

# europaean INDUSTRIAL PHARMACY



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Cover photo: Pharma IT security  
(see Raising the Bar on Pharma IT Security on page 4).



## A patient in every box

During a recent symposium on drug shortages, a community pharmacist colleague pleaded for more information from his industrial pharmacist colleagues. "We have to face the patients, and explain to the patients why their medicine is not available", he said. He was right, of course, but the point is another, more fundamental one. Down at the coalface of pharmacist-patient interaction, a single box is dispensed to a single patient, a very personal interaction at the core of our profession that is sometimes denied to industrial pharmacists. This is not to diminish for a single moment industrial pharmacists' constant commitment to quality, safety and efficacy of medicinal products, but our daily practice is centred around batch releases, market authorisations, pharmacovigilance, quality assurance – all of which are certainly a commitment as pharmacists to patients. However, it takes a moment of deliberate pause to stop and try to visualise the individual patient to whom the single box of medicine is destined, and, even then, how does one valorise the significance of that box of medicines to that patient, what it means to him or her to be able to get through the day with that much less pain, or to have the hope of another day of life without the fear of remission?

This "patient-centric" approach is a new concept that the pharmaceutical industry must embrace, and we feel that as industrial pharmacists, gathered through our national associations under the banner of EIPG, we must lead the way. Already, we can see elements of this approach in the new provisions of the Unique Identifier, which will seek to provide an assurance that each and every box of medicine delivered to each and every patient is not a falsified product. This is but the tip of the iceberg. Advances in technology have inculcated discussions of "personalised medicine", and it is already evident that this will pose challenges and paradigm shifts in our daily practice of industrial pharmacy. We must be prepared for these challenges and look forward to a future where we see a patient in every box, where our daily activities of ensuring quality, safety, efficacy, accessibility and availability are evermore a guarantee to each and every individual patient.

With this in mind, we would like to reflect on our recent Scientific Symposium and General Assembly in Edinburgh. We must thank the Royal Pharmaceutical Society for having put together an excellent three



days where our discussions centred on new technologies in pharmaceutical manufacturing, and the seeds of the challenges that these pose in the evaluation of the risk-benefit analysis of these products, the release of these products, and the training of future industrial pharmacists to be prepared to be active professionals in these new fields, as well as current challenges in drug shortages that we must necessarily solve in order not to let these existing problems undermine the benefits that future advances in health technology can bring to patients. We must also thank the delegates from the Member States as well as the representatives of organisations that so readily lent their views to our discussion to ensure that we have all come away enriched by the experience and better armed to continue forwards on our road as industrial pharmacists.

We would like to conclude with a look to the future with no small sense of anticipation as this road will lead next year to Paris to celebrate the 50th anniversary of the EIPG. We will have good reason to celebrate for we have come a long way in these 50 years. However, we will celebrate even more the advances in the industry that will enable us, every day in our professional lives, to see with greater clarity the patient in every box.

We wish you all well.

Jean-Pierre Paccioni and Claude Farrugia

# RAISING THE BAR ON PHARMA IT SECURITY

by Vijay Takanti

**Pharma information technology (IT) systems are responsible for sensitive information that cannot be allowed to fall into the wrong hands. Intellectual property on drug formulations and research results, targeted research including key relationships with the research community, preclinical studies, and analysis and product distribution control codes/systems are all becoming targets for global attackers interested in accelerating their competitive position in drug development and distribution. In order to protect this information, we must more tightly control access to pharma applications and data by more conclusively authenticating identities with strong credentials. As communities of engaged organisations and individuals become larger, more dispersed and more complex, identity hub providers can perform the critical identity and access management function – raising the bar on security while easing the burden on valuable IT resources.**

Vijay Takanti brings over 25 years of experience to his role as Vice President of Security and Collaboration Solutions at Exostar. He is responsible for the strategy and product roadmap, design, development, and customer delivery of the company's cloud-based solutions for the life science and healthcare industries. Exostar's Life Sciences Identity Hub brings together over 700 organisations, 15,000 individuals, and dozens of applications so pharmaceutical companies and healthcare providers can collaborate securely and productively.

