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Cover picture: Blow-fill-seal vial (see article in next issue). Image: Fotolia



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EIPG elects a new President: Martini passes the baton to Paccioni

On the 21st April, at the General Assembly organized by hosts VAPI-UPIP in Brussels, the European Industrial Pharmacists Group (EIPG) elected its new President, Jean-Pierre Paccioni, president of the Central Council of Section B of the French Ordre National des Pharmaciens and outgoing Treasurer of EIPG, after outgoing President Gino Martini decided to call it a day.

Gino Martini was elected President of EIPG at the General Assembly in Prague in 2007. Jane Nicholson, Executive Director of EIPG, recalls: *"Gino's Presidency was timely for EIPG, coming, as it did, when membership of the European Union was expanding, and the European pharmaceutical industry was coping with new challenges in the practice of industrial pharmacy. He recognized the need for EIPG to grow as the need for greater collaboration amongst industrial pharmacists across Europe became more important."*

Indeed, Gino believed in seeing EIPG reach out as far as its resources would permit and beyond. Malta, Latvia, Portugal, Spain – Gino took EIPG to the edges of Europe. His charisma and energy attracted new organisations to EIPG. In his eyes, none were too small or unimportant, and he was determined that all members could, and should, each in their own way, contribute to the association.

Jean-Pierre is no stranger to the Presidency of EIPG, having previously held the post between 1998 and 2002. However, it is a different EIPG that he now inherits from Gino, and the challenges that the organization faced a decade ago pale in comparison with those it faces today. Emerging markets, mergers and acquisitions, reference pricing, medicines shortages, the increasing role of biotechnology: these are but a few of the challenges facing the European industrial pharmacist. Yet it is not an unprepared EIPG that Gino is bequeathing to Jean-Pierre. Throughout his Presidency, Gino had long prophesied the

shape of things to come and prepared for them. Piero Iamartino, Vice-President Technical and Professional Development of EIPG, reflects: *"Gino's vision of the future of the industry, and the challenges that such a future would present to industrial pharmacists, were always of great concern to him. He strived tirelessly and selflessly to see EIPG mature into an association that could be, and be seen to be, a key player in industrial pharmacy and a point of reference to the professionals to which this industry owes its continued ability to serve society."*

The baton of EIPG's leadership has been passed into the capable hands of an individual with an equally remarkable pedigree. Crucially, it has been passed with Olympic-winning smoothness, a transition so necessary in these troubled times where the pharmaceutical industry appears delicately poised between Pharmageddon and Renaissance. Jean-Pierre has already declared the priorities of his Presidential mandate as an increased EIPG visibility: a strengthened influence on the European institutions and consolidated links with partner associations, and working groups on technical issues. Thus, in the words of the new President, Gino *"will continue to be part of the future of EIPG in the same unique way that he is part of its past and its present."*; but then, as those who have worked closely with them have long known, both men share a kindred, determined commitment to European industrial pharmacists. *"Industrial pharmacists in Europe should get to know each other better and raise their profile to be recognized by the European institutions. I am pleased to take over the presidency of EIPG to give a new impetus to that association and benefit from the pharmaceutical expertise of the different member countries."*, declared Jean-Pierre upon his election. A statement to fill us with hope for the future.

Bienvenue à la barre, mon ami.

Claude Farrugia, Vice President Communications
EIPG

STABLE CYTOCHROME P450 ENZYMES FOR TOXICITY AND METABOLISM TESTING

Attrition in drug discovery and development: The importance of CYPs in drug metabolism and toxicity

by Bob Chaudhuri and Bill Primrose

Despite an estimated \$50 billion in collective annual R&D spending by the large pharmaceutical companies, it is estimated that only 1 in 24 of drug discovery projects achieves a marketable product, and only 1 in 10,000 of new chemical compounds that are screened for a beneficial therapeutic effect is eventually approved as a new medicine. Most of the attrition occurs in the screening and pre-clinical development phases. However, notwithstanding this, still only approximately 1 in 11 compounds that do enter clinical trials eventually gets market approval. A major cause of attrition at the clinical stage is safety and toxicology, amounting to 30% of all failures. In addition, liver disease associated with drug toxicity is the most common reason for market withdrawal of drugs after approval.

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The failure rate for drug candidates in clinical trials clearly indicates the need for massive improvement in the predictive power of the pre-clinical tools used to assess drug safety. It is estimated that an improvement of 10% in predicting failures prior to clinical trials could save a company \$100 million in development costs per approved drug.

During the drug discovery process, it is imperative to determine the rate of metabolism, and the nature and toxicity of potential drug candidates, before a compound is introduced into expensive human clinical trials. Drugs are often taken in combination, and the interaction of two drugs may cause unexpected toxicity in one or either; this is

mediated by cytochrome P450 enzymes (CYPs) and is referred to as a drug-drug interaction (DDI).

CYPs are intracellular membrane-bound enzymes, belonging to a family of proteins which reduce molecular oxygen to reactive oxygen atoms. There are 57 different CYP isozymes in the human genome, with some expressed in significant quantities in the liver. They play a crucial role in detoxification, modification, and removal of natural or synthetic chemical entities, by rendering hydrophobic molecules more water soluble, making them easier for the body to excrete. Around 75% of the total metabolism in humans is mediated by CYPs.

Figure 1 shows the reaction mechanism of CYPs and a few of the

drug-metabolising reactions that particular isoenzymes can catalyse.

There are a variety of methods currently used to obtain information on the interactions of candidate drugs with CYPs. These include use of liver slices, primary hepatocyte cell cultures, stable cell lines, liver microsomes and isolated recombinant CYPs, as well as simulation of hepatic toxicity using *in silico* methods. Stem cell-derived hepatocytes offer potential advantages over cells obtained from resected human liver tissue in terms of product consistency and availability. However, it has not proved possible to reliably produce hepatocytes with defined CYP compositions, and a particular problem will be to accurately mimic mature hepatocytes present in an adult liver. Therefore, it remains necessary to use isolated recombinant CYP enzymes. In any case, if a particular CYP is identified as being inhibited by the compounds of a lead series, with potential for an adverse DDI, then direct optimisation against this CYP will be a critical part of the lead optimisation process.

Currently marketed recombinant human CYPs are available as membrane suspensions from bacterial and insect cells and are only stable at -80°C , thus requiring a cold chain. CYPs expressed in human cells are of low activity, with considerable batch to batch variation.

Alternative sources of high-quality recombinant human CYPs, suitable for high-throughput studies, would improve the drug development process. More predictive *in vitro* studies would be expected to inform decision-making at an earlier stage and drive the synthesis and selection of better drug candidates.

The technology

CYP Design Ltd. (CDL, www.cyp-design.com) is building on the technological breakthroughs of its founder, Professor Bob Chaudhuri, and his team at De Montfort University, Leicester, UK. CDL is marketing Sacchromes™, yeast microsomal membranes containing human CYPs as reagents for early stage drug discovery studies. These

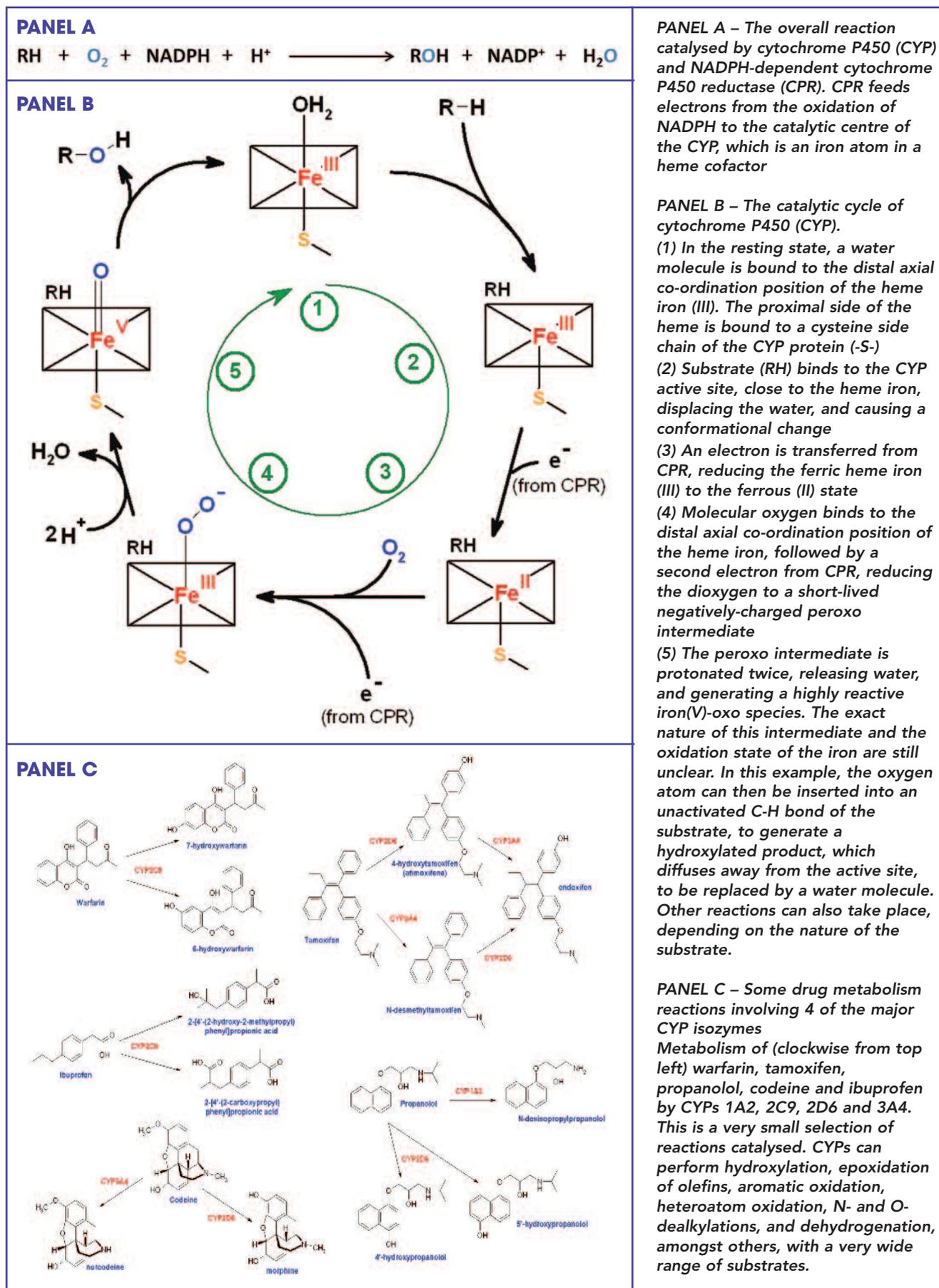


Figure 1: The mechanism of CYPs and some examples of the metabolism reactions they catalyse.

are straightforward to produce, more active and more stable than those from other systems, and more convenient to use than other commercially-available CYPs. Critically, they do not require a cold chain. These new products have been developed through a combination of three technologies:

(i) Expression of recombinant human CYPs in eukaryotic yeast cells

Active mammalian CYPs are naturally embedded within the cell in the membranes of the endoplasmic reticulum (ER). Baker's yeast (*Saccharomyces cerevisiae*) provides an ideal cell production model for recombinant CYPs as it mirrors the mammalian intracellular environment and also shares large similarities in the proteome. Yeast is also the simplest unicellular eukaryote, whose genetics are well understood, allowing rational manipulation and the expression of proteins of human origin. Yeast is also a favoured source for high yield "cell factories" with a world-wide knowledge base,

and sophisticated production technologies.

