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Cover picture: Highly porous structure of a freeze-concentrated phase of a formulation showing the air-filled voids previously occupied by ice crystals prior to primary drying – see page 14.

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EDITORIAL COMMENT

Dear Colleagues

This is the third issue of the journal that has been published under the auspices of EIPG. The feedback from our readers has been very positive and we hope to improve access to this fine publication. However, I do have concerns that with all things electronic and web-based perhaps the messages contain in this publication are not getting through to everyone.

I do urge you to encourage your fellow Pharmacists to read this journal that has been created specifically for you, ie. all Pharmacists working in Industry in Europe. If you are a member of your Pharmacy Association, eg. a member of the Royal Pharmaceutical Society of Great Britain, then by rights you will have access to this publication.

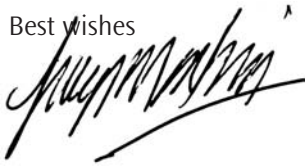
So please feel free and point out to your colleagues where they can access this journal within your country. You can find out more by accessing our website: www.eipg.eu

As usual we have provided a wide variety of topics for your interest and a report from our General Assembly in Riga, Latvia. I would like to thank Inta Saprovska for organizing an excellent meeting and John Jolley for standing in for me at the last moment. The General Assembly covered many topics from education to counterfeit medicines and the report is well worth a read.

If there are any questions you would like ask about the meeting or on topics discussed you can contact either me at: Luigi.G.Martini @gsk.com or our Executive Director Mrs Jane Nicholson at: jane@nicholj.plus.com

Finally, I would like to thank our sponsors GSK and Pfizer and, in particular, Dr David Tainsh and Dr Steve Wicks whose support was vital in making this publication available to all European Pharmacists working in Industry.

Best wishes



Dr Gino Martini FRPharmS
President, EIPG

SWEDISH ENVIRONMENTAL CLASSIFICATION OF PHARMACEUTICALS

by Pär Tellner

Since the end of 2005, pharmaceutical product texts in Fass.se may also include an environmental classification of the pharmaceutical substance. Fass.se is the biggest and most important information database for pharmaceutical information in Sweden, containing all information needed when prescribing or dispensing a medicine. Fass.se is open for everyone and widely used by prescribers and pharmacists as well as the Swedish public. The environmental classification is a unique system of transparency of environmental data on pharmaceutical substances.

Depuis la fin 2005, les textes relatifs aux produits pharmaceutiques sur le portail Fass.se peuvent également comprendre une classification environnementale de la substance pharmaceutique. Fass.se est la plus importante base de données de l'industrie pharmaceutique en Suède. Elle contient toutes les informations nécessaires pour prescrire et distribuer un médicament. Fasse.se est ouvert à tous et est souvent utilisé par les prescripteurs et les pharmaciens ainsi que le public suédois. La classification environnementale est un système inédit de transparence des données environnementales sur les substances pharmaceutiques.

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The most common way for pharmaceutical substances to reach the environment is after consumption. Active substances or metabolites follow the water in the drain to a sewage water treatment plant after excretion in urine or faeces. If the substances cannot be fully eliminated in the treatment plant, by degradation or deposit in the sewage sludge, they may reach the surrounding water compartments. We know however that the levels of pharmaceutical substance residues found in the Swedish waters are very low and have no immediate effects on animals or plants. The risk for adverse effects in the longer term is probably also low for most substances. Nevertheless, research in the area of long-term effects is important.

In the beginning of the 21st century, findings of residues of pharmaceutical substances in the water supply were a growing issue in the Swedish media debate. The question did also become a political topic and the Swedish government appointed a commission in 2002 in order to assess the knowledge of the environmental impact of pharmaceutical substances. The commission report from 2004 concluded that there were big data gaps and that a mandatory environmental classification in Sweden was not compatible with European laws. At the same time, the Swedish county councils started to demand environmental data from the pharmaceutical companies with the intention of taking this into account when making recommendations for the doctors on what medicines to prescribe. Due to the political pressure from the government and the different demands from the county councils, LIF, the Swedish association of the Pharmaceutical Industry, decided to initiate a voluntary environmental classification system in the Fass.se database. Fass.se, which is fully owned by LIF, is the most visited information database for pharmaceutical products in Sweden, used by prescribers, pharmacists and the public, and therefore an appropriate source for this type of information.

Together with several other Swedish stakeholders (the Medical Products Agency (MPA), the Swedish Association of Local Authorities and Regions (SKL), the Swedish monopoly pharmacy chain (Apoteket AB) and the Stockholm County Council (SLL)) as well as with international environmental experts from big pharmaceutical companies, a model was developed on how to present environmental data for prescribers, the public and others with special interest in this issue. A reference group with representatives from the academies, patients, physicians and governmental agencies was also part of the developing process.

Review and classification

Since the mid 1990s all new pharmaceutical substances in Europe are

assessed for environmental risk before approval by the authorities. It was decided to use the data already existing from the standardized studies in the approval process, but to classify the environmental risk in a scale of four steps from insignificant to high risk, to make it easier to understand.

The pharmaceutical companies are responsible for presenting data and making the classifications from the study results. To ensure that the classifications follow the developed guidelines, an independent party, the Swedish Environmental Research Institute (IVL) reviews the data before publishing on www.fass.se.

The first environmental classifications were published in October 2005 for SSRIs (selective serotonin reuptake inhibitors) and PPIs (proton pump inhibitors). By spring 2009, around 60 % of the substances in Fass.se have been reviewed. By the end of 2010, all substances should have been reviewed according to the plan.

Risks vs. hazards

The environmental classification was decided to focus primarily on the environmental risk instead of the hazard. The risk also takes into account the potential exposure in Swedish waters and not only the inherent hazard of the substance itself. Thus, a poisonous cytotoxic substance may constitute an insignificant risk for the Swedish environment if given to very few patients. Less poisonous substances used in greater quantities may result in a higher risk for the environment, something that could be missed if only studying environmental hazard. Even if the focus is environmental risk, the hazard is also presented in Fass.se in terms of how degradable the substance is or if there is any potential for bioaccumulation in aquatic organisms. Anyone can also read the background data to see the tests and results leading to the classification.

The environmental risk classification in Fass.se is based on the ratio between the predicted concentration of the substance in Swedish water systems (PEC, Predicted Environmental Concentration) and the concentration predicted to be safe for organisms and plants (PNEC, Predicted No Effect Concentration). The PEC value is calculated mainly by comparing the sold amount in kilograms during one year with the water consumption of Swedish citizens during the same period of time. The PNEC value is usually a concentration from acute ecotoxicity tests in organisms from three trophic levels (fish, daphnia and algae). The value from the most sensitive organism is used for the calculation. If the predicted concentration in the environment (PEC) is lower than the PNEC (i.e. PEC/PNEC is lower than 1), the risk of environmental impact is low or insignificant. If, on the other hand, PEC is higher than PNEC (the ratio PEC/PNEC is higher than 1), there is a moderate or high risk of impact on the environment.

Some pharmaceutical substances are exempted in the guidelines from EMEA (the European Medicines Agency) and no environmental risk assessment is demanded during the approval process. These include vitamins, proteins, peptides, amino acids, electrolytes, lipids, carbohydrates, vaccines and herbal medicinal products and they are also exempted in the Swedish environmental classification system. They are marked with the phrase “Use of X has been considered to result in insignificant environmental impact” (where X means “vitamins”, “electrolytes” etc.).

The results of the classification, so far, tell us that the average pharmaceutical substance has an insignificant environmental risk and no potential to bioaccumulate in aquatic organisms. Instead it has a slow degradation in the environment. Those results are not surprising as pharmaceutical substances usually are designed to be relatively stable in the human body. Very few substances have reached a high risk; among them we can find some sex hormones, known to have effects in low concentrations.

Is environmental information necessary for pharmaceuticals and how can it be used? There is a growing interest in the area of environmental impact of pharmaceuticals but the use of the classification is a complex question. The therapeutic effect for the patient must of course always have priority over potential environmental effects of the medicine and prescribers already have many other factors to take into account when choosing the right therapy for their patients. However, mapping the potential risks raises the level of knowledge of the potential problem and hopefully leads to more rational discussions and decisions.

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CONTINUING PROFESSIONAL DEVELOPMENT –

THE RPSGB AND TOPRA SCHEMES

by Tony Cartwright

The RPSGB CPD scheme

The RPSGB is the professional body for pharmacists in the UK. It introduced Continuing Professional Development (CPD) for pharmacists in 1999 via an initial pilot project with 500 pharmacists. Nine years later the Pharmacists and Pharmacy Technician Order 2007 introduced the need for mandatory recording of CPD. However statutory CPD will not be introduced before 2010 at the earliest under rule making for the General Pharmaceutical Council which will be the new regulatory body for pharmacists in the UK.

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Principle 5 of the August 2007 RPSGB Code of Ethics under "Develop your knowledge and competence" states that a pharmacist must undertake and maintain up-to-date evidence of CPD relevant to his/her area of practice[1]. The RPSGB consulted at the end of 2008 on a supplementary professional standards and guidance document on good practice[2]. This proposed that:

- A legible record must be kept in a format published or approved by the Society
- The record should be kept either electronically at the Society's website or on another computer or as hardcopy
- The record should comprise between 6 and 12 CPD entries per year
- The record should comply with good practice criteria for recording CPD, including how the CPD has contributed to the quality or development of practice
- The record must be submitted to the Society on request for review and feedback on maintaining a suitable record.