Information is perhaps our most precious resource. Those of us of a certain age remember when hard copies and manual processes were the sole means to document, store and share information. Today, we live in the Information Age. The vast majority of information is maintained digitally, and powerful systems and applications allow us to analyse and exchange information in less than the blink of an eye. Technologies like the cloud and mobility mean we can access information virtually anytime, anywhere. Looking ahead, the Internet of Things will put even more information at our fingertips.

IT and the emerging field of Operations Technology clearly improve our lives. We can work more productively than ever.

Information is far more difficult to misplace or lose. We can more quickly and accurately track sensitive information, such as an individual's medical records and history, to ensure we safely prescribe the optimal treatments and therapies that lead to improved outcomes.

With all of these advances and benefits comes a challenge – security. Physical security – locked buildings, rooms and file cabinets – is woefully insufficient in the Information Age. IT security is far more vast, complex and important. Think about the IT security breaches that have occurred in just the past several months, including Target, Home Depot and Sony. Now, consider that IT systems are responsible for the electric grid, the water supply, and even our personal

identities. There's little doubt that the wars of tomorrow will be fought in cyberspace, which makes IT security a top priority in virtually every industry.

Pharma IT systems in manufacturing and distribution are high-value targets for hackers and criminals. After all, these systems maintain information about all of the following.

- Drugs – what is in the research pipeline, how clinical trials are progressing, and what's in stock at the point of purchase.
- Healthcare providers – names, addresses, licenses, roles in clinical trials and more.
- Suppliers – contracts, points-of-contact, payments and more.
- Patients – personally identifiable information (name, birth date, social security number) and medical information (insurance company, insurance number, prescribed medications).

Protecting and securing these systems, information and assets is essential. In fact, it has become so important that it is no longer voluntary. Regulatory authorities, such as the Drug Enforcement Administration (DEA) in the United States, are issuing compliance mandates to mitigate the risks of security breaches and their devastating consequences.

Collectively, we have to raise the bar on pharma IT security. A May 2014 report from BitSight Technologies found the healthcare and pharmaceuticals sector lagging behind other S&P 500 sectors (finance, utilities and retail) in security performance, with a high volume of security incidents and slow response times<sup>1</sup>.

Access to IT resources and the assets they manage requires stronger controls to better confirm the identities of users. The most basic form of authentication, the username/password combination, is simply too vulnerable. This data is too easily forgotten, shared or compromised. As a result, we no longer can take for granted that individuals are who they claim to be when they enter a valid username



and password. Nor should we – the stakes are too high.

Improving pharma IT security requires implementing a two-factor authentication solution to more conclusively validate identities and control access to business-critical resources. The username/password, something an individual knows, can serve as the first factor. However, it must be augmented by a second factor, a strong credential, which is something an individual only can possess upon successful completion of an identity proofing event.

The second factor credential can take on a variety of hardware or software formats. It can be a one-time password delivered to an individual via a token, a text message, a voice message, or a mobile app. It can be a medium level of assurance public key infrastructure hardware or software certificate. Or it can be a common access card that also controls access to physical locations.

Regardless, the credential is issued and maintained by an identity provider. The identity provider can be the individual's employer or a trusted, certified third-party organisation with a track record of success in the field. For example, the SAFE-BioPharma Association certifies identity providers to the pharma industry as full-service Credential Service Providers. To receive this certification from SAFE-BioPharma, an identity provider must prove that

it meets regulatory compliance requirements. In the United States, the identity provider must comply with the National Institute of Standards and Technology's 800-63 standards mandated by the DEA.

The identity proofing event that is a precursor to issuing the second factor credential can be executed either in person or remotely via webcam or other form of communication. Remote proofing is an attractive option when there is a large, globally-distributed, multi-organisation user community.