Yeast microsomes offer particular similarities to microsomes obtained from human cells and are therefore well suited for human metabolic or toxicity studies. In contrast, insect cells have an intracellular environment quite different from that of mammalian and yeast cells. Bacterial (e.g. *E. coli*) cells have no ER, meaning that 'active' CYPs have to be packaged into artificial membrane structures after expression of the recombinant CYP.

CYPs can be produced by engineering yeast cells to express a desired human CYP isozyme, creating a unique yeast strain, which can be grown in liquid culture to produce biomass from which the CYP can be extracted. The system can be easily scaled using standard technology from shake flasks for a few litres of material up to industrial fermenters to produce thousands of litres. Per volume of cell culture, yeast produces 20-30 times more CYP than insect cells.

(ii) Novel NADPH-dependent P450 reductase

CYPs require a redox partner enzyme, cytochrome P450 reductase (CPR, see Figure 1), to deliver the electrons required for splitting molecular oxygen into oxygen atoms. In a eukaryotic cell, both CYP and CPR are naturally integrated into ER membranes, and must physically interact for activity. However, excessive quantities of CPR can cause cell collapse through the production of reactive oxygen species (ROS). Thus, CPR is toxic to cells when present in high concentrations.

Co-expression or post-expression combination of these two proteins is

necessary for an active system *in vitro*. However, production methods directed towards high production yields tend to yield final product with low activity.

We have discovered a novel, human variant CPR that allows CYP activity to be raised in combination with high-yielding production techniques, without over-production of ROS. The inclusion of this novel proprietary reductase therefore provides a leading competitive edge.

(iii) Stabilisation of Yeast Microsomes

The CYP-containing yeast microsomes are amenable to a proprietary process that allows them to be safely lyophilised and stored at room temperature. Full activity is maintained for at least 3 months (see Figure 2). This stabilisation process can also be adopted for microsomal CYP preparations from any production source.

Advantages of stable, active CYPs in drug discovery

Stabilised CYPs can be dried down into a number of formats, including 96- and 384-well microplates to fit in with drug discovery workflows. Active enzyme is regenerated by adding buffer to the microsomal films, which are then ready to use. In contrast, CYPs from other sources have to be thawed from -80°C, and then transferred to the testing system, a process which involves pipetting viscous and heterogeneous suspensions.

We have produced nine of the most important human CYPs (1A1, 1A2, 1B1, 2A6, 2C8, 2C9, 2D6, 2E1, and 3A4), responsible for the majority of all drug metabolism, and packaged them into Sacchrosomes™.

Sacchrosomes have specific benefits:

- Stable for storage at room temperature
- Full activity restored by simple reconstitution in aqueous suspension
- Enzyme performance unaffected by the stabilisation procedure
- Flexible presentation; samples can be formatted in vials, or aliquotted onto 96- or 384-well plates, prior to stabilisation

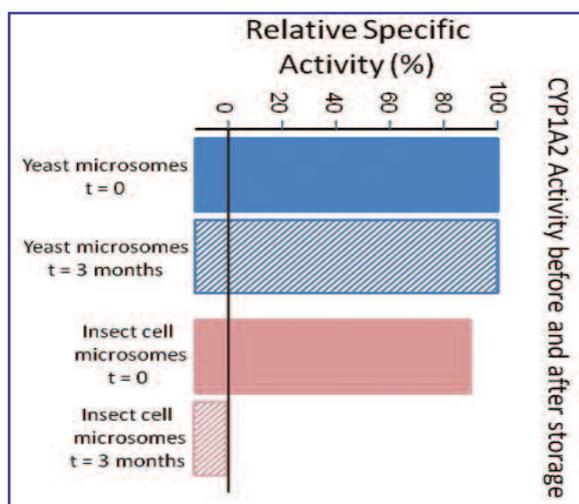


Figure 2: Comparative activity of CYPs expressed in yeast cells (Sacchrosomes™) compared to those from insect cells after storage at room temperature for 3 months.

The activity of CYP1A2 expressed in yeast and stabilised (blue bars) is shown at time 0 (solid) and after 3 months storage at room temperature (hatched). This is contrasted with CYP1A2 expressed in insect cells (pink bars) stored under the same conditions. Activity was measured using a fluorescence assay with 3-cyano-7-ethoxycoumarin (CEC) as substrate and 3-cyano-7-hydroxycoumarin (CHC) as product. Other CYPs give similar results on storage.

- Ready to use off the shelf and convenient to handle, simplifying routine analyses by medicinal chemists or within the DMPK laboratory

Sacchrosomes show specific activities comparable to, or better than, CYPs produced in insect cells or in *E. coli*, supporting our belief that yeast microsomes are more similar to the mammalian system than those expressed from other sources. Comparative data for nine of the most important human CYPs are presented in **Figure 3**.

Convenient-to-use CYPs will allow more compounds to be tested at an earlier stage for potential toxicity problems. Stabilised CYPs will also find further applicability in fully

automated drug discovery chemistry platforms, where toxicity and metabolism data are generated simultaneously with activity data.

Future developments

The technology can be further developed in other areas. For example:

- Making CYPs available within a living cell format for *in vitro* drug metabolism (cf hepatocytes) and biotransformations
- Multiple CYPs within artificial microsomes to mimic human liver microsomes
- Stabilised human CYPs in human cells for use at a later stage in the drug discovery

process, when a clinical candidate is being selected

- Biocatalysts for the manufacture of pharmaceuticals, agrochemicals and industrial chemicals (since CYPs facilitate mono-oxygenation reactions with exquisite regio- and stereo-selectivity under extremely mild conditions, which are challenging tasks for most chemical catalysts)
- Cellular systems containing CYPs that have the potential for use as bioremediation agents

Further Information

For further information on CDL's Sacchrosomes™, please visit our website: www.cyp-design.com.

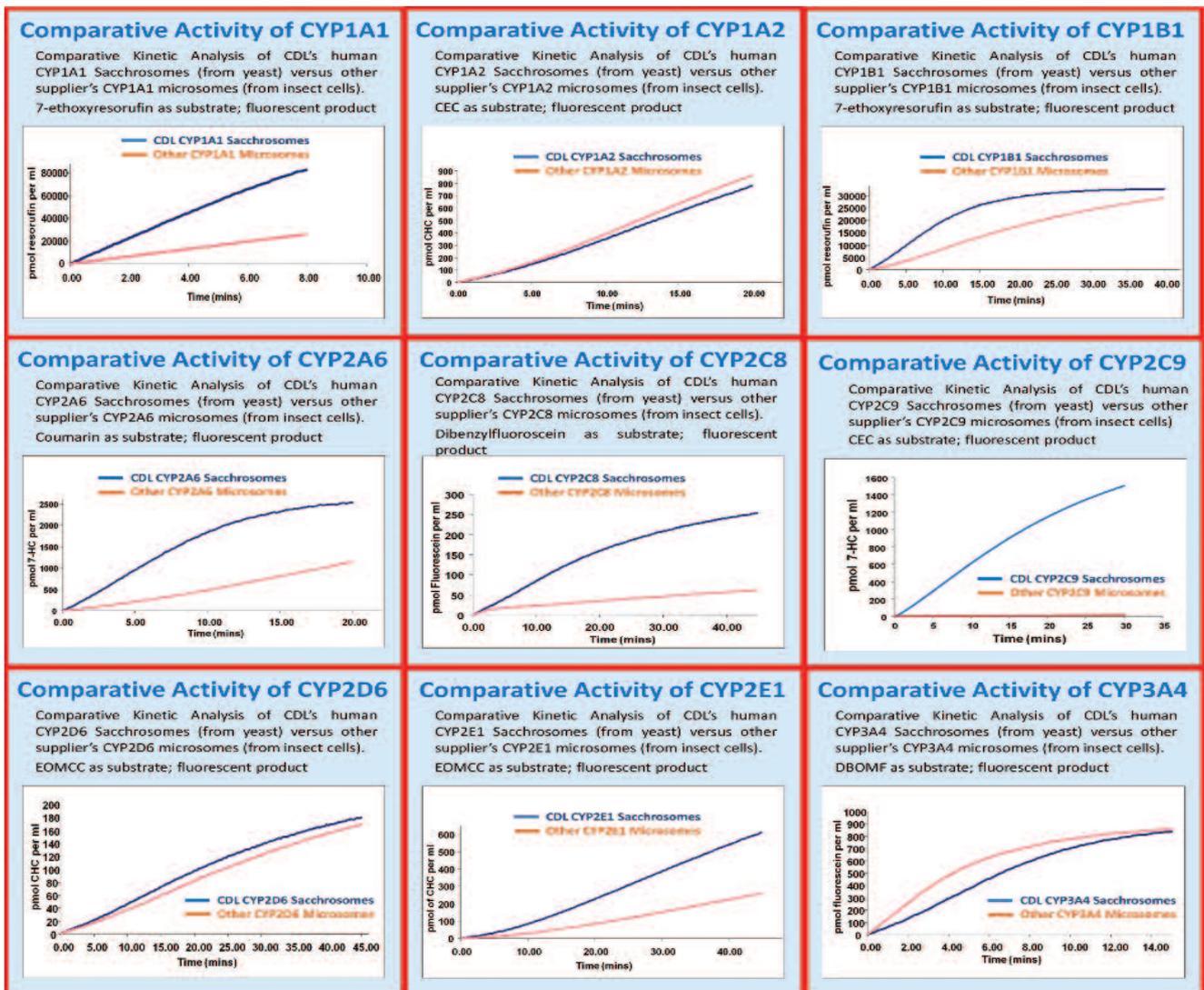


Figure 3: Comparative activities of CYP Design's Sacchrosomes™ for 9 major CYP isozymes with those produced in insect cells. Activities for yeast microsomes are shown with blue lines, activities for insect microsomes are shown with pink lines

CONTROLLED ENVIRONMENTS: THE NEW IEQ

by Chuck McKinney

Controlled environments, including laboratories and cleanrooms, consume tremendous amounts of energy, making them highly visible targets for efficiency initiatives. Comfort, safety, and quality control objectives often restrict building owners' and facility managers' ideas about potential energy savings. Standard operating practices and rules of thumb have morphed into pseudo-code requirements. As research begins to question these practices (and even standards), designers and operators grapple with the ultimate challenge: becoming more energy efficient without compromising the performance of critical facilities.

Chuck McKinney is VP/marketing for Aircuity Inc. The company's patented OptiNet technology offers demand-based control solutions for both critical environments and commercial offices, significantly reducing energy consumption and greenhouse gas emissions while maintaining quality parameters.

