourages the sterilization of powders with such a gaseous agent. Sorry, but I have some doubt on the successful issue of your project.

Purified water

Q We order demineralised water from an external supplier and it's delivered to us in 1L containers. Our supplier doesn't perform microbiological testing routinely. My question is: how should I ensure that this water complies with the requirements for Purified Water (PH.Eur)? Do we have to perform microbiological examination for each container and each time? And, for how long will this water remain "purified"?

Response 1 – Is the filling operation done in clean and closed conditions? Is the container re-usable? Is the water generated in a single batch? During the initial study you can perform 100% sampling and testing. And based on the supporting data you may reduce the number of test samples. My suggestion is to use the water within 48h from the time of filling. Any of this should be supported with a validation study.

Response 2 – Since you purchase the water from a supplier, you should have/ask for a CoA of the purified water from the supplier. And your QA department should audit the supplier and approve him as the qualified supplier. The first time you receive the water, it should be tested for microbiology and in time, based on the statistical data, you can reduce the quantity for testing.

Readers are invited to send their Q&As to www.pharmweb.net/gmp.html

job vacancies

NonStop RECRUITMENT

NonStop Recruitment is a market leader in European pharmaceutical Recruitment with specialist consultants covering major markets such as UK, Germany, Switzerland, France, Italy and the Netherlands. These consultants recruit for all major roles within the pharmaceutical industry, including clinical research, quality assurance, sales and marketing, pharmacovigilance, business development and regulatory affairs.

Head of Pharmacovigilance

A fantastic newly created opportunity with a growing Pharma for a GMC registered Physician with strong experience in Drug Safety.
Location: Berkshire/Middlesex, UK
Salary: £85,000 – £90,000 per annum + extensive benefits package
Reference: HM/46590/EIPG
Contact Harriet Maidman:
0207 940 2103,
h.maidman@nonstop-pharma.com

Clinical Development Advisor

Excellent hybrid role in Clinical and Medical Affairs for candidates with a Pharmacy background
Location: Surrey, UK
Salary: £40,000-£50,000 per annum + excellent benefits package
Reference: HM/46410/EIPG
Contact Harriet Maidman:
0207 940 2103,
h.maidman@nonstop-pharma.com

Pharmacovigilance Specialist

Urgent requirement for 3month+ contracts in diverse safety contracts gaining strong experience in a global organisation
Location: Middlesex/Surrey, UK
Salary: £24-£28 per hour
Reference: HM/46573/EIPG
Contact Harriet Maidman:
0207 940 2103,
h.maidman@nonstop-pharma.com

Klinikreferent - Hannover/Bremen

Our client is an international pharmaceutical company specialising in unmet therapeutic areas.
Location: Germany – home based
Salary:€40,000 - €50,000 p.a. plus 20% bonus
Reference: MS/46042/50/EIPG
Contact Marketa Smelhausova,
m.smelhausova@nonstop-pharma.com,
0044 (0) 207 940 2103

Klinische Leadmonitor - Munich, Berlin, Freiburg

This an exceptional role, ideal for an experienced Lead CRA who is looking to get the right experience for Project Management role.
Location: Germany – home based
Salary: up to €60,000 p.a.
Reference: MS/46318/50/EIPG
Contact Marketa Smelhausova,
m.smelhausova@nonstop-pharma.com,
0044 (0) 207 940 2103

Senior Clinical Data Analyst – Berlin

An exceptional opportunity has come up for an experienced Clinical Data Analyst to join one of the largest CROs as a Senior Clinical Data Analyst.
Location: Berlin, Germany
Salary: up to €45,000 p.a.
Reference: MS/46500/50/EIPG
Contact Marketa Smelhausova,
m.smelhausova@nonstop-pharma.com,
0044 (0) 207 940 2103

Clinical Project Manager – TOP PHARMA

Our client is one of the leading pharmaceutical companies headquartered in Germany. You will be the key member for managing risk assessment and mitigation plans and for organising the logistics of clinical studies.
Location: Germany
Salary: up to €65,000 p.a. – €70,000 p.a.
Reference: MS/46060/50/EIPG
Contact Marketa Smelhausova,
m.smelhausova@nonstop-pharma.com,
0044 (0) 207 940 2103

Drug Safety Director – Vaccines!