In either case, the proofing activity should be conducted by a trusted party, such as a notary, or a credit bureau, like Experian, that has access to a wealth of personal information. The trusted party examines government-issued documents, including a passport, birth certificate or driver's license, and/or asks individuals questions that they should be able to answer quickly, confidently and accurately to substantiate their identity. The trusted party confirms the results of its analysis and informs the identity provider that the individual can receive the desired credential.

Once an individual completes the identity proofing process, the identity provider works with the individual to deliver and activate the credential. When individuals subsequently wish to access IT resources, they enter their username and password and present their second factor

credential by typing a one-time password alphanumeric string or inserting a common access card or other hardware device into their laptop.

In this scenario, the end user experience is streamlined and straightforward. But how does IT ensure that system and information privileges and permissions are properly enforced now that both accounts and credentials must be managed? IT could take on the job itself, which is fine for small, stable groups of users. What happens when the user community includes pharmacists, suppliers, healthcare providers and even patients? How does IT keep up with a dynamic, dispersed community that extends beyond its enterprise boundaries? The task quickly becomes too complex, too resource intensive and too risky – potentially detracting from security rather than enhancing it.

An April 2015 report from Gartner confirms the challenge<sup>2</sup>. According to Gartner's research, since the Health Insurance Portability and Accountability Act breach notification requirement took effect in the USA in 2009, nearly 31.4 million people have had their protected health information compromised in privacy and security breaches. In the UK, there were 7255 recorded incidents of breaches of confidentiality by the National Health Service between April 2011 and April 2014<sup>2</sup>.

One answer is to turn to a third-party identity hub provider. The identity hub provider interacts with application, information and resource owners to gather the information about users, permissions and credentials. The identity hub provider creates and maintains a master repository of all security-related data. Asset owners send updates to this data to the identity hub provider. In turn, the identity hub provider accepts credentials issued by identity providers and enforces the rules for access developed by the asset owners. **Figure 1** illustrates how the process works.

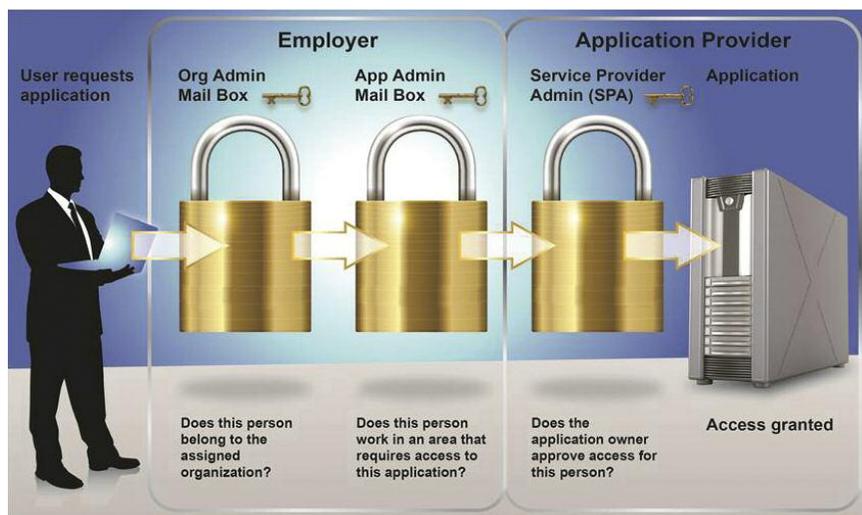


Figure 1: Illustration of access approval workflow

When an individual enters a username/password and presents a credential to access an application, the identity hub provider authenticates the individual and grants access based on the privileges for that user supplied by the application owner. IT security is strengthened without overburdening the IT organisation.