The energy savings opportunity in critical environments seems obvious. On average, labs consume 5 to 10 times more energy per square foot than typical office space, with highly specialized facilities such as vivariums and cleanrooms greatly surpassing those averages. The single largest energy component within these facilities is ventilation, which can account for 45 to 65% of energy use. Typical research facilities

operate at eight to 15 air changes/hr (ACH); vivariums often operate at 12 to 25 ACH. Cleanroom rates begin at 15 ACH for Class 8 environments and top out at an amazing 750 ACH!

Variable air volume (VAV) control systems equipped with demand control ventilation (DCV) solutions are now widely recognised as a successful way to balance energy efficiency with comfort and quality objectives.

The promise of DCV

DCV involves highly sophisticated environmental sampling and monitoring infrastructure. With DCV, air samples are routed to special sensors that analyse conditions and then interface with the Building Management system that automatically adjusts airflow in response. The people responsible for indoor environmental quality (IEQ) in the facility are the ones who determine the appropriate parameters. Airflow is tailored to the needs of each specific room or zone, rather than general "rules of thumb."

By monitoring individual room conditions and varying make-up air volume based on those conditions, building owners are realising significant energy savings while maintaining a high standard of IEQ.

Despite the success to date of DCV deployment in multiple types of facilities, questions remain:

- To what extent can DCV be used to optimise energy consumption without compromising performance and quality?
- How can managers, users, researchers, and quality assurance personnel be confident about the conditions of their facilities when implementing energy-efficiency initiatives that seek to lower their air change rates from previously established constant volume rates?

During the past few years, ideas about critical-environment management have undergone a sea change. Rather than prescribing strict operational processes, regulatory and accreditation organisations have begun to adopt performance-based metrics that involve actual environmental conditions, leaving the "how to" process of achieving those performance metrics to facilities personnel.

Research labs (such as conventional "wet" chemistry and biology labs) have been highly involved in this trend, and their experiences will eventually begin to influence developments in other



Figure 1: A graphic "dashboard" interface is an easy tool for helping facilities gauge the financial effect of adjustments in air change rates.

types of critical environments, including cleanrooms. Opportunity and confusion have both arisen, as researchers and facilities personnel strive (and sometimes struggle) to agree on management protocols that will consistently meet or exceed stipulated environmental conditions. The door has been opened to new approaches that may include energy-efficiency projects, but how best to proceed?

Data, data, data

Information services that can alert facilities personnel regarding the condition and performance of the spaces they manage will help build the confidence required to continue the expansion of DCV. In fact, the availability of information services that can document compliance with IEQ performance metrics may well be the driving incentive for implementing a monitoring and control strategy.

Information solutions must be multi-faceted, providing multiple perspectives relevant to different audiences. EH&S professionals will want to examine IEQ and building performance data, while energy managers will likely be more interested in monthly savings and identifying issues that may be impacting those savings.

Other key attributes of effective monitoring systems include:

- Visual displays of analysed information, not just raw data
- Short- and long-term trend information
- Alerts for high-priority issues based on persistence or pervasiveness, not just simple parameter thresholds
- Automated summary reports that can provide high-level views of how a facility is operating.

Information services have evolved to help organisations manage their critical environments proactively and report performance information in meaningful ways to building owners, facility managers, EH&S personnel, and accreditation and regulatory bodies.

Graphics improve understanding

The diagrams illustrate some easy-to-understand, yet sophisticated, IEQ graphics. **Figure 1** is a dual display showing both the flow reduction over the previous month and the average ACH rates during that period. ACH monitoring is important to help building owners meet regulatory guidelines and determine if energy savings objectives are being reached, and to give managers, users and/or researchers peace of mind that ventilation rates are appropriate for the conditions.

Continuous monitoring and reporting can also provide tremendous insight, showing how activities within a space directly affect the amount of airborne contaminants.

Combining parameters on a graph can quickly and easily illuminate adherence to (or departure from) prescribed IEQ boundaries. **Figure 2** comprises a "comfort analysis" graph in a vivarium, plotting humidity and temperature measurements. The shaded box reflects the acceptable ranges for a particular species; in one of the diagrams parameters are being met, but in the other, something has gone awry.

How far can DCV extend into critical environments? Given the fact that even a modest air change improvement of 10% can reduce energy consumption by almost 27%, the boundaries will continue to be tested. The new ANSI Z.9 regulation for fume hood airflow requirements resulted from years of analysis that challenged the status quo. Research relevant to controlled environments is underway now; the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) has recently commissioned a study to determine how DCV may be applied to cleanrooms.

As DCV applications expand, monitoring and reporting capabilities will play an increasingly important role in helping companies, institutions, and other organizations achieve significant greenhouse gas reductions while maintaining high-quality, high-performance critical environments.

All graphics courtesy of Aircuity

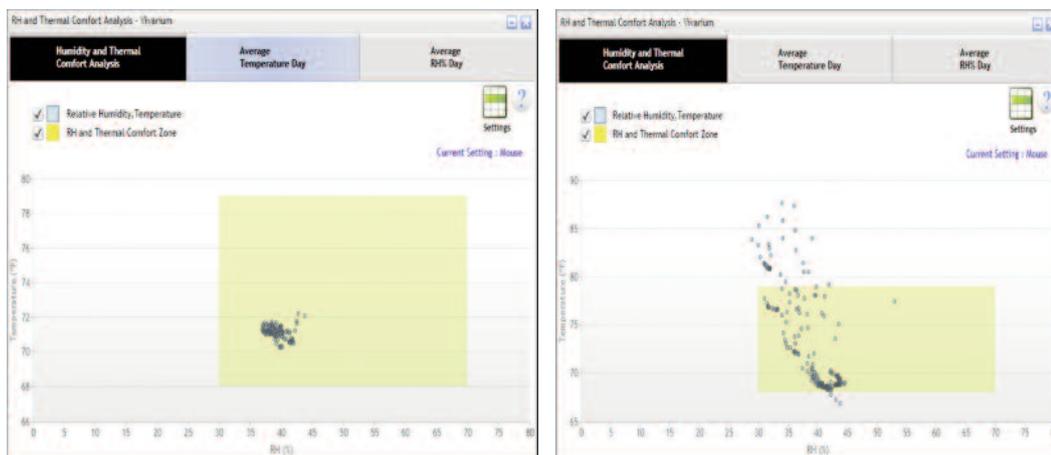


Figure 2: A "comfort analysis" for a vivarium includes a shaded box indicating the acceptable range of temperature and relative humidity parameters for a particular species (in this case, mice). The dots represent real-time sampling of temperature and humidity. Dots clustered in the box indicate acceptable conditions; the other diagram indicates problems.

COMPARISON OF BIOSAFETY TESTING REQUIREMENTS OF BIOLOGICALS AND VACCINES

by Daniel Galbraith

Advanced therapies and biologicals have introduced to us the possibility of treating and curing disease previously without remedy. With these treatments, because they use living cells during production and the inability to terminally sterilise the product, there is an increased risk of microbial contamination not seen with small molecule or chemically-produced drugs. This opens the possibility of introducing new animal or human pathogens to patients or possibly the wider community by administration along with the drug.

Daniel Galbraith is Chief Scientist with BioOutsource Ltd a Contract Testing Organisation based in Glasgow, Scotland, which supports the Biologics and Vaccine Industry.

This issue was well recognised by the regulators and almost in parallel with the first products the early regulations were put in place^{1,2,3}. The first products used a number of animal-derived products in their manufacture and the first regulations sought to contain the risk by testing starting reagents and process intermediate samples. As products and processes have changed over time, new guidelines have been introduced to almost keep pace with them. Along new guidelines⁴ there has been a harmonisation of the global guidelines to help manufacturers maintain product security.

Viral vaccine safety

The first medicines to use living cells as the basis of their manufacture were viral vaccines. These treatments were very successful in preventing previously untreatable disease, most famously poliomyelitis which is now almost eradicated worldwide. Vaccines are administered to healthy individuals who in many instances will never encounter the pathogen, as in the case of Poliovirus, the causative agent of poliomyelitis. The balance of safety risk of treatment versus the outcome (protection from serious disease) with these healthy

individuals must be carefully considered, especially in the case of children. Clearly these drugs must be very safe given the many millions of people who need to be given them.

The vaccine regulations are controlled differently from those of the biologicals. In Europe, the vaccines guidelines with regard to virus safety are contained within the European Pharmacopeia (EP 2.6.16) and have changed little over the past 20 years with respect to the format and methodology. In the United States the vaccine guidelines were specified within a number of different areas, both the Pharmacopeia and the Code of Federal Regulations being involved, but more recently the FDA have published guidelines on vaccine virus safety⁵.

The nature of vaccine production methods makes them susceptible to contamination, which has occurred on several occasions. Polio vaccine batches, for example, have been contaminated with a number of different monkey pathogens, particularly during early batches where primary monkey kidney cells were used. The contaminating viruses hitchhiked with the cells taken from the monkey kidney used

in the production, thereby contaminating the batch. Stringent controls were put in place to ensure the safety of vaccines by pre-screening cells prior to use and this has been successful in preventing contamination. However, we can only ever prevent our known risks and it is clear that new viruses are being discovered and described each year. Therefore we need not only specific assays for known pathogen risks, but general assays capable of detecting a broad spectrum of agents which could appear.

Guidelines

More recently, a new category of drugs has been developed which also used living cells during production. This has been governed by a raft of guidelines most usefully covered by the ICH Q5A: ICH harmonised tripartite guideline on "Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin". This guideline was agreed by representatives from the USA, Europe and Japan to cover the relevant testing required for biotechnology products and has been enacted into guidelines in each of these areas. Recombinant DNA technology has allowed a number of different cell types to become the mode of manufacture of biologic or large protein drugs. These drugs have again revolutionised disease treatment allowing many more conditions to become treatable. Cell lines from rodents, insects, yeast, bacteria, birds or even human origin are now used in the manufacturing of biologic drugs. All of these products together present a myriad of different safety risks, particularly viral, which need to be understood and controlled to maintain safety in the final product.

Safety profiles

Regardless of the species or source of cells, the safety profile is constructed from three principles: i) testing of the starting materials such as cell banks or media ingredients, ii) testing of "in process" material and iii) validation of the process for clearance of contamination.

Contamination with infectious agents can come as two main types – microbial (bacteria or fungi) or as viruses. Virus contamination is seen as the more critical contamination type because viruses can destroy cells in culture resulting in production loss and in some instances are very resistant to biocides. Viruses are also able to cause serious disease and in some instances the contamination is discrete and not easy to detect. The testing for viruses takes a number of different methods, and includes *in vitro* (tissue culture) and *in vivo* (animal culture) cultivation to support the growth of virus, molecular techniques to detect viral nucleic acid and also microscopy (electron) which is the only means we have to visualise viruses. The reason for the variety of techniques is that no individual method is capable of identifying all the potential range of viral contaminants described, in addition to being able to spot a previously unrecognised virus.