The RPSGB CPD competences

The RPSGB CPD website[3] includes a framework of general competences which might apply to pharmacists working in any sector of practice[4]. These are not core competences. They include interacting and working with people, being a manager, upholding quality and continuous improvement, helping others to learn and develop, working with information, and participating in research and development.

There are some more specific competences in a list entitled "Competences for Pharmacists in the Pharmaceutical Industry"[5]. The list of nine competency areas includes for example "knowledge and application of the principles of Good Manufacturing Practice and quality assurance", "knowledge and application of the laws applying to the pharmaceutical industry, including current EU directives" and "knowledge and application of the principles of Good Clinical Practice (in respect of clinical trials), including current EU directives".

TOPRA

The Organisation for Professionals in Regulatory Affairs (TOPRA) is a global organisation for Regulatory Affairs (RA) professionals with members in 40 countries. Members are drawn from the industry, the regulatory agencies, the consultancy and contract community. Members work in pharmaceuticals, biotechnology, veterinary products, medical devices, cosmetics and complementary therapies.

TOPRA is a voluntary membership body for RA professionals. There is no legal requirement for RA professionals to belong to TOPRA or indeed any other professional body. TOPRA members include pharmacists, lawyers, chemists and physicians, all of which have their own professional bodies with specific CPD requirements. Most members have a life sciences degree, and may not belong to any other professional body.

Categories of TOPRA members are:

- Members
- Registered Members – who are currently working in RA, and who sign a declaration that they are qualified to degree level, have a minimum of 2 years RA experience, and are taking

steps to keep their knowledge and skills up to date

- Fellows – Members with at least 10 years RA experience and who have made a significant contribution to the profession.
- Honorary Life Members – appointed by the TOPRA Board

Registered Members make an annual declaration that they are taking steps to keep their knowledge and skills up-to-date. Registered Members can use the designation MTOPRA and Fellows FTOPRA.

TOPRA's mission is to seek to advance the status of the regulatory profession through education and provision of information to its members. It provides a very wide programme of training and continuing education to its members, including an introductory course for new entrant, an annual symposium and two modular MSc/Diploma qualifications.

TOPRA lifelong learning scheme (LLL)

TOPRA set up its Lifelong Learning Committee in 2004 to propose a scheme for CPD for its members. It reviewed CPD requirements in a range of professional bodies (including the RPSGB), and benchmarked a range of the CPD schemes using the Professional Associations Research Network (PARN). It also surveyed existing CPD arrangements used by TOPRA members by a series of annual questionnaires sent out at subscription renewal. All of the Registered Members stated that they already undertook CPD. The areas of CPD undertaken by Members was investigated in these questionnaires and published in reviews in the TOPRA journal (the *Regulatory Rapporteur*).

The "user requirement" for Lifelong Learning agreed by the TOPRA Board included the following:

- The emphasis of Lifelong Learning is for it to be a service to its members which helps focus their personal and professional development
- Compliance with CPD to be initially voluntary
- Compliance with CPD to be self-certified annually
- Type of CPD record to be left to the discretion of the member, but to be as simple as practicable, recording only items of CPD undertaken and not the process of review, planning and output achievement

The TOPRA Lifelong Learning Scheme was approved by the TOPRA Board as a tool for professional planning and development of members, and which would also provide managers with a more systematic way to analyse and review the development needs of staff. The scheme was rolled out to members in 2008. It sets a target of 50–100 hours per year of LLL. A library of information is provided on the TOPRA website[6] and this includes a Practical Guide, a Personal Learning Plan, a form for recording Lifelong Learning, a list of the key Regulatory Competences, and an overview of the key competences with the numbers of hours of LLL associated with each of the TOPRA conferences and training events.

The definition of LLL includes attendance at formal in-house or external training events, but also includes mentoring, using the Internet to access professional websites, reading technical and professional publications, preparation of presentations, E-learning, work-based projects, attending TOPRA working party meetings, and attending industry or agency working party meetings.

TOPRA regulatory affairs competences

TOPRA has produced lists of competences for each of the major areas of regulatory work of its members – human medicines, OTC products, medical devices, cosmetics and borderline products, chemicals, food additives, pesticides and biocides, veterinary medicines, the national regulatory agencies, IT skills and "soft skills". Examples of soft skills include negotiation and influencing, presentation, team working in a global environment, project management and strategic thinking, leadership, performance management, marketing and crisis management.

The Human Medicines Regulatory Competences include 20 specific competences ranging from "knowledge about the discovery and development of pharmaceutical products" to "knowledge and application of advertising and promotional material clearance". It includes such topics as clinical trial applications, Good Clinical Practice, GMP, European registration procedures, and technical, chemical, pharmaceutical and biological requirements for registration of chemical entities.

Customisation of the TOPRA list of competences to provide a personal listing

The lists of competences are "pick and mix" lists which individual TOPRA members are expected to use to develop their own customised list which reflects their own particular job, experience and seniority within their company. This list would need to be discussed and agreed with the line manager in a company, and could then be used to secure appropriate training and development to ensure that the relevant competences are acquired.

An example of the way this customisation can be applied for different levels of responsibility is shown below for the competence relating to "knowledge and application of European registration procedures".

Level of responsibility within organisation	Competence
Entry level	Understanding of procedures, systems and guidelines, needs of particular authorities, timelines
Intermediate	Ability to assess drug development activities against regulatory requirements of procedures
Senior	Ability to evaluate and analyse basis of approval of competitor products to inform strategic decisions about company's new products
Director	Analysis and interpretation of new legal requirements for impact on company development pipeline

Comparison of RPSGB and TOPRA Schemes

Aspect of Scheme	RPSGB CPD	TOPRA Lifelong Learning
Mandatory or voluntary	Mandatory	Voluntary, but will become mandatory at some future time
Sanctions likely if no records kept	Yes	No
Format of records	Defined, approval needed for other formats	Not defined, format given only as an example
Recommended extent of CPD	6–12 entries per year	50–100 hours per year
List of competences	General list of competences + 9 specific ones for industrial pharmacists	Detailed list of competences for all RA specialisms
Review of members record	Every 3 – 5 years by contract reviewers	No individual review, but analysis of records to provide TOPRA with information on training needs of its members

TOPRA personal learning plan

A key element of LLL is to write down a Personal Learning Plan to define the key skills the RA professional wants to acquire in the next one or two years. This can then be used to develop a plan to develop these competences via LLL.

Recording of LLL

Recording of LLL can be done in any suitable way. Since RA professionals who belong to other professional bodies may already record their CPD, these records will be suitable. There is no formal TOPRA requirement to use any particular form of record, but the website does give an example of a format which would suit most TOPRA members.

Members will be asked to submit a summary record every year, but these will not be audited or reviewed, only analysed by an independent company to provide information to TOPRA on the changing future training needs of its members.

Future developments

The lists of competences are being reviewed to provide further definitions for each competence for staff at Entry Level, Intermediate, Senior Level and Director. E-learning is being extended – which will be particularly useful for one man consultants and staff on maternity or paternity leave to enable them to keep up to date.

Consideration is also being given to the development of an on-line tool to help members to record their LLL, analyse their development needs against the lists of competences, and then to find suitable training to meet these needs.

In due time the TOPRA LLL scheme will become mandatory, when the time is right, it will then be a valuable formal reassurance that RA professionals will maintain and improve their commitment to patient safety.

Implications for industrial pharmacists

Membership of the RPSGB and in future of the General Pharmaceutical Council is not legally essential for many industrial pharmacists in the UK; they may therefore be interested in the more flexible TOPRA voluntary scheme as a model for their own CPD. The TOPRA list of competences for Regulatory Affairs professionals are a much more detailed listing than the RPSGB currently provides. The TOPRA listings are an important reference for industrial pharmacists in the UK and elsewhere to devise a personal list of competences which they can use to produce their own personal and professional development programme.

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BIOSIMILARS: EXTENDING BIOLOGICALS' BENEFITS

by Mark Greener

Generic substitution helps contain healthcare costs. Biologicals account for more than a fifth of new chemical entities and cheaper versions ("biosimilars") should increase accessibility to these important medicines. However, a plethora of issues inherent in biopharmaceutical manufacturing resulted in the EMEA requiring a more extensive clinical trial programme and more rigorous quality control for biosimilars than would typically apply to a small molecule generic.

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The inherent complexity of manufacturing biopharmaceuticals also means that the difference in price between a typical brand and its small chemical generic is much greater than that between the reference product and biosimilar. Nevertheless, even a 20% price reduction on five off-patent biopharmaceuticals could save the EU more than €1.6 billion per year.

Current techniques may not detect all potentially clinically relevant differences between the biosimilar and the original brand, mandating effective pharmacovigilance and prescribing by brand. While such issues pose challenges for manufacturers and regulators, biosimilars should release some of the pressure from increasingly compressed healthcare budgets.

Governments worldwide employ generic substitution to help contain the spiralling costs of medical care. In the USA, each 1% increase in generic prescribing reduces drug costs by $1.32 billion annually[1]. In the UK, the average costs of a generic and the original brand are £4.83 and £19.33 respectively [www.britishgenerics.co.uk/marketkeyfacts.htm]. Health services invest the money released through generic substitution to help meet other health needs.