Electronic prescribing of controlled substances (EPCS) offers an excellent use case to illustrate the relevance and value of strengthening pharma IT through identity proofing and second factor credentials issued, administered, maintained, and enforced by identity providers and identity hub providers. Because of the dangers controlled substances pose if abused, healthcare providers and pharmacies must incorporate stringent processes and special forms and documentation into their

operations to manually issue and fill prescriptions. These requirements create time, cost, training, and other pains that can be eased by transitioning to secure EPCS solutions delivered via pharma IT solution vendors.

Security is the key. A study published in the *Journal of the American Medical Informatics Association* showed that over 75% of providers surveyed believed EPCS would lead to fewer medical errors and improved management of therapy by pharmacists, but nearly 15% were concerned EPCS would cause system breaches of patient confidentiality<sup>3</sup>.

Pharma IT vendors must overcome two challenges to make EPCS a reality. First, they must extend their electronic health records product suites in a manner that ensures a seamless, consistent user experience for physicians and

pharmacists who use the software for other functions. Second, they must mitigate the risk of abuse by controlling access to the EPCS solution in compliance with the DEA or other regulatory body standards, which brings identity proofing, two-factor authentication and strong credentials into play.

For the former challenge, pharma IT vendors must implement an EPCS extension that encapsulates the relevant business processes in their product's user interface. For the latter, they should outsource to a service provider that specialises in these capabilities. In this scenario, when individuals initially request access to EPCS functionality, they will be directed to an identity provider who can conduct the identity proofing event and create and send a SAFE-BioPharma or similarly compliant credential. When individuals are ready to execute