Safety testing

There are two main repositories for guidance on the viral safety aspects of vaccines and biologicals: the European and United States Pharmacopoeias and the International Conference on Harmonisation (ICH). The Pharmacopoeias focus mainly on

vaccine production whereas ICH has set down global testing guidelines for biologicals. ICH Q5A is the core guideline for virus safety assessment of cell banks used in the production of cell banks for biologicals. For the first time this brought together a number of older documents in different countries and created a co-ordinated approach to safety testing. There are a number of ICH guidelines in a series to provide assistance with the testing and safety profile of biologicals. Many of the methods used are borrowed from the vaccine regulations.

All sets of regulations follow the same patterns. Testing of starting materials includes cell banks and media ingredients that may or may not have an animal component. The cell banks themselves have an inherent risk of virus contamination dependent on their source and history. Some cell lines are from exotic species such as Chinese Hamster or African Green Monkey. The risks associated with each species can be difficult to quantify as the study of the viruses that infect more exotic animals is poorly understood and therefore presents some difficulties when determining the most appropriate virus testing regimen. Despite these difficulties, there is a formulaic approach to safety testing. Virus risks are split into three types for most regulatory

requirements; adventitious virus, species-specific viruses and retrovirus.

Adventitious viruses (see **Figure 1**) are those which can contaminate the production process from the environment or one of the supplements used to grow the cells. These are very unpredictable and can be from a variety of sources. Species-specific viruses are those viruses which are endogenous contaminants of cells; an example of these is various Simianpolyomaviruses which are contaminants of monkey cells and can remain latent in these cells. Also included in this subset would be the bovine virus contaminants associated with the use of serum to aid in cell growth or the porcine viruses associated with the use of porcine trypsin in cell passage. These viruses are more predictable and a list of the critical viruses can be created and used to screen all those cells of this species.

One particular virus risk which is seen with all cell lines is that from retroviruses (see **Figure 2**). These attained notoriety during the 1980s with the jump of the HIV virus to humans causing the devastating AIDS outbreak. This virus family is singled out for special consideration from regulators as these viruses can cause serious disease and become silent infections in cells. Retroviruses fall into two types for the purposes of safety considerations – endogenous viruses such as Murine leukemia virus (which can be exogenous in some instances) and exogenous viruses such as Human immunodeficiency virus type 1 (HIV-1). Exogenous viruses can be screened typically by nucleic acid detection and can be readily excluded; endogenous retroviruses, being integrated into the genome of the cells, have specific testing requirements as specified in the earliest biologics guidelines.

All animal cell lines have some retrovirus sequences integrated into their genome, some can express virus and others have only damaged sequences incapable of generating an infectious particle. Some of the early mouse cell lines used for the

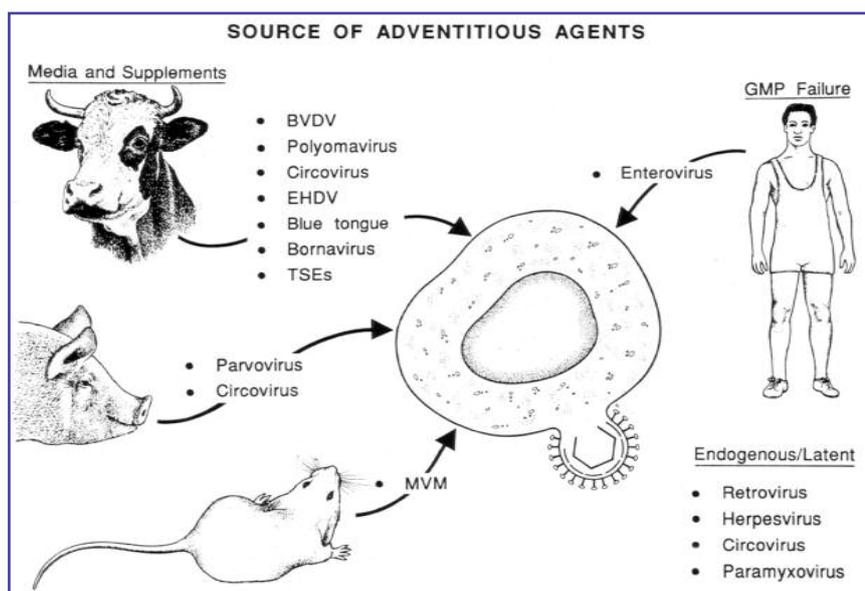


Figure 1: Source of adventitious agents.



Figure 2: Photomicrograph of retroviruses.

production of biologicals were positive for the expression of C-type retrovirus which was a known risk. The presence of these viruses in cells caused concern but did not prevent these products being used in humans as long as the appropriate controls were in place. This resulted in there being an assessment of each fermenter harvest of product to ascertain the titre of virus present and this number was used in a risk assessment comparing the clearance values of the virus determined experimentally during the downstream purification to drug product. In this way the manufacturers could convince the regulators that these viruses did not represent a risk to patients given these drugs.

Other viruses

During the manufacture of each batch of biologic or vaccine there is the risk of new viruses being introduced into the production process and this has been recorded by a number of different manufacturers and products. One of the highest risk contaminants was from bovine serum used in the media to supplement the growth of most virus vaccine products and used to a lesser extent in biologics production due to the advent of "serum free" media. Bovine serum has been systematically reduced in biologics due to an increase of risk factors, particularly the bovine-transmissible spongiform encephalitis (BSE) outbreak seen in

Europe in the 1990s.

As well as the BSE risk, there is also a virus risk with the serum as it is harvested from animals open to the environment and capable of being infected from numerous viruses especially those transmitted by insects (Arbovirus). Arboviruses are perhaps the most

common contaminant of bovine serum and have resulted in the contamination of fermenter batches. Testing of the fermenter harvests, along with the viricidal steps in the downstream purification (DSP) of the drug, has ensured that these viruses have never reached patients. Other contaminants of fermenters include Mouse minute virus that is thought to infect cells in a fermenter due to rodent contamination of reagents. Viruses are fundamentally impossible to exclude from the process and therefore best practice is to test as much as possible the higher risk starting materials and perform in-process testing to pick up anything that has been missed. Virus clearance during the DSP cannot prevent virus being introduced with the starting material but this ensures comfort that infection, should it occur, will be prevented from reaching the patient.

Virus detection methods

The current methods we use for virus detection have in many cases remained unchanged in 60 years. *In vivo* and *in vitro* methods for virus identification can be traced back to the work by Steinhardt from 1913 and Enders and colleagues' work to grow Poliovirus in tissue culture in 1949. Other techniques such as nucleic acid detection have been successfully introduced in the past 20 years but the programme of testing for biosafety still includes many older techniques.

A new technique which has

attracted much interest recently could revolutionise the detection of virus in biologic samples. Massively parallel sequencing is a process by which the entire nucleic acid sequences in a sample are determined and a software algorithm used to identify which sequences are viral in nature. This method can not only identify those viruses we already are aware of but also those sequences which are as yet unreported but have a "virus-like" characteristic – maybe pointing to a new virus species. Although in its infancy as a technique, this method may be a faster and more efficient method that these older technologies and could speed up the current somewhat lengthy protocols.

Conclusion

Biosafety of vaccines and biologicals is still something that requires to be closely considered with respect to risk and regulatory requirements. Failure to adequately take account of both of these will cost drug developers both time and money. These products do, however, offer the promise of curing or preventing some devastating diseases and the current risk based approach which is used has stood us in good stead. The future does offer some new technologies that may improve our abilities to detect contamination and these must be stringently tested before they can be put in place.

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BRIDGING API MANUFACTURING AND FORMULATION THROUGH PARTICLE DESIGN

by Márcio Temtem, Filipe Neves, Conrad Winters

The interface between the Active Pharmaceutical Ingredients (API) manufacturing and formulation development is of paramount importance in the pharmaceutical world. Chemists, engineers and formulators are not exposed, by training, to the same challenges. As presented in Figure 1, on the one hand there are API suppliers, characterised by a service orientation mindset, used to addressing synthesis route issues (e.g. impurities, yields), solid state characterisation (e.g. polymorphs, polymorph control), raw material sourcing, etc); on the other hand, formulators are used to a different type of language and daily concerns (e.g. bioavailability, patient compliance, administration route, efficacy and processibility).

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Particle size is a good example of a Critical Quality Attribute, often difficult to control during the final API synthesis step but with the potential to have a tremendous impact on the performance of the final dosage form. Herein two examples are addressed: particle size reduction aiming at bioavailability improvement through nanoparticles with a focus on oral and IV administration, and particle size control in the form of microparticles, targeting effective inhalation delivery. **Figure 2** provides an example of typical particle size distributions after a particle engineering step.

With the advent, in the 90s, of combinatorial chemistry, computational molecular modeling and high throughput screening in drug discovery there was a significant increase in the number of poorly soluble drugs (Class II and IV compounds – poor solubility – according to the Biopharmaceutical Classification System, BCS¹). Today

more than 90% of drugs, under development, present low aqueous solubility². Therefore, there is an increasing need to use and further develop new formulation platforms, which increase oral bioavailability of Class II and IV compounds.

Nanoparticles have proven the value (the size reduction leads to an increased surface area and according to the Nernst equation to

an increased dissolution velocity³), utility and commercial viability to improve bioavailability over the last decades with multiples products approved in the market (**Table 1**). The majority of those using NanoCrystals[®] technology by Elan Nanosystems (now Alkermes). On NanoCrystals[®] a bead/pearl mill is typically used to achieve particle size reduction of a suspension (generally in water) containing the drug along with stabilisers. Although very efficient, the platform also presents disadvantages as the potential for product contamination due to the erosion of the beads, limited batch size or the fact of being a batch process. Other examples of top down approaches, not encountering some of these disadvantages are the homogenisation methods being the most important: Microfluidiser technology (IDD-P[®] technology from SkyePharma), Piston gap homogenisation in water (Dissocubes[®] technology from SkyePharma) or in mixture of solvents (Nanopure[®] technology owned by PharmaSol³). Although microfluidisation and piston-gap homogenisation have been used with success it is important to highlight that piston-gap homogenisation generally imparts greater turbulent energy by cavitation, resulting in the exposure of the drug to higher temperatures and pressures with potential impact on the stability (physical and chemical).

Drug nanoparticles can also be produced using bottom up

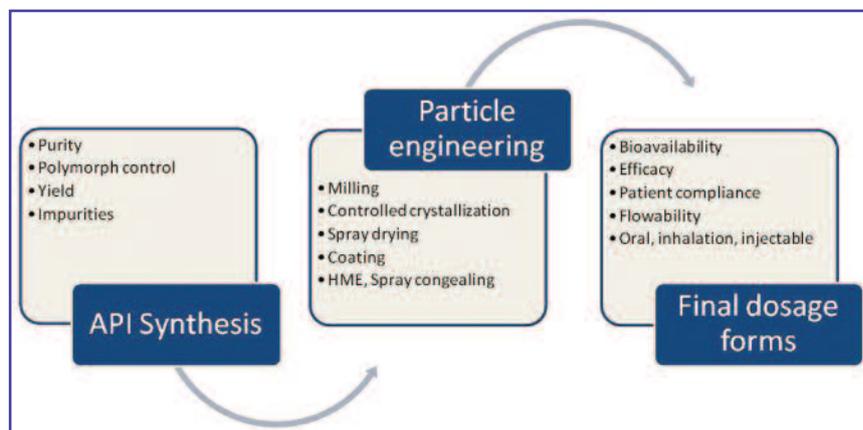


Figure 1: Bridging API manufacturing and formulation through particle design.