A fantastic opportunity has arisen with one of the leading biotechnology companies for a Drug Safety Director to join their site in Germany. This is a challenging opportunity that should not be missed.
Location: Germany
Salary: up to €130,000 p.a.
Reference: MS/45258/50/EIPG
Contact Marketa Smelhausova,
m.smelhausova@nonstop-pharma.com,
0044 (0) 207 940 2103

Associate Director, Regulatory Development

High-level Regulatory Project Management with Phases I to IV focus, across Pharma and Biotech. 8+ years' experience
Location: Cambridge, UK
Salary: £70,000-£80,000 basic, plus car allowance and excellent benefits
Reference: JT/46205/7/EIPG
Contact Julian Turner, 0207 940 2108,
j.turner@nonstop-pharma.com

Regional Manager Regulatory Affairs

Leading CRO. Line management of Regulatory Project Leads and Regulatory Officers. Clinical Regulatory Affairs Phases II to IV. 5+ years' experience
Salary: Negotiable depending on experience.
Location: Eastern Europe based – flexible regarding location
Salary: Negotiable depending on experience
Reference: JT/46585/2/EIPG
Contact Julian Turner, 0207 940 2108,
j.turner@nonstop-pharma.com

Regulatory Affairs – Project Leads

Leading CRO. Project Management. Clinical Regulatory Affairs Phases II to IV. Organising Regulatory Officers. 3+ years' experience
Location: Western/Eastern Europe based – flexible regarding location
Salary: Negotiable depending on experience
Reference: JT/46587/3/EIPG
Contact Julian Turner, 0207 940 2108,
j.turner@nonstop-pharma.com

Regulatory Affairs Team Leader

Leading small Team. Development, Registration and Post marketing activity. EU Procedures knowledge. 3+ years' experience
Location: Essex, UK
Salary: Circa £40,000 basic, plus good benefits
Reference: JT/45706/42/EIPG
Contact Julian Turner, 0207 940 2108,
j.turner@nonstop-pharma.com

Title: Regulatory Affairs Project Manager - CMC

Specialist Pharma. Development, Registrations and Post marketing – CMC expertise. 4+ years' experience
Location: Middlesex, UK
Salary: Very competitive package
Reference: JT/46566/18/EIPG
Contact Julian Turner, 0207 940 2108, j.turner@nonstop-pharma.com

Regulatory 6 months Contract

Regulatory Contract, Post marketing and Life-cycle focus. 3-4 years' experience
Location: West of London, UK
Salary: £40-£50 per hour rates
Reference: JT/46527/6/EIPG
Contact: Julian Turner , 0207 940 2108, j.turner@nonstop-pharma.com

Qualified Persons Netherlands, Impressive Package

A multinational with a facility in The Netherlands has excellent opportunities for QPs who would like to take on roles broader and more involved than run of the mill QP positions.
Location: Amsterdam, NL
Salary: €60,000-€80,000
Reference: SK/44884/EIPG
Contact Stephen Kenny, s.kenny@nonstop-recruitment.com, (0) 20 7940 2105

Soon to Qualify QP? Gain Niche Pharma Experience inc Sterile

A niche pharmaceutical company in Berkshire have an opportunity for a Quality professional who has recently qualified as a QP or is due to qualify within the next few months.
Location: Berkshire, UK
Salary: £40,000 - £50,000 + Car + Bonus
Reference: SK/42578/EIPG
Contact Stephen Kenny, s.kenny@nonstop-recruitment.com, (0) 20 7940 2105

IMP QP, ASSOC DIRECTOR, BROAD POSITION, BIOTECH

In the market place at present there are a variety of opportunities for QPs with IMPs however there are few as rewarding or with the breadth of responsibility as this one.
The client is a well known blue chip biotech with an impressive portfolio.
Location: Cambridge, UK
Salary: £60,000 – £73,000
Reference: SK/46340/EIPG
Contact Stephen Kenny, s.kenny@nonstop-recruitment.com, (0) 20 7940 2105