Producing a generic version of a small molecule drug is relatively straightforward. Essentially, the generic company needs to show identical chemical composition and similar pharmacokinetics to the originator brand[2]. For example, regulatory authorities may consider the drugs to be bioequivalent when the 90% confidence intervals for the ratios of AUC and C_{max} of the generic to brand fall between 80% and 125%[1]. Synthesising small molecules is usually relatively inexpensive, resulting in marked savings compared to the original brand.

Applying the same principles to biologicals – therapeutic substances produced by, or extracted from, a biological source[3] – is more difficult. For example, a typical biological is between 100 and 1000 times larger, and is more complicated to manufacture, than a small molecule drug. Moreover, a biological's activity often depends on maintaining a specific, but fragile, 3-dimensional structure. Finally, the cells used to produce the biological usually release several isoforms[4] rather a single, distinct chemical.

Nevertheless, biologicals accounted for 22% of new chemical entities approved by the European Medicines Agency (EMEA) between 2003 and 2006[3]. Some biologicals, such as bevacizumab and trastuzumab, markedly improve outcomes in difficult-to-treat cancers. Other biologicals, including recombinant human epoetin (rHuEPO) and granulocyte-colony stimulating factor (G-CSF), reduce the incidence of problematic complications, such as anaemia and neutropenia respectively. For example, rHuEPO reduces the need for blood transfusions in patients with end stage renal disease[5].

Biosimilars

Several first-generation biopharmaceuticals are approaching or have passed the end of patent protection. This allows rival companies to develop cheaper alternatives to the original brand – so called biosimilars. As a recent review[2] comments, "Biosimilars should provide cost savings and greater accessibility to biopharmaceuticals". The EMEA approved the first biosimilar – the human growth hormone Omnitrope (somatropin; somatrophin) from Sandoz – in April 2006 and the numbers are increasing steadily. For example, in September 2008 ratiopharm direct

launched Ratiograstim, the first EMEA-approved biosimilar filgrastim.

However, the EMEA rejected a biosimilar interferon-α. Side effects and disease recurrence were more frequent with the biosimilar compared with the original brand. The biosimilar company also failed to satisfy the EMEA that the manufacturing process and immunogenicity testing were adequate. In another case, the EMEA approved different precautions and warnings for a biosimilar growth hormone to the reference brand. The differences probably arise from the different cell lines (yeasts and *Escherichia coli*) used during the manufacturing processes[4]. The EMEA also requires a much more rigorous clinical trial programme before approving a biosimilar than would typically apply to a small molecule generic. This feature examines G-CSF biosimilars to illustrate these points.

An important biopharmaceutical

G-CSF is the major cytokine that controls neutrophil production. G-CSF allows oncologists to use intensive chemotherapy regimens – such as the combination of doxorubicin, paclitaxel, and cyclophosphamide – that would otherwise cause profound and prolonged neutropenia[6]. Furthermore, between 25% and 40% of patients receiving common chemotherapy regimens for the first time develop febrile neutropenia[7]. As a result, oncologists increasingly use G-CSF to support less intensive regimens[6].

Clinicians also use G-CSF to treat congenital and acquired neutropenias, as well as to mobilise haematopoietic stem cells before stem cell donation from healthy people. G-CSF may also enhance regeneration of the heart following myocardial infarction and reduce infarct size following acute ischaemic stroke, although the latter applications remain experimental[6].

Natural G-CSF is a 18.8 kDa protein that contains 174 amino acids, two disulphide bonds and single glycosylation site. Glycosylation reduces the risk of aggregation but does not influence activity. Recombinant G-CSF is identical to the endogenous protein apart from an extra methionine on the peptide's N-terminal and the lack of glycosylation[8].

The clinical trial programme that supported Ratiograstim enrolled approximately 900 patients. For example, randomised, single blind, crossover studies in 190 healthy volunteers compared the pharmacodynamic and pharmacokinetic profile of Ratiograstim and the reference product Neupogen, from Amgen, after subcutaneous and intravenous administration. Ratiograstim's key pharmacokinetic parameters (including AUC, C_{max}, t_{max} and elimination half life) were generally within 80% to 125% of the respective parameter for Neupogen. Relative bioavailabilities were estimated to be 12% and 4% higher for Ratiograstim compared with Neupogen at 5 and 10µg/kg respectively.

Another study enrolled 348 patients with high-risk stage II, stage III or IV breast cancer who received docetaxel and doxorubicin. Patients received Ratiograstim, Neupogen or placebo. Patients on placebo switched to Ratiograstim after one cycle. In the per protocol analysis of 320 women, mean duration of severe neutropenia (DSN) in cycle 1, the primary end point, was 1.1, 1.1, and 3.9 days with Ratiograstim, Neupogen and placebo respectively. DSN ranged from zero to 5 days with Ratiograstim and Neupogen, compared with zero to 9 days in the patients who received placebo. The overall incidence of febrile neutropenia across all cycles was lower with Ratiograstim (20.7%) and Neupogen (22.1%) than placebo (41.7%). The difference in the incidence of febrile neutropenia between Ratiograstim and Neupogen was not statistically significant.

According to EMEA guidelines, as Ratiograstim demonstrated clinical comparability in chemotherapy-induced neutropenia, clinicians can assume that this biosimilar filgrastim is equivalent to Neupogen in other indications. Trials that enrolled 240 patients with lung cancer and 92 people with non-Hodgkin lymphoma confirmed that Neupogen and Ratiograstim show equivalent safety and efficacy.

Manufacturing issues

Living cells – often genetically engineered micro-organisms – produce biologicals. The expressed protein is purified and formulated to yield the final biopharmaceutical. Much of the process is the original manufacturer's proprietary knowledge. Therefore, the biosimilar manufacturer needs to establish a proprietary cell line, DNA expression vector, and manufacturing and purification process[4]. As a result, companies need to invest more in the manufacturing process for a biosimilar than in developing a standard generic, with the average cost €50 million to €80 million to bring a new biosimilar to market.

Partly because of the complexity of manufacturing, EMEA imposes strict quality standards on biosimilars. Small differences or changes in any one of these manufacturing steps potentially influence the active product's characteristics, such as three-dimensional structure, acid-base variants and glycosylation profile[2] and, therefore, potentially influence immunogenicity, tolerability[3] and efficacy. For example, deamidation of asparagine and glutamine side chains,

oxidation of methionine, dimerisation and a range of other changes can reduce activity to only 15% of that of naturally produced G-CSF8. Attaining the strict quality control standards imposed by the EMEA also requires considerable investment. One in ten employees at the manufacturing facility responsible for the distribution of Ratiograstim, works solely in quality control.

As a result, the difference in price between the original brand and small chemical generic is much greater than that between the reference product and biosimilar[2]. Nevertheless, according to the European Generic Medicines Association, a 20% price reduction on five off-patent biopharmaceutical medicines could save the EU more than €1.6 billion per year[9].

Post-marketing pharmacovigilance

Despite the investment in quality control, current analytical techniques and preclinical experimental studies cannot detect or predict all the biological and clinical differences, including immunogenicity, between the biosimilar and the original brand. Therefore, biosimilars require intensive post-marketing scrutiny to ensure that the small difference in the product that potentially arise from manufacturing variations do no cause clinically significant reactions[2,4].

Pure red cell aplasia (PRCA) associated with rHuEPO offers a striking, albeit rare, example of the potential impact of seemingly small manufacturing changes. The risk of this immune-mediated adverse event increased among patients with chronic renal disease taking rHuEPO that had been reformulated so that polysorbate 80 and glycine replaced human serum albumin[3]. However, cancer patients do not seem to develop PRCA, despite the widespread use of rHuEPO. Differences in immune competence, concurrent therapies and reduced exposure between cancer and chronic renal disease patients might account for the discordance[10].

PRCA associated with rHuEPO underscores the difficulty in extrapolating between biopharmaceuticals and patient groups, as well as the need to cognisant of the potential impact of differences in the manufacturing process for the reference brand and the biosimilar. EPO-associated PRCA also highlights the potential for biologicals to induce immunogenic reactions. Many cases of immunogenicity are asymptomatic. However, immunogenicity can undermine therapeutic efficacy (for example, by stimulating production of neutralising antibodies) or induce autoimmunity to endogenous molecules[3].

Effective pharmacovigilance depends on being able to trace the product responsible for the adverse event4. Therefore, clinicians should use brand names when prescribing biosimilars and when spontaneously reporting suspected adverse reactions. This principal is accepted in other therapeutic areas. Clinicians proceed cautiously when substituting drugs used to manage epilepsy[1]. In some cases, even relatively small changes in blood concentration – such as those arising from switching between generics or from generic to brand or vice versa – can lead to breakthrough seizures. Therefore, clinicians often prescribe antiepileptic drugs by brand.

The savings arising from a switch to biosimilars are potentially important. However, the various issues mentioned above means that regulators, manufactures and clinicians must scrutinise each biosimilar in detail and remain alert for any reactions that emerge once the biosimilar enters regular clinical use. Nevertheless, biosimilars should release some pressure on increasingly compressed budgets and allow more patients to benefit from the fruits of the molecular biological revolution.