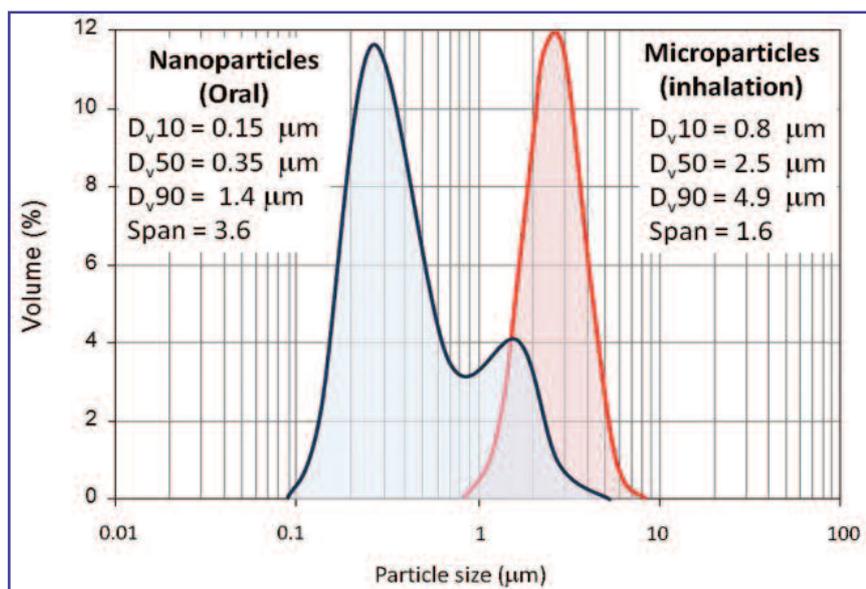


Figure 2: Typical particle distributions of a micronised powder (Nanoparticles/Oral vs microparticles/inhalation).

techniques where the drug is dissolved in a solvent and subsequently precipitated by

controlled mixing with a non-solvent. PureNano[®] from Microfluidics is a good example of a

Table 1: Examples of market products using Nanoparticles⁴

Trademark (API)	Therapeutic application	World Sales (2011) M\$	Platform (Developer)
TriCor NanoCrystal (Fenofibrate)	Lipid Lowering	632	Nanocrystal ^(a) [®] (Elan/Alkermes)
Invega Sustenna (Paliperidone palmitate)	Schizophrenia	499	Nanocrystal [®] (Elan/Alkermes)
Emend (Aprepitant)	Nausea-Emesis	419	Nanocrystal [®] (Elan/Alkermes)
Abraxane (Paclitaxel)	Cancer	386	Nanoparticle Albumin Bound – NAB ^(b) [®] (Abraxis BioScience)
Rapamune (Sirolimus)	Organ Transplantation	372	Nanocrystal [®] (Elan/Alkermes)
Megace ES (Megestrol acetate)	Cachexia, AIDS-related Anorexia	58 (US only)	Nanocrystal [®] (Elan/Alkermes)
Triglide (Fenofibrate)	Lipid lowering Hypertriglyceridemia	NA	IDD-P Microparticle ^(c) [®] (SkyePharma)
Feraheme (ferumoxytol)	Anemia, Iron Deficiency	52 (US only)	Advanced Magnetics Nanoparticles ^(d) (AMAG Pharmaceuticals)

(a) NanoCrystal[®] – Small particles of drug (less than 2,000nm) are produced using various wet milling approaches but typically with Pearl or Ball milling. The nanosize particles are then stabilised against agglomeration by surface adsorption of stabilisers. On September, 2011, Alkermes and Elan Corporation, announced the completion of the merger between Alkermes, Inc. and Elan Drug Technologies (EDT), the drug formulation and manufacturing business unit of Elan.

(b) Nanoparticle Albumin Bound – Nab[®] – Technology exploiting the transportation properties of human serum albumin (a natural carrier of lipophilic molecules) to improve the bioavailability of hydrophobic drugs – the drug is surrounded by an albumin shell to form a nanoparticle.

(c) IDD-P Microparticle – Insoluble Drug Delivery-P (IDD-P) technology involves drug particle size reduction by high pressure microfluidisation in the presence of membrane-forming amphiphatic lipids to form stable dry powders from 0.1 to 10 micron with narrow particle size distributions.

(d) Advanced Magnetics Nanoparticles – Iron oxide polysaccharide colloids comprised of nanosized iron oxide particles coated with carboxymethyl reduced dextran to improve circulation time. Particles are prepared by precipitation and filtering.

continuous crystallisation process where the contact between the two solvents is made with the use of interaction chambers/reactors. Nanomorph[®] (Soliqs – Abbot) is another example, where a drug in solution is precipitated inside a polymeric system that maintains the drug substance with the desired polymorphic form and maintains the nanoparticulate state, preventing particle aggregation and/or growth.

Regarding inhalation applications, and as shown in **Table 2**, drug delivery systems can be divided into two main categories: pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) – none of the devices is clinically superior and device selection should be guided by other factors, such as convenience, cost, and patient preference⁵. In a DPI (seven of the top nine products in the market consider this delivery system – see **Table 2**) the solid drug is fluidised when the patient inhales and this offers unique benefits and unique challenges. The benefits compared to pMDI's are that little or no coordination is required between activation and inhalation, and they provide for superior stability since they are typically formulated as one phase, solid-particle blends. The challenges relate to the unique formulation strategies required and the susceptibility of dry powders to forces of interaction caused by their surface and bulk energies, which can inhibit their dispersion and limit aerosol delivery and, therefore, efficacy⁶.

The inhalation dosage technology has primarily been focused on two parallel development pathways: i) fabrication of novel inhaler devices with enhanced efficiency and actuation control), such devices tend to be complex and costly, and their reliability and practicality have been questioned. Conversely, superior delivery efficiency may be achieved more cost-effectively by developing

Table 2: Inhalation market⁴

Trade name (API)	Therapeutic application	World Sales (2011) M\$	Platform (carrier/media)
Advair (Fluticasone propionate/Salmeterol xinafoate)	Asthma & COPD	8132	DPI (lactose carrier) MDI-suspension (HFA-134A)
Spiriva (Tiotropium bromide)	COPD	4391	DPI (lactose carrier)
Symbicort (Budesonide/Formoterol fumarate)	Asthma & COPD	3148	MDI-suspension (Amafurante, PEG, Povidone K-25)
Flovent (Fluticasone propionate)	Asthma	1306	DPI (lactose) MDI-suspension (HFA-134A)
Pulmicort (Budesonide)	Asthma	892	DPI (lactose) Nebulizer**
Foradil (Formoterol fumarate)	Asthma & COPD	312	DPI (lactose)
Serevent (Salmeterol xinafoate)	COPD & Asthma	293	DPI (lactose)
Asmanex (Mometasone furoate)	Asthma	206	DPI (lactose)
Alvesco (Ciclesonide)	Asthma	93 (2010)	MDI-solution (HFA-134A, ethanol)

** Edetate disodium, polysorbate 80, sodium chloride, citric acid, purified water, sodium citrate

optimised particulate formulations for use with simple and user-friendly inhalers⁸. This alternative strategy, which is synonymous with the controlled production of drug particles in pure physical forms (or with carriers as composite materials) of optimised size, morphology and structure, has been boosted due to recent advances in particle engineering.

Here the main goal of particle engineering is to incorporate into the particles desirable attributes such as optimal particle size distribution and improved dispersibility, thus favouring enhanced drug stability and optimised bioavailability⁹. Among these attributes, particle size is one of the most important design variables, and this is valid both for DPI and MDI delivery systems; particle size relates with the aerodynamic diameter and this is a critical measure of the particle dynamic behavior, describing the main mechanisms of aerosol deposition (both gravitational settling and inertial impaction) – generally, an aerodynamic particle size distribution of 1-6µm is required

for successful inhalation therapy¹⁰. Additionally, specific optimisation of the particle size distribution is important for several reasons:

- To reduce dose variability into the lung
- To maximise the proportion of drug in the finished product formulation that reaches the target airway site; this in turn minimises the active content in the formulation required for an efficacious response and reduces the likelihood of potential side effects
- In the area of generic product development, to be able to demonstrate *in vitro* and subsequently *in vivo* equivalence to a reference product

Different size-reduction techniques may be capable of targeting similar particle size distributions; however, even when the same size is obtained, the dispersibility of the powder (a critical attribute, as mentioned before) tends to vary depending on the employed technology. This is a consequence of a delicate balance

between adhesive/cohesive forces that, besides size, also depend on other factors (e.g. particle morphology and surface energy). Historically, the production of such particles has been performed using the processes of batch crystallisation followed by size reduction using air jet milling (micronisation), a technology available for more than 100 years. Micronisation (see **Table 3**) has been used for the development of inhalation products since the 1960s, with significant challenges commonly referred in the literature:

- It is a high energy size reduction process that breaks down active substance crystals, impacting surface energy and crystal form. The output material often contains significant amorphous content, which can influence the stability of the finished product formulation¹¹.
- In order to produce the desired particle size, jet milling frequently requires a number of repeat runs. It is therefore an inefficient process that creates the potential for metal contamination from the extended high energy contact with the microniser metal components and lower yield due to repeated number of passes.

Other techniques for making micron-size particles involve direct particle formation from solution; in this field, spray drying (SD) has emerged as a noteworthy approach for controlling particle size¹². This technique is distinctly different from milling in the sense that particles are built up by dissolving and spraying the drug into fine droplets that, once dried in a heat expansion chamber, leave behind tiny particles; compared to milling, SD can produce more spherical particles; however, these tend to be mostly amorphous, thus having a higher potential for stability problems (see **Table 3**) if not properly stabilised with polymer/excipients.

Table 3: Particle engineering technologies: Advantages/Disadvantages

	Technology	Advantages	Disadvantages
NANOPARTICLES	Pearl and Ball milling	<ul style="list-style-type: none"> Multiple products in the market Simple High drug loading 	<ul style="list-style-type: none"> Time consuming Limited batch size Susceptible to product contamination Requires an isolation step
	Controlled nano-crystallisation "Bottom up"	<ul style="list-style-type: none"> Very efficient in obtaining nanoparticles with reduced PS 	<ul style="list-style-type: none"> Complex systems requiring a good understanding of the process
	Homogenisers/ Microfluidisers	<ul style="list-style-type: none"> Good control on the PS distribution and highly reproducible Insignificant levels of contamination Easy scale up 	<ul style="list-style-type: none"> Unsuitable for thermolabile compounds Requires an isolation step
	Controlled crystallisation	<ul style="list-style-type: none"> Eliminates addition PS reduction steps 	<ul style="list-style-type: none"> Typically PS Control (PS distribution, targets) is not as straightforward as in other top down approaches Requires strict control of the process
MICROPARTICLES	Spray drying	<ul style="list-style-type: none"> Ideal to produce amorphous materials Good control over powder properties Easiness of scale up Processing of thermolabile materials Continuous process 	<ul style="list-style-type: none"> Solvent based process (post drying may be required) Amorphous content may be undesirable Expensive
	Jet milling	<ul style="list-style-type: none"> Solvent free Ease of operation Cost effective 	<ul style="list-style-type: none"> High amorphous content Lack of control over, size, shape and surface properties Susceptible to product contamination

the target PS against a typical range of 10 to 20% in jet milling). Additionally, in specific cases¹⁴, Wet Polishing may be an enabling technology, to avoid the formation of amorphous domains or keep the required polymorphic form.