Impressive Swiss Biopharma, API Manufacturing, QP

An innovative midsize biopharma with a strong pipeline and exciting collaborations have an opportunity for a Qualified Person with experience of API manufacturing to come on board and join their high calibre quality team.
Location: Switzerland
Salary: €50,000 – €70,000
Reference: SK/46484/EIPG
Contact Stephen Kenny, s.kenny@nonstop-recruitment.com, (0) 20 7940 2105

QP QA Specialist Position. Broad Role Big Biotech

As the Quality Assurance Specialist QP you will have a broad position that not only involves the duties that comes with a QP position but you will also be involved in QMS and managing a QA team.
Location: Berkshire, UK
Salary: £60,000–£80,000+Car+Bonus
Reference: SK/45980/EIPG
Contact Stephen Kenny, s.kenny@nonstop-recruitment.com, (0) 20 7940 2105

Head of Quality/QP, Pivotal Position New Pharma!

An established Specialty Pharma that has recently introduced a new management team and have an opportunity for a Head of Quality to take over the Quality function at their manufacturing site.
Location: Berkshire, UK
Salary: £70,000–£80,000+impressive package
Reference: SK/45660/EIPG
Contact Stephen Kenny, s.kenny@nonstop-recruitment.com, (0) 20 7940 2105

DATES FOR YOUR DIARY

JUNE

24 June 2010 – London, UK
4th European Forum for Qualified Person for Pharmacovigilance (QPPV)
www.diahome.org

29 June 2010 – London, UK
A risk-based approach to medicinal products and medical devices – the common challenges for all stakeholders
www.topra.org

29 June-1 July 2010 – Nice, France
Impurities, Impurities, Impurities
www.management-forum.co.uk

JULY

10-14 July 2010 – Portland, USA
37th Annual meeting & exposition of the Controlled Release Society
www.controlledrelease.org/meeting

13-16 July 2010 – Prague, Czech Republic
XIVth International conference on luminescence spectrometry
www.isls2010.org/contacts.html

26-30 July 2010– London, UK
Working through drug development – Management Forum's Summer School
www.management-forum.co.uk

AUGUST

2-7 August 2010 – Glasgow, Scotland
42nd IUPAC Congress, chemistry solutions
www.iupac

28 August-2 September 2010 – Lisbon, Portugal
World Congress of Pharmacy & Pharmaceutical Sciences 2010 and 70th International Congress of FIP
www.fip.org/lisbon 2010

SEPTEMBER

1-3 September 2010 – Nottingham, UK
UK-PharmSci 2010: the Science of Medicines
www.ukpharmsci.org

5-9 September – Brussels, Belgium
International symposium on medicinal chemistry
www.ismc2010.org

14-15 September 2010 – Manchester, UK
Analysing and trending data to drive quality improvement
www.DBA-global.com

16 September 2010 – Basel, Switzerland
Post-Approval Summit – practical issues and considerations
www.basel.postapproval.org

20-24 September 2010 – Bath, UK
Fundamentals of GMP; a practical approach
www.phss.co.uk

21-22 September 2010 – Berlin, Germany
Formulating better medicines for children
www.apv-mainz.de

27-28 September 2010 – Amsterdam, Netherlands
Amorphous Pharmaceutical Materials
www.pharmaamorphous.com

27-28 September 2010 – Amsterdam, Netherlands
Pharmaceutical Co-Crystals
www.pharmacocrystals.com

29-30 September 2010 – London, UK
Quality by Design: on a small budget
www.management-forum.co.uk

OCTOBER

1 October 2010 – London, UK
Linking pharmaceutical quality and pharmacovigilance systems
www.DBA-global.com

5-7 October 2010 – Paris, France
CPhI worldwide
www.cphi.com

14 October 2010 – Manchester, UK
Best practices in microbiological control and documentation
www.pharmig.org.uk

14-15 October 2010 – Prague, Czech Republic
Quality of medicines in a globalised world: dreams and reality
www.edqm.eu

27-29 October 2010 – Barcelona, Spain
13th APIC/CEFIC European Conference on active pharmaceutical ingredients
www.api-conference.org