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FREEZE-DRYING OF SHAPED PHARMACEUTICAL DOSAGE FORMS

by Kerr H Matthews

The technique of freeze-drying is interchangeably referred to as lyophilisation and is traditionally used in the pharmaceutical industry to give parenteral solutions containing hydrolysable therapeutic agents a greatly extended shelf life.

The ubiquitous glass vial with foil-sealed septum being a common manifestation of such products. Closer scrutiny of the contents of such a vial reveals a (white) friable plug or 'dry' powder as opposed to a liquid. Traditional lyophilised products obtainable in this form include vaccines, blood products and certain classes of antibiotics. In fact, proteinaceous compounds, that increasingly include recombinant DNA technologies, are inevitably processed or stored as such. In microbiology, freeze- dried bacterial colonies are regularly sold as white powders in sealed glass ampoules that are brought to life by the addition of a suitable growth medium.

Freeze-drying or lyophilisation is, by and large, a well understood physical process that doesn't require much thought or planning… or so the popular myth prevails! This article sets out to try and expound some of these ingrained beliefs and uses the example of shaped, pharmaceutical dosage forms to do so.

Practice and theory

Unfortunately, it is not uncommon to see undergraduate and even postgraduate students 'freeze-drying' samples in a cylinder drier, common to most biomedical laboratories, not appreciating that they are in fact merely vacuum drying at low temperatures! Similarly, there is the common misconception that successful freeze-drying requires a 'trial and error' approach to determine a useful process cycle. On the contrary, anyone who attempts to freeze-dry anything should first of all consider the following:

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Freezing

A liquid is subjected to low temperatures so that it may solidify. In the case of an aqueous solution, the solution concentration does not change until freezing occurs, ie. water crystallises as ice. The onset of ice formation causes the solute to concentrate and form a saturated solution. Continued cooling causes more ice to form and the solution becomes supersaturated. If the solute is a crystallisable salt such as sodium chloride (NaCl), eventual solidification of the supersaturated solution will occur at the eutectic composition (4 mol/L and –21ºC for $NaCl/H_2O$)[1].

More formally, the eutectic temperature can also be defined as the lowest temperature, on the equilibrium solubility curve, at which the liquid phase can exist in a system that is in thermodynamic equilibrium. This definition suffices for simple solute/solvent, binary systems where a clear eutectic transition exists.

In the case of dosage forms containing water soluble polymers, however, a different scenario is presented as the freezing cycle proceeds. High molecular weight polymer chains are incapable of crystallising to any great extent and further cooling only serves to increase the viscosity to a point where translational molecular motion is effectively stopped and the viscosity increases by several orders of magnitude. This vitrification process is characterised by a critical temperature Tg' (Tg prime) at the point of maximum freeze concentration. This is the single most critical parameter for defining the maximum temperature at which freeze-drying, to preserve the cast shape of the liquid formulation, can be undertaken. Exceeding this temperature during the primary drying process will result in the freeze concentrate losing the required shape due to the 'melt-back' of ice into the glassy phase causing collapse of the shaped glass.

Primary drying

At some point below Tg, the pressure is reduced, controlled amounts of heat are applied and the ice is removed by sublimation. A notable temperature difference between the product and a

cooler, proximal condensing surface drives the sublimation process.

Other factors that affect the efficiency of sublimation include heat transfer coefficients, chamber pressure, product composition, the total volume of water to be removed and the overall efficiency of the freeze-drier.

As the ice front travels from the top of the sample to the bottom during sublimation so the dried product offers a barrier to the further diffusion of water vapour. The sample fill depth should therefore be minimised and sample area maximised where possible to optimise the primary drying cycle. It is critically important for the production of a shaped article that the product temperature should not exceed Tg until all of the ice has been removed so that melt-back may be avoided.

Secondary Drying

At some indistinct point in the freeze-drying process, water molecules 'trapped' in the freeze concentrate that were unable to form ice during the freezing cycle, are desorbed to the gaseous phase. The removal of this 'non-freezing' water is referred to as 'secondary drying'. Low pressure is maintained for the remainder of the cycle and the process temperature increased at a controlled rate as an increase in temperature allows desorption of more water.

As for primary drying, however, care must be exercised to avoid exceeding the Tg of the lyophilised matrix formed from the freeze concentrated phase. Residual water acts like a plasticiser to the lyophilised matrix and although the value of Tg increases as residual water, ie. plasticiser concentration, decreases, the process temperature (and hence the sample temperature) must not rise above the instant value of Tg. Collapse of the matrix structure will result in the irrecoverable loss of the intended shape.

Assuming that collapse has been avoided, the final water content of the shaped product may be as low as 1-2% towards the end of the secondary drying cycle.

For hygroscopic materials such as polysaccharides, the equilibrium moisture content (EMC) under normal laboratory conditions (say, 18-25ºC/50-70%RH) will increase quickly when the vacuum is released to atmosphere. Interestingly, collapse does not generally occur even at EMCs of 15-20%w/w as the Tg of lyophilised polysaccharide structures is above room temperature thus ensuring the stability of such shaped products.

Shaped dosage forms

Despite all this sound physical science, the final shape or form of the lyophilised product is generally of no consequence to the end-user. This is not the case however, with bioadhesive products designed as oral, topical, nasal or buccal dosage forms. In these cases, the final shape will be suitable for the particular application and will be determined by the mould into which the solutions or gels are cast.

Fast-dissolving tablets

A good example of a shaped product is the 'fast-dissolving' oral dosage form known as Zydis™ (Catalent Pharma Solutions, Swindon, UK). This is a small, blister-packed 'tablet' designed to disintegrate within a couple of seconds of placing on the upper surface of the tongue. It will improve patient compliance in children, geriatrics or those individuals where swallowing of conventional tablets and capsules is problematic. For these products, often wrongly referred to as 'fast melt', the size and shape of the lyophilised form is also important as the lyophilised form must be coherent and non-friable to be successfully removed from the blister-pack and applied.

Wound healing wafers

Of particular interest to this author is the use of lyophilised wafers as topical delivery systems. Recently developed for the direct delivery of therapeutic agents to chronic ulcers, these highly porous, lyophilised polymer matrices are able to incorporate many times their weight of both soluble and insoluble compounds[2,3]. They are produced by the casting and subsequent freeze-drying of polymer solutions and gels (including gel suspensions) in an appropriately shaped mould (**Figure 1**). Scanning Electron Microscopy (SEM) of the final product indicates a highly porous network structure that reflects the freeze-concentrated phase of the frozen formulation (**Figure 2**). The bulk of the product is composed of air-filled voids previously occupied by ice crystals prior to primary drying.

As an example of this type of lyophilised product, wound healing wafers containing proprietary inhibitors of proteinases that are over-expressed in chronic wound fluid have been described[4,5]. These novel materials are designed to be placed directly onto the surface of a moderate to heavily suppurating wound where they immediately adhere and revert, at a controlled rate, to the pre-lyophilised state, releasing the contained therapeutic agent directly to the wound bed.

The rheological properties of the reconstituted solution or gel will reflect those of the material or material combinations used. Natural and semi-synthetic water-soluble polymers that form weak gel networks at given concentrations are particularly useful as they will remain *in situ* on the wound for days at a time.

This advantageous state of affairs is possible if a balance between fluid uptake and loss of water to the atmosphere is achieved. Additionally, from consideration of

desirable conditions for efficient freeze-drying already discussed, wound healing wafers tend to be less than 5 mm deep and 1-100 cm^2 so they are ideal for relatively short process cycles.

Buccal dosage forms

Nicotine has been delivered to sheep and insulin to humans via a lyophilised nasal insert composed predominantly of shaped, freeze-dried hydroxypropyl methyl cellulose (HPMC)[6,7] and there are many examples of buccal dosage forms fabricated from lyophilised polymers. The hydrophobic cerebrovascular treatment, denbufylline has been administered to rabbits using modified chitosan[8] but like most such dosage forms, the freeze-dried polymers are inevitably compressed into buccal tablets. More recently, selegiline, a treatment for Parkinson's disease, has been formulated as a multiparticulate, lyophilised Carbomer™ formulation[9]. For this recent example, for Zydis™ and for wound healing wafers in particular, the shape, mechanical properties and storage stability are all critical to the success of the application.

Critical considerations for shaped dosage forms

As discussed, carefully designed process cycles originating from a rational knowledge of the freeze-drying process and the thermal properties of the formulation to be processed are required to ensure the shape and form of the lyophilised product during freeze-drying. A sound knowledge of critical thermal events such as the point of maximum freeze concentration (Tg') or eutectic melting points[1] are necessary to ensure that no collapse of the product during processing occurs.

The freeze-thaw properties of polymer solutions and gels containing either soluble or insoluble compounds can be studied using thermoanalytical methods such as Differential Scanning Calorimetry (DSC) or Hot/Cold-Stage Optical Microscopy (HCSOM) – more popularly known as a 'freeze-drying microscope'. The latter technique has been developed by Biopharma Technology Limited to include a vacuum chamber in which the general conditions inside a freeze drier can be modelled.