When drug particles greater than a few microns are transformed into nanoparticles an important aspect of particle size reduction is the surface energy generated. The increased surface area creates a positive gain in free energy inducing the potential to agglomerate/aggregate to a less energetic state. The micro-encapsulation of such instable materials in polymeric systems (in this example using spray drying) can support improvements in two distinct critical quality attributes: stability (i.e. agglomeration, crystal growth, changes in the polymorphic form) and manipulation of powder properties (e.g. flowability, density, PS). The properties of the micro-capsules will greatly depend on the materials used, but can also be modified to a great extent by manipulation of the spray drying process operating parameters (e.g. temperatures, droplet size, atomisation, concentration) (Figure 4b).

As presented in Figure 3, Spray drying is a versatile technology, frequently used to dry/isolate the suspensions of microparticles after crystallisation or wet milling processes or microencapsulate and stabilise nanoparticles¹³. Wet Polishing® – a proprietary term used by Hovione to describe a platform that uses a range of particle size processing technologies (both bottom up and top down techniques) combined with a suitable isolating method, often using spray drying technology is a good example of the latest. In general terms, the advantages of Wet Polishing for inhalation applications are the production of size reduced APIs with tunable PSDs and a high level of reproducibility as demonstrated in Figure 4a (2% standard variability in

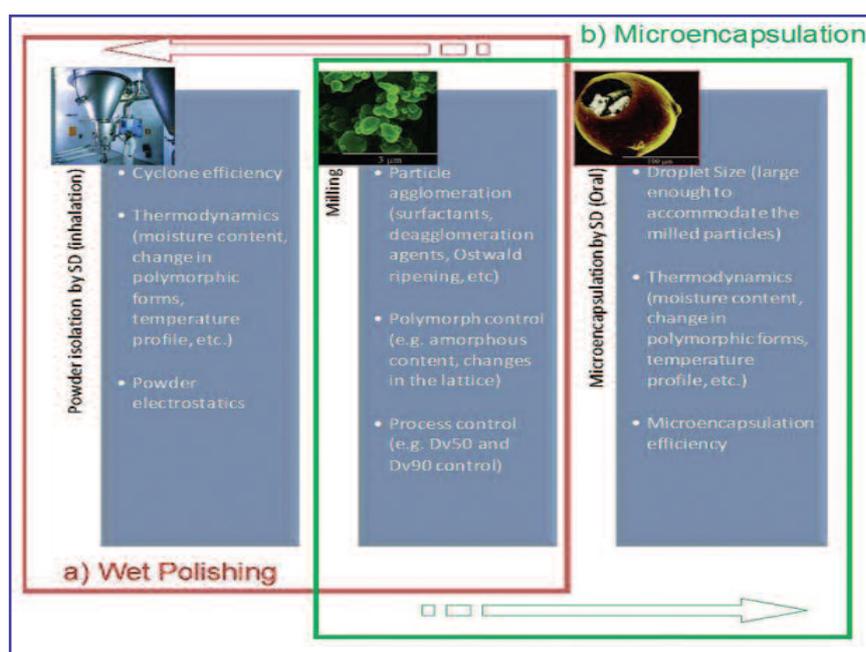


Figure 3: Key points during spray drying application on a) Wet Polishing® process and b) Microencapsulation of nanoparticles.

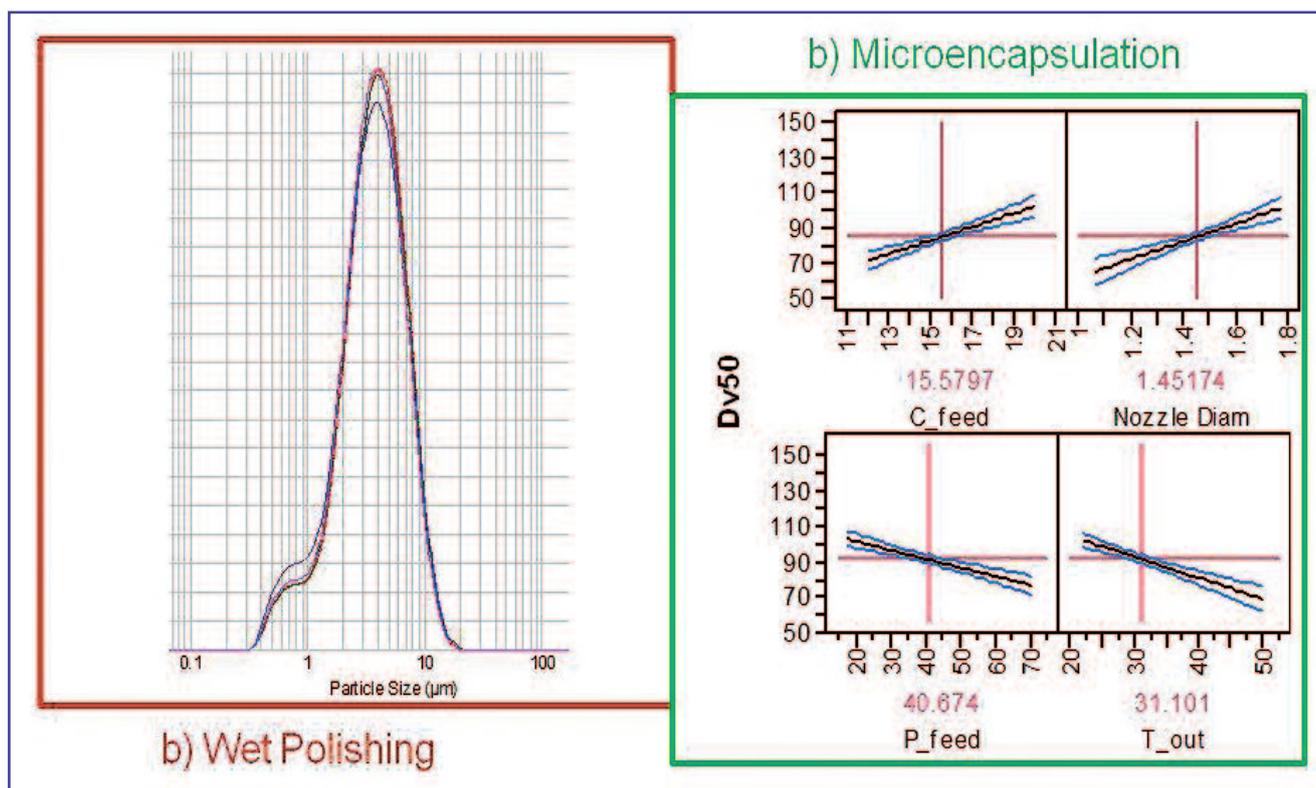


Figure 4: a) High reproducibility of the wet polishing process and b) Powder properties improvement during a microencapsulation process.

Conclusion

Through the use of particle design it is possible to bridge two distinct realities: Drug Substance and Drug Product. Independent of the administration route (e.g. oral, IV, inhalation) the selection of the most appropriate technology is key to obtaining high performance materials.

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PHARMACOPOEIAL COMPLIANCE

by Kevin F Goode MRSC

Pharmacopoeial Compliance is a potential minefield. This article covers an introduction into the world of Pharmacopoeias, what they are, what they contain, their impact on industry, their legal status and how they should be interpreted and used. The use of alternative methods is discussed and a short summary of Pharmacopoeial Harmonisation is also given.

Kevin worked for the Wellcome Foundation/GlaxoWellcome/Glaxo Smith Kline for over 38 years in a variety of roles including Analytical Development and Quality Assurance, but most recently for 15 years liaising with the Pharmacopoeias and interpreting Pharmacopoeial requirements. He was a member of the British Pharmacopoeia Expert Committee B, a member of the PhRMA Compendial Liaison Team and the Mid-West Compendial Discussion Group. He was a member of the organising committee for the 2008 PDA Compendial Conference. He took early retirement in 2009.

What is Pharmacopoeial Compliance?

To understand this, you first need to know what the Pharmacopoeias are, what they contain and how to use them. So what are they? Essentially they are a repository for quality standards and test information for medicinal products and materials used in their manufacture. They cover everything from the actives and excipients used to make products, to packaging and labelling instructions and guidelines. So how many are there, and why are they important?

The WHO Index

The World Health Organisation (WHO) maintains an index of Pharmacopoeias. Currently there are about 45 Pharmacopoeias on the list. For the majority of cases, it is only necessary to consider the major Pharmacopoeias (British, European, Japanese and United States Pharmacopoeias) since many of the others are either subsidiary to or recognise the specifications of these. This article will concentrate on these, however the importance of emerging markets is growing and the respective governments are now insisting on compliance with their own Pharmacopoeias unless they do

not have a specification within them for a specific item. For example, India requires that products are labelled compliant with the Indian Pharmacopoeia by law and China will test all products in accordance with the stricter of registered and Chinese Pharmacopoeia requirements.

The British Pharmacopoeia

The British Pharmacopoeia was founded at the height of the British Empire in 1857 and first published in 1864. It was an amalgamation of the Pharmacopoeias of London, Edinburgh and Dublin. It now operates under the MHRA and is mandated under UK legislation. It is recognised as the Official Pharmacopoeia by several Commonwealth countries.

The European Pharmacopoeia

The European Pharmacopoeia, founded in 1964 and first published in 1969, is the umbrella Pharmacopoeia for the majority of countries within Europe. Pharmacopoeias from those countries that are signatory to the European Pharmacopoeia Convention (including the British Pharmacopoeia) are subsidiary to

the European Pharmacopoeia. The European Pharmacopoeia is administered by the EDQM, which is part of the Council of Europe. It can be considered as the first attempt at harmonisation of the Pharmacopoeias for all signatory countries and is mandated under EU law. It has influence outside the EU with many Eastern Europe and Western Asiatic countries as observers.

The United States Pharmacopoeia

The United States Pharmacopoeia was first published in 1820 and is the oldest continuously published and revised Pharmacopoeia. It is also the only private, voluntary Pharmacopoeia, independent of Government, although it has been legally recognised by the US Government since 1906. Its standards are recognised in the Federal Food Drugs and Cosmetics Act (1938) and they are enforced by the FDA. It is recognised by several other countries, particularly within Latin America.

The Japanese Pharmacopoeia

The Japanese Pharmacopoeia was first published in 1887. It is administered and its standards are enforced by the MHLW and the Pharmaceutical Affairs Bureau.

Purpose of Pharmacopoeias

Their purpose is primarily to protect the patient, which they achieve by establishing and disseminating officially recognised quality standards for the preparation and testing of medicines. The important words here are officially and quality standards. These standards are not tied to a particular company but establish minimum standards for quality with the market territory observing that Pharmacopoeia.