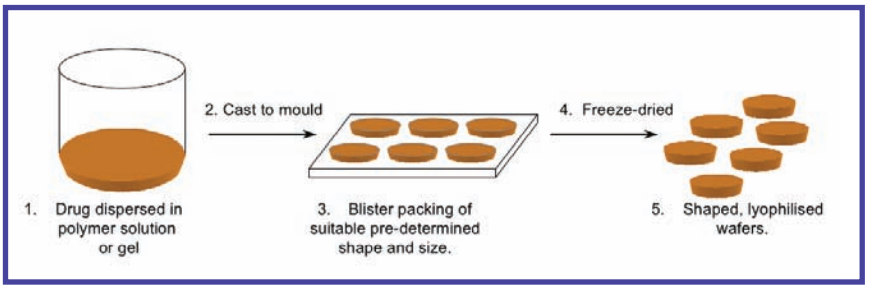

Figure 1. Casting and freeze-drying to produce lyophilised wafers

The formulation, prior to lyophilisation, is placed on the hot-stage, enclosed within a vacuum chamber, and frozen by the controlled circulation of liquid nitrogen. Specific conditions of temperature and pressure can be applied to the sample and changes of morphology and state can be viewed and digitally recorded in real time. The progress of ice sublimation, the collapse temperature (exceeding the glass transition of the freeze-concentrate), 'melt-back' (exceeding the melting-point of ice and/or a eutectic melt) can all be discerned. This knowledge can be applied to the design of a process cycle that should consistently produce the required shaped products.

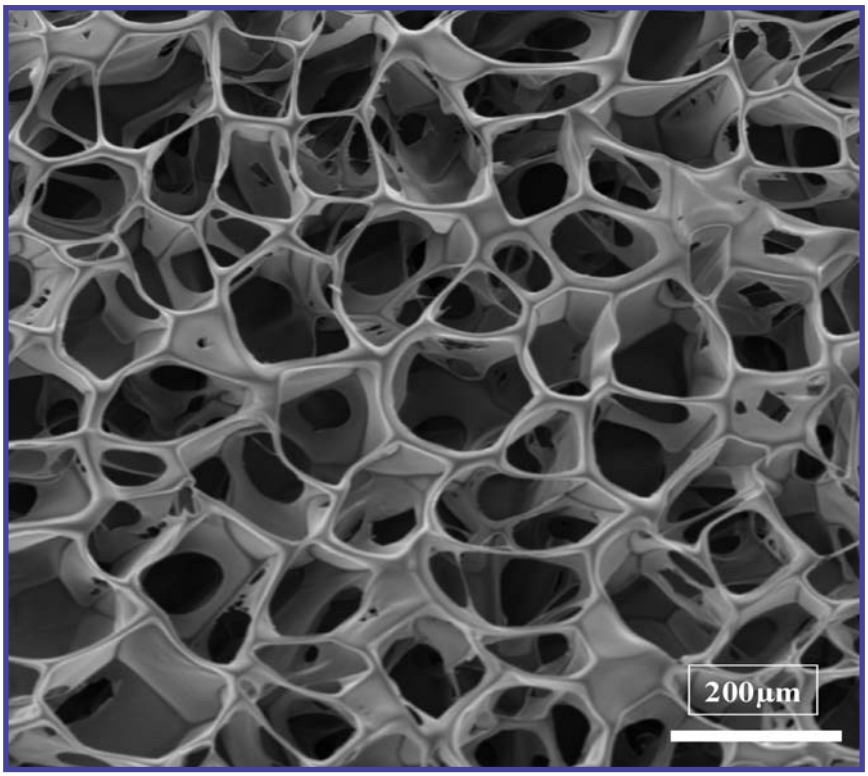

Figure 2. Porous network structure of the frozen formulation.

The future

Although freeze-drying is generally recognised as an expensive batch process for producing stable dosage forms of hydrolysable and thermo-labile therapeutic agents, the relative expense of the purified proteins, peptides and cytokines that are necessarily freeze-dried, negates such considerations. Furthermore, if a generic drug can be delivered with improved patient compliance, bioavailability and bioequivalence than existing methods, and/or the inherent properties of a shaped, mucoadhesive dosage form are more suited to a specific application than a parenteral injection, then lyophilised products are considered 'value-added' and priced accordingly.

Whatever one's standpoint, freeze-drying is an important process in the pharmaceutical industry with an assured future. An improved understanding of the scientific principles underpinning it and an ability to exploit its non-traditional capabilities, ie. the production of shaped dosage forms, can contribute to the development of modern medicine.

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MAKING SUPERIOR PARTICLES FOR DRUG DELIVERY USING POWER ULTRASOUND

by Graham Ruecroft

Drug delivery by inhalation offers significant potential for administering otherwise injectable drugs. Therapeutic areas to be addressed by this approach now and in the future include diabetes, cancer, pain, migraine and osteoporosis.

Pharmaceutical manufacturing is committed to making particles and then modifying their properties in order to turn them into structured products but, surprisingly, 5-10% of manufactured formulations fail to meet specifications. Typically, particles for drug inhalation are manufactured by very primitive pharmaceutical technologies such as micronisation, a destructive and energy-inefficient technique to turn large, regular crystals into irregular 1-5µm particles that can undergo morphological change and surface polymorph transformations leading to amorphicity and decreased stability[1]. The particles can also be highly charged, which affects the flow-rates essential for aerosolised and dry powder inhalers.

Many molecules with excellent biological activity – but poorly water-soluble – can be used by formulating them into crystalline nanosuspensions[2], sub-micron colloidal dispersions of pure particles of drug substance stabilised (usually) by surfactants. Oral nanosuspensions have been specifically used to increase the rate of absorption and bioavailability of drug compounds. Also, marketed drugs can be reformulated using more suitably engineered particles, potentially leading to new drug products.

Such mesoscopic crystals need to be engineered by 'ground-up' molecule-to-crystal approaches, in order to control their micro and macro structure and fully characterise their performance enhancing attributes. This will allow control of surface characteristics and geometry while maintaining high throughput, low cost and industrial scalability. Thankfully, emerging crystallisation and particle engineering technologies are now being developed to assist in both drug development and manufacture. Production of drug particles using supercritical fluids has generated significant interest, albeit with limited success to date. Questions are being asked about scalability, cost-effectiveness due to high pressure, limited productivity and inherent amorphicity. Conversely, the Solution, Atomisation and Crystallisation by Sonication (SAX) technology, developed in conjunction with the inventor, Dr Rob Price of the University of Bath, avoids all these issues to give superior engineered drug particles[3,4] see **Figure 1**.

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Power ultrasound and crystallation

Almost all chemical processes utilise crystallisation – cooling, evaporative, anti-solvent or reactive – but this can be one of the most difficult unit operations to control. Ultrasound is used routinely in areas such as medical imaging, diagnostics and biological cell disruption and now the application of power ultrasound (20-100kHz) has risen to prominence in sonochemistry (to modify chemical reactions) and sonocrystallisation[5]. High energy transient cavitation is particularly effective for primary nucleation and reproducibly generating micro-crystalline seed crystals (to avoid conventional seeding). As a result we can control crystal size distribution, morphology, impurities and solid-liquid separation. The in-line continuous flow or batch mode process can be applied to intermediates, excipients, APIs, binders and sugars and, importantly, can be validated across scale in cGMP environments.

Polymorph control with ultrasound

An understanding of the metastable zone (MZ) and the zone width (MZW) is

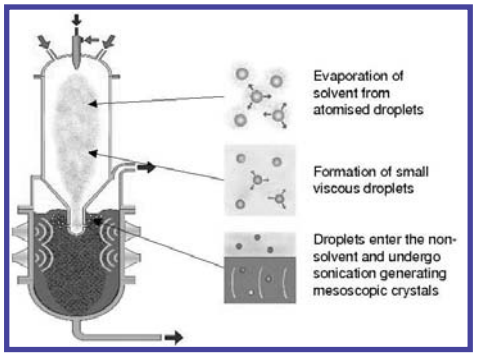

Figure 1. The SAX process.

fundamental to controlling crystallisation. The application of high-intensity 20kHz ultrasound can lead to narrowing of the MZW and, by so doing, it is possible to 'tailor' a crystal size distribution using a short burst of ultrasound to nucleate at low supersaturation and then allow growth to large crystals, and the production of small crystals via continuous insonation and mechanical disruption of crystals or loosely bound agglomerates. The optimum needs to be determined by experimental investigation. Ultrasound can also induce secondary nucleation by mechanically disrupting crystals or loosely bound agglomerates.

The overall technique lends itself extremely well to polymorphic systems; polymorphism is common amongst organic materials resulting in the existence of two or more crystalline phases with different packing in the crystal lattice. Isolation of the 'wrong' polymorph brings substantial problems in pharmaceutical applications but, by careful application of ultrasound, the ground state polymorph (the most thermodynamically favoured and least soluble) can be isolated.

From laboratory to manufacture

One of the principal barriers to the adoption of power ultrasound technology in pharmaceutical manufacturing has been the lack of industrial scale equipment. To address this need Prosonix has designed industrial equipment to allow effective and focused distribution of acoustic energy into a liquid by using a number of low-power transducers bonded to the outside of a cylindrical duct[6]. This avoids the problems of using high-powered probe-based equipment where metal particles can be shed into the crystallising liquor.

The technology can be applied from kilogramme to tonne scale for fine chemical and pharmaceutical manufacture. Value-added benefits can include identification of new process patents for individual products, thus securing and extending marketing timescales. An attractive feature of sonocrystallisation is that it can be applied at any stage in a product pipeline, then ensuring that success in the laboratory can be replicated across scale.

Mesoscopic particles

We have seen specific benefits in the production of particles for inhaled therapeutics, and also see potential in the production of nanosuspensions, pharmaceutical co-crystals and combination-based products (**Figure 2**). SAX allows production of spherical particles, with a well-defined size range and with control of the macroscopic morphology, including polymorphism and surface topology. These properties are invaluable in defining aerodynamic properties of particles, shelf life, stability, bioavailability and efficacy.

Combination particles

Combination particles are single particles containing two or more APIs or API and excipient such as lactose. These particles should have a high degree of crystallinity with respect to both ingredients. Often the two drugs have synergistic action (at molecular and cellular level) and need to be delivered in an exact ratio such as in inhaled corticosteroid (ICS) and Long-Acting Beta-Agonist (LABA) formulations (**Figure 2**). For optimal interaction the two drugs must be delivered to the same site of action in adequate doses, since the synergistic action may be reduced with variable ICS and LABA doses.

SAX introduces the potential for a novel particle engineering solution whereby a single droplet containing the two APIs in an exact ratio can be converted to a particle containing the very same drug substances as separate crystalline entities. Indeed triple therapy should be possible with SAX.

Future for sonocrystallisation

Power ultrasound can be applied to crystallisation at manufacturing scale and now in technologies to produce micron-sized particles for drug inhalation. Sonocrystallisation can become a core technology in the pharmaceutical industry and we can expect to see many more industrial applications in the near future. Processing techniques such as SAX should become superior technology for the manufacture of microcrystalline drug substances, complex APIs, combination particles, and nanosuspensions leading to significant benefits to drug innovator, technology provider and, importantly, the patient.

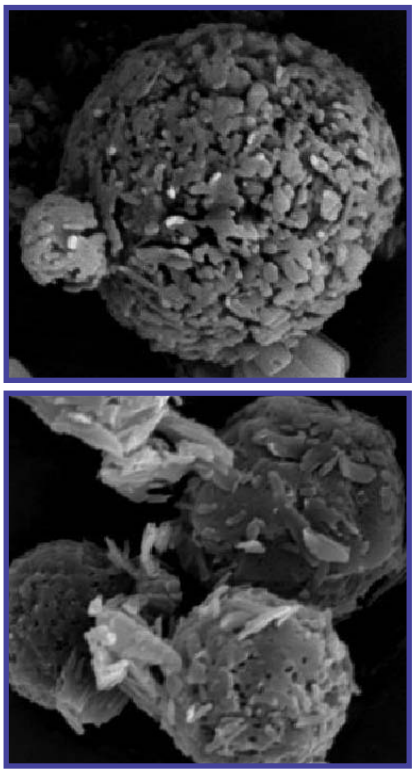

Figure 2. SAX particles of budesonide x7,000 (top) and ICS/LABA combination particles x5,000 (bottom).

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WEB 2.0 – WHAT DOES IT MEAN TO THE PHARMACEUTICAL INDUSTRY?

by Marta Garrido

We are bombarded with information about Web 2.0 and how to benefit from this influx of digital marketing in the coming years. What does it really mean? We have moved from a straight based Web 1.0 linear marketing paradigm, where information is presented to the client without any thought to the individual's need, to a world of social communication. This shift has paved the way for increased interactivity between businesses and consumers[1]. The information age has moved from a static model to one in which data are dynamically presented. Interactive technology has moved beyond the browser.

Web 2.0 facilitates communication between two universes. It fills the human need to connect, share information and support over the internet[2]. An individual does not need to leave his/her home in order to have meaningful communications with Email buddies, colleagues, and like-minded individuals. Nowadays, consumers are well-informed. They seek information through the internet, family doctors and friends. Patients seek not only support but often second opinions through web sites.

By the year 2011, pharmaceutical companies' online spending will reach $2.2 billion but is this budgetary expenditure benefiting the bottom line? How can a regulated industry participate in a deconstructed environment? First, it must look at Web 2.0 as more than a social medium with open-ended parameters. The wisdom of the crowd in this new social networking must be closely monitored. Pharma must comply with regulations and codes of practice, which spell out what it can and cannot do. According to Amber Link, the principles inherent in the codes of practice remain the same regardless of the medium used[3].

Consumers now want fast, efficient access to information that can answer their questions. What often happens is that when a patient logs into a company's web page, the information presented is stagnant and does not relate to the patient. A video clip about a product is not going to generate return visits or develop loyalty to a brand. It may answer a momentary question but ideally, patients would like information tailored to newly prescribed drugs, their own symptoms and side effects. The new technology of Web 2.0 provides the opportunity of interactive communication with the patient, provided that patient's information is kept secure and private, and the patient is aware of how his/her personal information is being used.

Pharmaceutical e-marketing can enhance health by alerting specific populations to problems and solutions. This particular mode answers the question of "who is sick?" and matches the information to the particular segment being targeted, such as individuals with diabetes, Parkinson's disease, or other disease-specific group. It can augment patients' compliance, by sending out personal messages, such as RSS (Rich Site Summary) to remind them to take their medications, or to keep appointments. These instant feeds can be routed to computers, ipods, mobiles, and/or telephones. Put simply, an RSS is a web feed, like Email or similar to a mailing list. You can get information straight to your desktop. You choose the information that you want and you can read it in your own time. The consumer signs up with individual sites to receive information of relevance to their lives.

Pharmaceutical marketing is still behind when it comes to taking advantage of new interactive technology because it continues to function in the areas it has always used, such as print and television. Using the web as a means of disseminating information creates a life of its own. For example, clinical trial information which, if positioned appropriately, can enhance credibility, information sharing and positive outcomes. The industry can use web-based applications for efficiently and effectively communicating with critical audiences such as thought leaders, speakers, advisers, and investigators. The web can become a living market research.

Maintaining credibility

The challenges facing the industry lie in using the new interactive technology while maintaining credibility, and

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adhering to the different parameters of the various codes of practice. It must do this while enhancing its image as patients' advocates, and reducing the public's view of controlling attitudes and data management to enhance revenues at the expense of consumers' health. While the social media of the web can effectively enhance the industry's image, it still is an uncontrolled medium. The 'wisdom of the crowds' can end as not wisdom at all. Inaccurate information can be generated and swiftly spread like wildfire through the web. It must be closely monitored and regulated perhaps by a neutral third-party, therefore limiting liability to the pharmaceutical company.

Social media

Conversely, social media can be an unknown quagmire for the pharmaceutical industry and careful scrutiny and vigilance are required to stay abreast of regulatory codes and avoid potential problems.

One example is Blogs, which can either be beneficial or detrimental to the industry. If a company undertakes blogging, it has to be open to the opinions of others, which can be both good and bad. Also, there is the possibility of patients reporting adverse reactions, and pharma has to be ready in advance to deal with these eventualities.

Podcasts, which can be customised to specific conditions, can add tremendous impact to e-marketing campaigns. Podcasts are maintained on a regular basis to keep them on the cutting age of new development in a particular field. YouTube also provides an opportunity to reach the public with information relayed within a real setting. Using real-life patients speaking about positive experiences can do for a brand what a leaflet will never accomplished.

The Pharma Industry has to recognise the influence of the connected consumer.

FAQs can be a useful tool where patients can actually send in personal questions and have them answered by a clinician on the web. An off-shoot of FAQ sites, patient-generated health journals are on the horizon, such as the recently launched 'Knol' by Google. Knols are lay-person orientated, authors are identified and their identities checked. The initial Knol on the web is on health issues and consumers can find information written about anything from migraine headaches to shingles. Also available is 'Trusera', an online health network with real health stories by real people. Additionally, Caring.com provides help and checklists for those caring for elderly parents.

The new consumer

As a result of this amazing influx of information and interactive technology, there is a new breed of consumers on the receiving end of the marketing landscape. Today's consumer is hungry for information and fully understands the various companies' marketing strategies and how they affect their bottom line. Web 2.0 has levelled the playing field and it can be seen as being against pharma's controlling attitudes and data management. The Pharma industry has to recognise the influence of the connected consumer. Millions are linked in a worldwide network and these consumers have become similar to KOLs (key opinion leaders) within the lay community. Social computing is growing exponentially and it cannot be ignored.

Social media has empowered patients by giving them an opportunity to voice opinions and experiences and consequently learn from one another. The era of non-transparency and keeping information from the consumers is past. Patients' forces will impact healthcare policies worldwide and they will have to be heeded and harnessed.

Now it is time for the pharmaceutical industry to ask whether it can meet the challenge of social media and take this opportunity to answer patients' needs and offer sophisticated educational and behavioural support, tailored to the individual. By doing so, the industry could regain public trust, improve health outcomes and in the process, see their ROI soar.

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MANAGEMENT AND REVISION OF DOCUMENTATION

by Michael Hiob

All pharmaceutical and biopharmaceutical companies depend on documentation systems as a major part of GMP compliance. In this article, we take a look at a typical system for organisation of documentation. We also review a typical documentation life cycle and considerations to be taken at each stage.