A Legal Requirement

All medicinal products must comply with the general requirements and standards of the Pharmacopoeias which are legally applicable in the countries where they are to be sold. Conformance with Pharmacopoeial standards is a legal requirement. These legal requirements include:

UK: the Human Medicines Regulations 2012, Part 15; EEC: Directive 2001/83/EC; USA: Section 501 (b) of the Food, Drug and Cosmetic Act; Japan: Pharmaceutical Affairs Law.

So what might happen if you fail to comply?

Any of the following: Legal action; Loss of marketing rights; Loss of product/import licence; Product rejected by customer and/or country; Adverse comments and/or citation at audit; Warning letter from Regulatory Authority. Examples of these are the tendency for China to suspend or revoke import licences for repeat offences, or the penchant for FDA to send Warning Letters for product adulteration. Any of these actions could have an adverse effect on a manufacturer's ability to market their products.

But what is Pharmacopoeial compliance?

Pharmacopoeial commissions/agencies and regulatory authorities tend to be separate from each other. Pharmacopoeias establish compendial standards for the manufacture and testing of medicinal products, primarily for established products. Regulators establish standards and requirements for new drugs and products, and enforce compendial standards.

A Difference

There is however a difference between Pharmacopoeial compliance and Regulatory compliance. Compendial standards established by the Pharmacopoeias have a degree of flexibility which is not present in Regulatory standards, which are strictly applied. In order to understand this, it is essential to understand what is in the Pharmacopoeias and how to use them.

Deliberately Vague

Pharmacopoeias are frequently written in terms of "should" and "may" rather than in a prescriptive manner. Many parts of the Pharmacopoeia are non specific or

deliberately vague. This can lead to difficulties in interpretation, which then lead to differences in understanding between the manufacturers and regulators and thus issues during inspections. It is therefore essential to correctly interpret the requirements and to be clear as to what is mandated and what is guidance.

General Notices – the most important section

All the Pharmacopoeias have similar content, consisting of sections as follows: General Notices and Requirements; General Test Methods; General Monographs; Specific Monographs; Reagents; General Information. The reality for manufacturers is that it is mainly the Monographs that are used, along with the linked or associated general tests, methods and chapters. It is easy for an analyst to go to a specific monograph and try to make sense of the requirements, but this is dangerous since without adequate knowledge of the General Notices, which tell you how to use and interpret the specific monographs, they could completely misunderstand what the actual requirements are. And who reads the General Notices? They are in fact the most important section since they define the rules and standards to be applied when using a particular Pharmacopoeia.

General Notices is the most important section since it tells you how to use the Pharmacopoeia. This is probably the least understood or appreciated section of the Pharmacopoeia by users. The Pharmacopoeias do not all operate in the same way or have the same requirements. This is where the flexibility for monograph use can be found, and this is the most critical section in the Pharmacopoeia.

General Test Methods

Pharmacopoeias contain a wide range of general test methods which provide input into specifications and system suitability requirements, and not just for commercial product. They are also applicable to drugs/

actives in R&D and can be used as a basis for developing test methods and procedures. They also give guidance on validation requirements for new test methods. They are frequently cross referenced from other parts of the Pharmacopoeia, particularly the monographs themselves.

General Monographs

General monographs define the tests, methods and specification requirements to be applied to types of products and materials. General monographs are requirements just as much as specific monographs that define the tests, methods and specification requirements to be applied to individual products and materials.

General Information Chapters

General Information Chapters provide additional useful information on a wide range of related topics. These sections are usually considered to be non-mandatory, however some regulators seek to make them obligatory which can cause problems for manufacturers during inspections. It is often the case that the Inspector's understanding is not correct, and the manufacturer should be prepared to justify their interpretation of the requirements.

Can you use alternatives?

It is permissible to use different standards, controls and methods to those cited in the Pharmacopoeias to ensure product quality. However, the use of alternatives must comply with the general requirements of both the Pharmacopoeias and the Regulatory Authorities of the markets in which the products or materials are to be sold. Where compliance with a Pharmacopoeial monograph or test method is not adequate to assure the quality of a product, action must be taken to register or certify appropriate alternative standards and/or methods. It is obligatory for the European Pharmacopoeia and advisable for others to offer the

alternative to the Pharmacopoeia as an additional or replacement method.

The use of any alternative control, standard, method or technique must be shown to be equivalent to or better than that defined in the Pharmacopoeia in terms of accuracy, precision, reliability and/or quality. Any alternative test methods employed must be validated to a suitable standard, usually ICH. However, the Pharmacopoeias usually incorporate into their General Notices that "In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative".

What is Pharmacopoeial Harmonisation?

That different test requirements caused extra work and other problems was recognised by the United States, European and Japanese Pharmacopoeias in the 1980's and they were aware of the impact on Industry. They set up the Pharmacopoeial Discussion Group (PDG) prior to the formation of ICH to try and resolve some of the issues. The aim was to harmonise methods for key general tests and procedures and to create harmonised or interchangeable monographs for the excipients in common use within the Industry. ICH includes Pharmacopoeial Harmonisation as Topic Q4, however the PDG operates independently of ICH.

Consensus is reached where possible, but this does not guarantee that the monograph is identical. Differences may still remain due to specific local circumstances. It does not prejudge the level of harmonisation obtained, and does not mean that the process

is complete. The concept of "Interchangeability" has recently been introduced, and the Pharmacopoeias are now working towards this end.

The biggest drawback of this process is that it very bureaucratic – a 7-Stage process that is slow and cumbersome and taking far too long. Having said this, the PDG process has led to some interchangeable methods with more to follow. The long term hope is that more of these will come through at a faster rate.

Regulatory Acceptance

The latest initiative under Q4 has been the introduction of the concept of Regulatory Acceptance (Topic Q4B). A working group was created to give advice on regulatory acceptance of PDG harmonised texts. A guideline was produced – Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC). Statements on individual texts are being included as annexes, of which 14 have now been published. This has major benefits to Industry since it simplifies procedures as only a single test regime need be applied.

How does this work? Following sign-off of the harmonised texts by PDG at Stage 6 of the harmonisation process, the co-ordinating Pharmacopoeia prepares a package for Q4B including the sign-off text, details of publication in the Pharmacopoeias and a briefing note. Q4B examines this package and either publishes an annex to the guideline or refers questions back to PDG. De facto harmonisation is achieved when all three Pharmacopoeias publish the sign-off text. Each Pharmacopoeia

will indicate harmonisation in its publication.

Other New Initiatives

Other initiatives which are of interest include the following, but there is insufficient space to give details here:

- WHO Global Good Pharmacopoeial Practice guide, with the European and Indian Pharmacopoeias being the biggest supporters of it
- MERCUSOR activities – Brazil, Argentina etc collaborations.
- ASEAN collaboration – Korea, Indonesia etc.
- European and United States collaborations on API monographs outside of the PDG
- British and United States collaborations on product monographs

Pharmacopoeial Compliance – the How

The provisions in the general statements must be adhered to but there is a degree of flexibility. Specification limits must be applied. Tighter limits could be considered but it would be difficult to justify wider limits. Suitability standards are a given. It is possible to use in-house Chemical Reference Standards but you have to show that these are equivalent to the Pharmacopoeia CRS's. Ambiguities must be assessed and a judgement made and documented. Validated alternative methods could be used. You must also take into account the musts and maybes which are open to interpretation and can both help and hinder manufacturers. Above all, you must be prepared to justify the approach you take, and do not assume that the Regulators or Inspectors interpretations are correct – frequently they are not.

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regulatory review

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

United States of America

Guidance for Industry -Non-Penicillin Beta-Lactam Drugs

This Final cGMP Framework for Preventing Cross-Contamination clarifies that manufacturers generally should utilise separate facilities for the manufacture of non-penicillin beta-lactams. Beta-lactam antibiotics include the following five classes:

- penicillins (e.g., ampicillin, oxacillin)
- cephalosporins (e.g., cephalexin, cefaclor)
- penems (e.g., imipenem, meropenem)
- carbacephems (e.g., loracarbef)
- monobactams (e.g., aztreonam)

The guidance recommends that as with penicillin, the section of a facility dedicated to manufacturing any one of the above five classes should be isolated from each other and areas in which other products are manufactured.

Recommendations are also made in regard to beta lactamase inhibitors.

Guidance for Industry SUPAC: Manufacturing Equipment Addendum

SUPAC equipment addenda referencing specific equipment were misinterpreted as equipment required by FDA. This could discourage advancements in manufacturing technologies. Therefore, the revised draft SUPAC addendum contains general information on SUPAC equipment and no longer includes tables referencing specific equipment.

Europe

EudraGMP database now contains information on good distribution practice (GDP)

The new database, – EudraGMDP, is a key deliverable of the European Falsified Medicines Directive. It will make the supervision of manufacturing and distribution of medicines more robust by allowing all the actors in the supply chain to check information

available on their suppliers.

It will be gradually updated with distribution-related information and include:

- wholesale distribution authorisations;
- GDP certificates;
- statements of non-compliance with GDP;
- registrations of manufacturers, importers (including information on their suppliers) and distributors of active substances.

A non publicly accessible module exists on planning GMP inspections outside of the EU.

Implementation of the new rules on importation of active substances

This update gives an overview on some 20 major API supplying countries and their status of preparation for compliance with the requirements of the Falsified Medicines Act with regard to import of APIs into the EU.

The July 2 deadline is fast approaching with very few countries listed as equivalent to EU. India and China need to do more to comply with the EU requirements, but the situation is reported as being "Under control" for 14 of the countries listed.

MHRA is developing contingency plans that would allow the Agency, in cases where there is an overriding need to ensure continued supply of specific ASs after 2 July 2013, to provide an opinion on the importation of the AS to permit manufacture, QP certification and supply of finished medicinal products.

Revised Q&A on rules for importation of API V4.1

V4.1 no longer contains Q&A on atypical active substances. It has 2 new Q&As re:

- Written Confirmation for blood plasma and APIs manufactured with them
- Written Confirmation for Starting Materials for the manufacture of APIs

EDQM provides an update on its eTACT traceability project, for medicines

EDQM's aim is to achieve a secure, patient-friendly and cost-effective

traceability service for medicines. It has been consulting business stakeholders in order to fine-tune the details of all business processes to be handled in the deployment of such an anti-counterfeiting traceability service for medicines. This paves the way for the establishment of a real-scale pan-European eTACT service that is fit-for-purpose.

New Q&As on GMP

EMA has published 5 new GMP Q&As. Two of these relate to Annex 1: Manufacture of sterile medicinal products, and relate to bioburden monitoring of aseptically filled products.

The remainder concern MA holder's audit reports concerning active substances used as starting materials. They cover why inspectors ask to see reports of such audits, what expectations they have for the content of the reports and how active substance auditors should be qualified.

New tracking system for high-risk medical devices in development

MHRA announced that four NHS trusts have committed to piloting a new tracking system for high risk medical devices that will improve the monitoring of medical devices such as breast implants, heart valves and pacemakers.