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Organisation

In order to administer the vast number of documents in a pharmaceutical company, a hierarchical structuring of the document system in three levels (see **Figure 1**) is useful.

Strategic level

Documents at this level describe cross-company objectives. Typical examples are the quality management policy and the quality management handbook.

The highest level of company management determines this procedure itself and also authorises it.

Operational, cross-company level

The quality policy defined at the highest level should be applied across the company in the form of (standard) process instructions. Therefore, documents at this level apply to all departments, or across the company, and are generally not product-related. However, they already include the detailed provisions required in order to implement the objectives defined in documents at the strategic level.

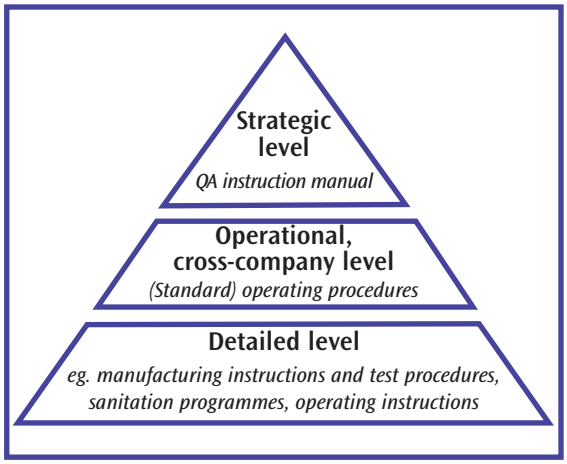

Figure 1. Organisation of a documentation system

Detailed level

This level contains detailed provisions such as manufacturing instructions, test procedures or sanitation programmes for specific products, procedures or areas. These are compiled on-site on the basis of higher-level instructions (eg. procedure for the compilation of instructions).

Life cycle

As is the case with facilities, equipment or procedures, documents must also be adapted to accommodate changing operational, scientific and regulatory requirements. A document will pass through a number of typical stages in its life cycle (see Figure 2) that reflect its current status. The document should be handled at each stage in accordance with established requirements to ensure that it is suitable for its intended purpose.

Compilation and changes

New documents should only be compiled and existing documents should only be changed by the person who deals in practice with the provisions in the document and is familiar with the procedure concerned.

Analysis

Once the above has been carried out, the form and content of the document should be analysed. The formal analysis to verify compliance with the organisational and format requirements can be carried out by the quality assurance department. The technical check should be carried out independently of the compiler by a person who has the appropriate technical knowledge and experience to evaluate the provisions set out by the compiler.

Implementation

GMP-relevant documents must be formally approved before use. This approval should be carried out by the person who is responsible for the area

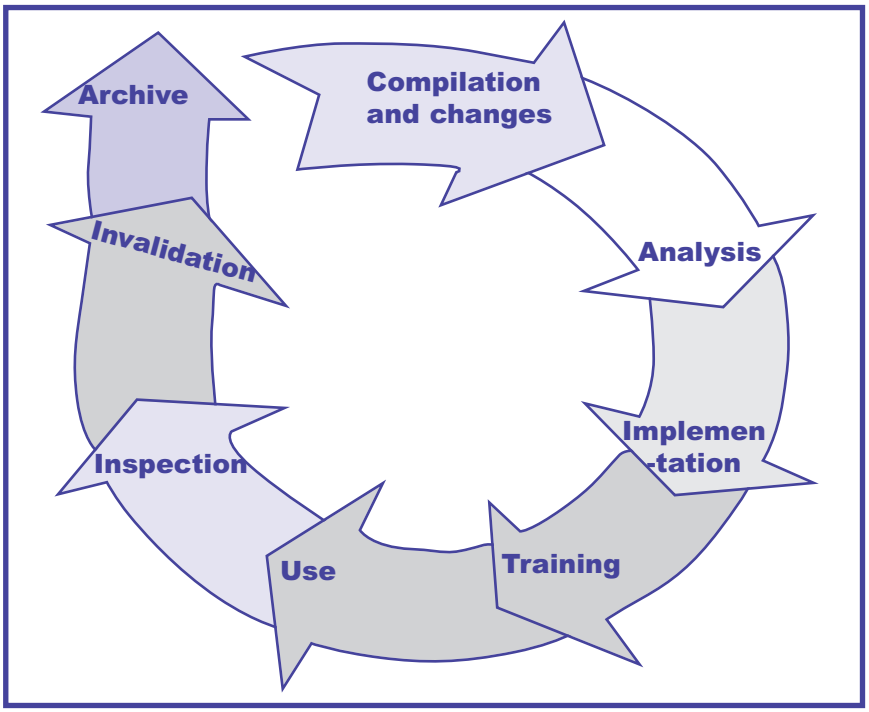

Figure 2. Life cycle of a document

regulated by the document – examples being the head of production or the head of quality control. The start and end of the document's period of validity must be defined independently of the approval. Where no specifications are made in this regard, the document's period of validity is unlimited and begins automatically on the day it is implemented/approved.

Training

In order to be able to implement the contents of the documents, the relevant staff must know, understand and also be able to apply them. These requirements must be acknowledged by signature. Managers must check whether training in the handling of the document is required and, if so, arrange for this to be carried out.

Use

The document should be available on-site for the duration of its validity. This may be achieved by using a hardcopy or providing authorised access to a corresponding file in a computer system. Provisions should exist that specify whether personal working copies may be made and passed on to third parties, if required. The procedure used for the distribution of new versions must be defined.

Inspection

Checks should be carried out within the scope of self-inspections to determine whether the documents are being complied with and whether their contents are still up-to-date and suitable.

Invalidation

Documents that become invalid must be withdrawn from current operations by means of a regulated procedure in order to prevent unintentional use of non-valid documents.

Archiving

The national regulations apply for the storage of documents once they have been used.

Implementation

In addition to requirements in relation to documents, specific prerequisites must also be fulfilled by staff to ensure that the documents are actually "lived out" – ie. complied with and implemented. Staff must not only know and understand the provisions laid down in the documents, it is also extremely important that they are prepared to implement these and that the required general operating conditions (organisation, resources) exist.

This article is based on excerpts from the GMP Manual, a comprehensive reference book published by Maas & Peither AG Publishing, www.gmp-publishing. com.

NEWS FROM EFPIA

EFPIA launches anti-counterfeiting pilot project in Sweden

Pharmacists in Sweden will check a unique identification code on individual packs as an anti-counterfeiting measure. The codes will be generated and applied by manufacturers as a barcode that pharmacists will be able to scan and check when the product is dispensed.
www.efpia.org/content/default.asp?

Innovative Medicines Initiative

Funds of 246 million euros will be made available through a joint initiative of the EC and EFPIA to support public-private research co-operation for the fast development of better medicines.

The projects will involve health issues such as diabetes, pain, severe asthma and psychiatric disorders, while increasing drug safety.
www.efpia.org/content/default.asp?

NEWS FROM THE EIPG

2009 General Assembly of EIPG in Riga, Latvia

The 2009 General Assembly of the EIPG was held in Riga on the 18th and 19th April. During the meeting, the Association for Industrial Pharmacists of the Hungarian Society for Pharmaceutical Sciences was welcomed as a new member of the EIPG. Dr Sylvia Marton and Emoke Kiss-Csikos were congratulated on their persistent and successful negotiations to achieve the resulting membership.

The Italian delegation, represented by Piero Iamartino, was elected as Vice-President of EIPG for the next 3 years.

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

A report by John Jolley (Great Britain) of the EMEA meeting with "interested parties" demonstrated a large number of pending GMP related issues. Although legislation, including Annex 16, is still to be updated and the QP discretionary powers remain under discussion in Brussels, it was agreed that the updated EIPG Code of Practice for Qualified Persons should be issued subject to further amendments in line with new regulations.

A discussion of the threat from counterfeit medicines was led by Claude Farrugia (Malta). Further representation to the European Commission concerning the responsible pharmacist and draft EIPG Guidelines on Good Distribution Practice of Medicinal Products were agreed.

A working group considered a draft document on Continuing Professional Development for Regulatory Affairs prepared by regulatory staff in Germany and Great Britain, and chaired by Valérie Lacamoire (France). Two new sections will be added and the final document published on the EIPG website in October.

European Industrial Pharmacy, the EIPG Journal was successfully launched and feedback on the first two published issues was presented by the editor, Joe Ridge.

The President of EAFP, Jeffrey Atkinson (France) led a discussion on Working Party 5 (pharmacists in industry) of PHARMINE, the EU Lifelong Learning Programme. At the next General Assembly, Greece will lead on a brain-storming session of the employment opportunities available for pharmacists in the future pharmaceutical industry.

Several country initiatives were reviewed at the meeting, including a Belgian document submitted to their Agency on the Guidance on GMP requirements in Phase 1 and exploratory clinical trials. Previously, it had been agreed that this should be "Europeanised" and a group of delegations will provide further input to Philippe Van der Hofstadt.

Harold Smeenge (Netherlands) agreed to take the lead in developing contacts with the European Pharmacy Students Association (EPSA) that had been initiated by Denmark over the past 12 months. A Belgium representative of EIPG attended the EPSA Annual Congress in April, in Reims (his report is below).

Piero Iamartino issued an invitation from Associazione Farmaceutici dell'Industria (AFI) to hold the 2010 General Assembly in Italy and this was agreed with acclamation. A vote of thanks was made to Inta Saprovka, Berlin-Chemie and all members of the IPS of the Pharmacists Society of Latvia, who helped organise the meeting and provided generous hospitality.

Jane Nicholson
Executive Director EIPG

Report on the EPSA Symposium

I was invited by Philippe Van der Hofstadt to represent EIPG at the EPSA Symposium on 21 April. The Symposium's topic was "Information to the Patient" and, at first I wondered how industry could be involved in information to patients – typically a matter for community pharmacists, regulators and consumer associations. But, from my own experience in industry, I quickly realised that pharmacists working in the industry may have to deal with information to patients at several stages of the development and production of medicinal products. My abstract paper emphasised those various functions and the influence they have on such information. Starting with Regulatory Affairs, I moved to Medical Information, linking this to Marketing and Regulations on promotion and ended with Manufacturing and the need to have compliant packaging information.

During the Symposium and the panel discussion, it was clear that most of the students were not aware of the role an industrial pharmacist may have concerning patient information. The other panel members (Mr Rothert (DG Enterprise), Mrs Dr Moulon (EMEA), Mr Parrot (Association des Pharmaciens Français) and Mr Tromp (EuroPharm Forum) explained the links between the various stakeholders the patients, the Regulators, the community pharmacists and the pharmaceutical industry. I drew the students attention to the fact that pharmacists have an optimal education to interface and integrate that process. Pharmacists' role in medical information clearly goes further than just information to patients.

Roland Schots

REGULATORY REVIEW:

Review of major developments in GMP and the regulation of medicines in the EU and on the International Scene, September to December 2008

by Steve Fairchild

The past quarter has been relatively quiet regarding regulatory developments that affect the pharmaceutical industry.

Thus the items covered in this issue are limited to the following:

- New Quality related Q&A from the EMEA.
- New guidance on justifying the use endotoxin testing of plasma derived products.
- Draft Guidance from the FDA on data requirements for injector pens and similar devices.
- New Q&A on the implementation of ICH Q8, Q9, and Q10.

Europe

The European Medicines Agency (EMEA)

New questions and answers on stability testing

The EMEA's Quality Working Party has added two new items to its list of Q&As.

These are pretty straightforward questions concerning endotoxin testing and sterility testing at the end of the shelf-life period (during stability studies).

You can find this new information under the heading "Stability" in the Quality Working Party's Q&A pages on the EMEA's website.

Guideline on the replacement of rabbit pyrogen testing of plasma derived products

This document sets out the points to consider in justifying (in marketing authorisation submissions) the use of a test for bacterial endotoxins as an alternative to the rabbit pyrogen test for plasma derived products.

It covers:

- The scope and legal basis of the guidance.
- The limitations of the LAL test.
- Process related and clinical considerations.
- Regulatory issues.
- Alternative test methods

To see this new guideline go to the EMEA website under CHMP.

It is due to come into effect on November 1st 2009.

United States of America

The US Food and Drug Administration (FDA)

Draft guidance on pen, jet and related injectors

The FDA has recently issued the draft version of a document intended to provide points to consider in developing technical and scientific information to support a marketing application for pen, jet or related injector devices intended for use with drugs or biological products.

This draft document covers injectors supplied alone and products combining the injector and the drug dosage form.

It can be seen on the FDA website under "Draft Guidance for Industry and FDA Staff".

Comments can be submitted to combination@fda.gov. until July 27th 2009.

International

International Conference on Harmonisation (ICH)

New questions and answers on the implementation of ICH quality guidelines Q8, Q9 and Q10.

Towards the end of 2007 the ICH set up a working group to facilitate the implementation of its quality guidelines on:

- Pharmaceutical development (Q8),
- Quality risk management (Q9) and
- Pharmaceutical quality systems (Q10).

This group recently published a set of answers to frequently asked questions on the implementation of these guidelines by pharmaceutical companies and drug regulatory authorities (DRA).

These Q&As cover the following topics:

- The need to have a defined "Design Space" or implement "Real Time Release" testing in order to implement "Quality by Design "("QbD").
- The development and use of "Design Space" in relation to the manufacture of a medicine.
- The operation of "Real-Time Release Testing".
- Control Strategies and GMP requirements for "QbD" products.
- The relationship between "Design Space" and "QbD".
- The benefits of a "Pharmaceutical Quality System" in accordance with ICH Q10, its operation and relevance to regulatory activities.
- The impact of ICH Q10 on (regulatory) GMP inspection practices.
- The impact of ICH Q8, 9 and 10 on "Knowledge Management".
- The relevance of specific software solutions to the implementation of ICH Q8, Q9 and Q10.

These Q&As provide useful information on the implementation of these guidelines. They can be seen by going to the ICH website under "Quality Implementation Working Group on Q8, Q9 and Q10".

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Email: sbfairchild@aol.com

For a list of useful website addresses associated with "Regulatory Review" go to www.industrialpharmacy.eu

DATES FOR YOUR DIARY

JUNE

22-25 June 2009 – Cork, Ireland
Active pharmaceutical ingredients
www.DBA-global.com

30 June-1 July 2009 – London, UK
Supply chain assurance
www.DBA-global.com

JULY

1 July 2009 – London, UK
6th Eudra vigilance information day
www.diahome.org

2-3 July 2009 – London, UK
EU pharmaceutical regulations – for the pharmaceutical and biotechnology industries
www.management-forum.co.uk

6 July 2009 – London, UK
The contract QP
www.management-forum.co.uk

8-10 July 2009 – Edinburgh, UK
British Pharmacological Society (BPS) Summer Meeting
www.bps.ac.uk

18-22 July 2009 – Copenhagen, Denmark
36th Annual Meeting and Exposition of the Controlled Release Society
www.controlledreleasesociety.org

29-31 July 2009 – Bonn, Germany
Phytopharm 2009
www.adaptogen.ru

AUGUST

2-7 August 2009 – Glasgow, UK
42nd IUPAC Congress – Quality assurance of medicines and detection of counterfeits
www.jpag.org

3-7 August 2009 – Vienna, Austria
11th International Congress on amino acids, peptides and proteins
www.meduniwein.ac.at

SEPTEMBER

2-9 September 2009 – Manchester, UK
science@BPC 2009: Technologies for healthcare
www.bpc2009.org

3-8 September 2009 – Istanbul, Turkey
FIP 2009 – Responsibility for patient outcomes – are you ready?
email: registration@newbrooklyn.nl
www.fip.org/istanbul2009

7-9 September 2009 – Manchester, UK
The British Pharmaceutical Conference – Technologies for healthcare
www.bpc2009.org

7-11 September 2009 – Manchester, UK
Auditor/lead auditor for pharmaceutical QA, IT and engineering personnel (3 different courses)
www.iagtgroup.com

8-9 September 2009 – Munich, Germany
Introduction to Quantitative Pharmacology and PK/PD for Drug Discovery & Development Scientists
www.lakemedelsakademin.se

15-18 September 2009 – London, UK
World Drug Safety Congress Europe 2009
www.healthnetworkcommunications.com

16-18 September 2009 – Washington DC, USA
PDA/FDA Joint regulatory conference: Securing the future of medical product quality
www.pda.org

17-19 September 2009 – Stockholm, Sweden
Rosenšn Meeting 2009: DMPK aspects of drug combinations
www.swepharm.se

21-24 September 2009 – Manchester, UK
Pharmaceutical GMP
www.DBA-global.com

21-25 September 2009 – Sheffield, UK
Hands-on Workshops on concepts and applications of population based *in vitro-in vivo* extrapolation of ADME properties
www.simcyp.com

21-25 September 2009 – Bath, UK
Fundamentals of GMP – a practical approach
www.phss.co.uk

24 September 2009 – London, UK
Recent developments in wound management: intelligent biomaterials to novel antimicrobials
www.rpsgb.org

27 September-1 October 2009 – Rovinj, Croatia
1st World Conference on physico-chemical methods in drug discovery and development
www.iapchem.org

28-30 September 2009 – London, UK
Practical aspects of controlled temperature storage and distribution
www.DBA-global.com

28-30 September 2009 – Manchester, UK
Human error: causes and prevention
www.DBA-global.com

30 September-1 October 2009 – Berlin, Germany
Modern concepts in pharmaceutical profiling and pre-formulation – from compound screening to candidate selection
www.apv-mainz.de

OCTOBER

1 October 2009 – London, UK
Anti-counterfeiting measures: implications for quality professionals and QPs
www.DBA-global.com

5 October 2009 – London, USA
International conference on pharmacokinetics: spearheading advances and delivering the science
www.eufeps.org

5-8 October 2009 – Bethesda, MD, USA
PDA's 4th Annual Global Conference on pharmaceutical microbiology
www.pda.org

12-13 October 2009 – London, UK
FIP Quality International 2009 – managing quality across the drug supply chain: from product inception to patient utilization
www.rpsgb.org

15 October 2009 – London, UK
Analysis of inhaled products
www.rpsgb.org

25-29 October 2009 – Barcelona, Spain
The 16th intermediate workshop on PK/PD data analysis
www.lakemedelsakademin.se

26-28 October 2009 – Antalya, Turkey
3rd BBBB Conference on Pharmaceutical Sciences
www.bbbb-eufeps.org