The new tracking system will ultimately incorporate unique device identifiers into hospital patient electronic records and national Hospital Episode Statistics databases. Subsequent analysis will enable the MHRA to better assess the performance of high-risk medical devices and to trace patients in the event of a device recall or safety alert. This project is one of 11 that the MHRA has established to strengthen the regulation of medical devices.

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

General Assembly 20-21st April, 2013

During the April General Assembly, Jean-Pierre Paccioni was elected as President of EIPG and Valerie Lacamoire as Treasurer for the next 3 years. Gino Martini agreed to chair a new Finance Commission in his position of Past-President.

The Associazione Farmaceutici Ticinese (AFTI, the South Switzerland Association of Industrial Pharmacists) became a member of EIPG.

Working Group on the Falsified Medicines Directive (FMD)

A Working Group on the Falsified Medicines Directive (FMD) reconfirmed the EIPG positions on the concept papers of December 2011 and January 2012 on GMP and Inspection of API manufacturers. In addition they agreed the former EIPG positions on the concept paper of November 2011 regarding the unique identifier and the safety features. Various concerns were expressed about the FMD including the July implementation date, non-compliance issues which will result in shortages, control at receipt of APIs and excessively long chains of wholesalers and brokers.

On the issue of the supply of APIs, India who currently supply from 496 manufacturing sites, has decided the local health authority will issue a GMP certificate for each API. In China there has been some progress with the issue of certificates although they will not be issued for manufacturing sites which are not under their FDA certification. This will involve 30 of the 428 raw material manufacturing sites in China.

Regarding the unique identifier, there is still no final decision on

what is to be implemented resulting in some large companies appearing to influence the legislation by implementing what they feel is appropriate, whilst leaving smaller companies behind. The risk assessment is unclear and it is not known whether there will be a white or black list. The position of over-the-counter products has not been clarified.

A second **Working Group on Medicines Shortages** noted that many countries have shortages due to parallel export from their countries such as Finland, Norway, Romania and France.

Pharmaceuticals are in a highly competitive domain and Health Authorities are causing parallel exportation by driving down prices in reimbursement systems. It was suggested that short line wholesalers should not be allowed to parallel export. As has been stated previously by EIPG, companies should be undertaking risk assessments of all critical products as predicting critical product shortages and planning for safety stocks is of major importance.

It was noted that hospitals in some countries enter into agreements with companies without confirming that they are capable of producing the volume requested.

There have been problems with reimbursement in Romania since 2008 as this was the last time the list of new molecules approved for reimbursement by the Ministry of Health was open for additions. Since then more than 100 new products have been awaiting reimbursement and people who can afford to do so, travel overseas for treatment.

There is an acute problem in Bulgaria because the Government has reduced the price of 700

products by between 10 to 80 % so that generic companies can no longer afford to manufacture at the prices set. There are 150 new wholesalers and the chain of product supply is often through community pharmacies where traceability is a problem.

In Hungary, wholesalers are not allowed to export whereas in Portugal, where there are too many wholesalers, they need to export medicinal products if they are to survive as many pharmacies buy direct from manufacturers.

The meeting felt that there should be better collaboration between health authorities and all the players in the chain. Manufacturers, wholesalers and community and hospital pharmacists should review their missions of supplying medicines to the patient. There should be improved monitoring systems, coordinated by the European Medicines Agency as is done by the FDA.

The meeting suggested that we need solid numbers of how much it is costing per man hour to manage out of stock situations.

EPHA Conference on Access to Medicines

Some of the above points were made at the European Public Health Alliance (EPHA) May Conference on Access to Medicines held in the European Parliament at which Gino Martini acted as a respondent. At the meeting, a joint press release was issued by the three organisations representing pharmacists, PGEU, AEHP and EIPG as shown opposite.

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



JOINT PRESS RELEASE 16 May 2013

European pharmacist organisations make joint call for action on medicines shortages

The representative organisations for European community, hospital and industrial pharmacists have issued a joint call for action by Governments, regulators and the European Commission to tackle the growing problem of medicines shortages.

Presenting evidence at the European Parliament on the scale of the difficulties being experienced across sectors, spokespersons from the Pharmaceutical Group of the European Union (PGEU), European Association of Hospital Pharmacists (EAHP) and European Industrial Pharmacists Group (EIPG) called for:

- heightened awareness by Governments and national regulators of the critical impacts medicines shortages have in relation to patient welfare and safety, and the accompanying need for urgent action;
- greater investigation of the impact that national strategies on medicines pricing and reimbursement are having on the operation of the supply chain; and
- better sharing and implementation of best practices between countries in responding to medicines shortage, including the operation of information portals and early warning systems.

John Chave, Secretary General of PGEU said: "Evidence from PGEU members suggests that this is a problem affecting countries from all corners of Europe, and a huge range of medicines. While all stakeholders need to work together to address the causes, as a minimum community pharmacists need to be in a position to properly inform patients when a medicine is, or is likely to become, unavailable, and the causes and duration of the shortage. The pharmaceutical sector as a whole has a duty to avoid leaving patients in the dark".

Roberto Frontini, President of EAHP said: "EAHP's recent pan-European survey on medicines shortages clearly demonstrates that the shortages problem does not respect national borders and is affecting virtually every hospital in Europe. Immense amounts of hospital pharmacists' time are being diverted from other elements of patient care to simply source medicines. With the evidence strongly suggesting the problem is becoming worse, doing nothing is no longer an option. Action is required and our organisations believe the proposals in our joint call today represent a firm basis for European Governments and regulators to begin improving the situation."

Luigi Martini, Immediate Past President of EIPG said: "Each field of the pharmacy profession brings an important perspective to the issue of medicines shortages. From the industrial pharmacist perspective we have strong concerns that some of the requirements of the otherwise welcome 2011 Directive on falsified medicines may unintentionally increase the experience of medicines shortages. This relates in particular to new conditions placed on the import of active pharmaceutical ingredients from outside the EU, scheduled to be enacted this year. Overall, it reemphasises the multi-factorial nature of shortages, and the need to understand the inter-relatedness of pharmaceutical policy decisions. All supply chain partners need to work together in sharing their experiences, identifying the problems, and advancing solutions."

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NOTES TO EDITORS:

1. The context of the organisation's joint call was an event in the European Parliament entitled "The Economic Crisis & Access to Medicines in Europe". The event included presentations from PGEU, EAHP and EIPG on pharmacist experiences of medicines shortage problems. More information here: <http://www.eph.org/spip.php?article5674>

2. The Pharmaceutical Group of the European Union (PGEU) is the European association representing more than 400,000 community pharmacists. PGEU's members are the national associations and professional bodies of pharmacists in 32 European countries. www.pgeu.eu

3. At the beginning of 2012, PGEU conducted a survey among its members, national community pharmacy associations, in order to better understand the extent of medicine shortages in the EU. According to the survey results, although some countries are more affected than others, medicine shortages have been reported by all respondents to the survey and the problem is increasing. According to the survey, a broad range of medicines is affected, including even basic medication such as aspirin. The survey suggests that the prevalence of medicine shortages has increased in the past year – just in the UK over 1 million branded medicine supply failures occur each year. More information on the PGEU Statement on Medicines Shortages here: <http://www.pgeu.eu/en/library.html>

4. The European Association of Hospital Pharmacists is an association of 32 national organisations representing hospital pharmacists at European and international levels. It represents and develops the hospital pharmacy profession within Europe in order to ensure the continuous improvement of care and outcomes for patients in the hospital setting. This is achieved through science, research, education, practice, as well as sharing best-practice and responsibility with other healthcare professionals. <http://www.eahp.eu>

5. The results of a recent pan-European survey by EAHP revealed that 99% of hospital pharmacists report experiencing problems with medicines shortages in the past year, with 63% of hospital pharmacists reporting medicines shortages to be a weekly, sometimes daily, occurrence. 77% consider that problem has become worse in the last year. More information here: <http://www.eahp.eu/press-room/99-hpsexperience-medicines-shortages-past-year>

6. The European Industrial Pharmacists Group (EIPG) is a European association representing the national, professional organisations of pharmacists employed in the pharmaceutical or allied industries of the Member States of the European Union, the European Economic Area, or European countries having a mutual recognition agreement with the European Union on compliance control of regulated medicines. <http://www.eipg.eu/>

7. At their recent General Assembly, EIPG members discussed the various causes of product shortages which include single source strategies by purchasers, fewer manufacturers, low levels of contingency stocks, parallel trade, downward pressure on generic prices and the complexities of outsourcing. It was agreed that it is crucial for all players in the pharmaceutical supply chain to exercise their best efforts to honour their main public service obligation of supplying medicines to the patient, and for cost containment policies in pharmaceutical spending not to seek to achieve savings through measures that risk compromising the pharmaceutical supply chain.

events

JULY

4 July 2013 – London, UK
Meeting stability challenges
www.jpag.org

AUGUST

31 August-5 September 2013 – Dublin, Ireland
73rd FIP World Congress of Pharmacy and Pharmaceutical Sciences
www.fip.org/dublin2013

SEPTEMBER

2 September 2013 – Edinburgh, Scotland
Progress in stability testing
www.jpag.org

8-9 September 2013 – Birmingham, UK
RPS Annual Conference and Awards 2013
www.rpharms.com

10-12 September 2013 – Barnard Castle, UK
Sterilisation: Principles in Practice
www.honeyman.co.uk

11-12 September 2013 – Basel, Switzerland
PDA Europe 6th Workshop on Monoclonal Antibodies
<https://europe.pda.org/Monoclonal2013>

11-13 September 2013 – Barcelona, Spain
3rd Annual Pharma Emarketing Congress
<http://pharma.flemingeurope.com>

17-18 September 2013 – Copenhagen, Denmark
GMP for Beginners in Sterile Manufacturing
www.gmp-compliance.org

19-20 September 2013 – Copenhagen, Denmark
Risk Management in Sterile Manufacturing
www.gmp-compliance.org

17-18 September 2013 – Berlin, Germany
2nd Annual Pre-filled Syringes & Novel Injector Devices
www.informa-ls.com/prefilled

24-26 September 2013, London, UK
Pharma Compliance
www.terrapinn.com

24-27 September 2013 – Düsseldorf, Germany
Pharmaceutical Freeze Drying Technology
<https://europe.pda.org/FreezeDry2013>

30 September-1 October 2013 – Brussels, Belgium
The Future of European Pharma
www.ispe.org

30 September-4 October 2013 – Chicago, USA
GDP & Temperature Management Logistics
www.coldchainpharma.com

OCTOBER

1-2 October 2013 – Berlin, Germany
9th Annual Quality & Opex in Pharma & Biotech
<http://pharma.flemingeurope.com>

8-11 October 2013 – Berlin, Germany
Pharmaceutical Cold Chain Integrity
<https://europe.pda.org>

10 October 2013 – London, UK
Is there a scientific basis for therapeutic equivalence?
www.jpag.org

15-17 October 2013 – Barnard Castle, UK
Pharmaceutical Water Systems: Principles in Practice
www.honeyman.co.uk

17-18 October 2013 – Berlin, Germany
Operational Excellence
www.ispe.org

22-23 October 2013 – Dublin, Ireland
BioProduction 2013
www.bio-production.com



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