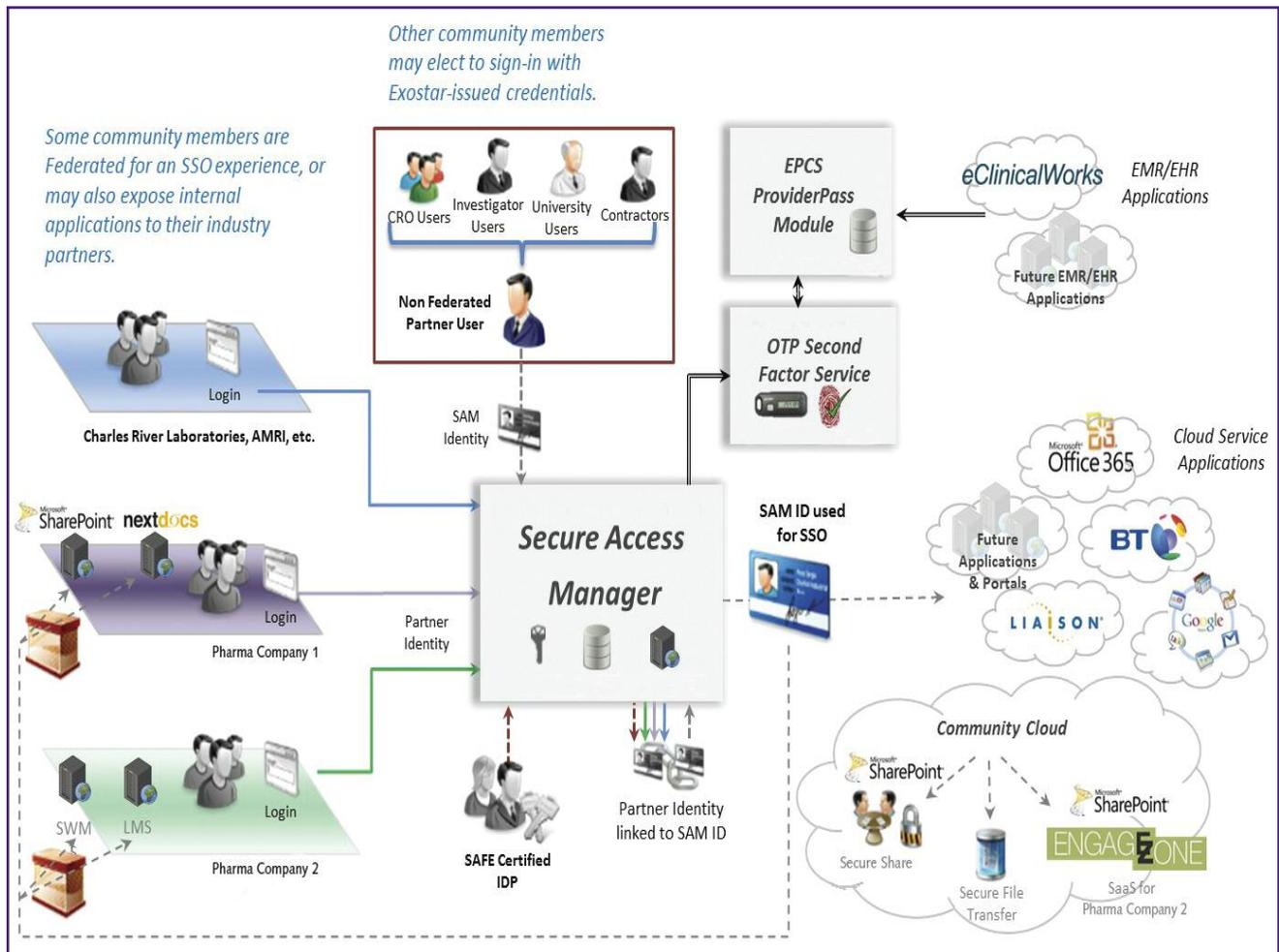


Figure 2: Identity hubs bring together users, identity providers, and applications for secure access to pharma IT assets.

EPCS functionality, they will present their second-factor credential for authentication by an identity hub provider, who, in turn, will enforce access privileges and allow individuals to proceed with writing, viewing or filling the digitally-signed prescription.

Note that the identity provider and the identity hub provider can be one and the same organisation, simplifying the underlying integration requirements and the burden on the pharma IT organisation. **Figure 2** shows how Exostar fills both roles with our cloud-based Life Sciences Identity

Hub and ProviderPass service offerings, which are being used today to promote EPCS by pharma IT vendors, including eClinicalWorks and Cerner.

Making the move to two-factor authentication to more effectively control access to pharma IT systems and mitigate the risk of information compromise must be a top priority. We invest enormous sums of money in the research, development and distribution of vital drugs and therapies. We must protect those investments, along with the privacy and well-being of providers, pharmacies and patients, by

committing the resources necessary to raise the bar on pharma IT security.

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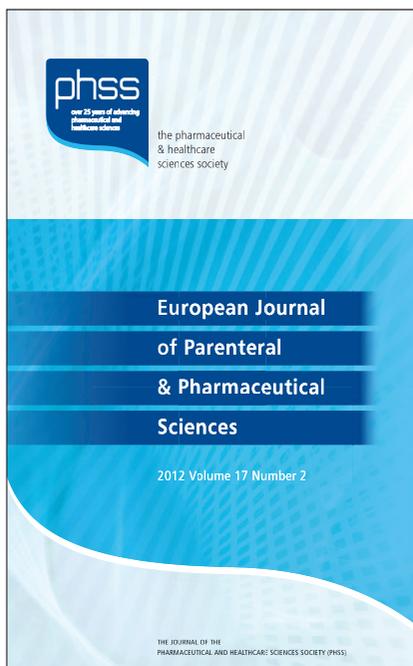
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# THE OFFICE OF PHARMACEUTICAL QUALITY: FDA'S NEW "ONE QUALITY VOICE"

by Gary Bird

**The Center for Drug Evaluation and Research (CDER) in the US Food and Drug Administration (FDA) signalled its intentions to address the significant issues of drug product quality on 14 April when it announced the establishment of its new super office, the Office of Pharmaceutical Quality (OPQ)<sup>1</sup>.**

Thomas Gary Bird is President, PharmaConsult-US LLC and Managing Partner, PharmaConsult Global Ltd., an international cooperative supplying GXP quality consulting services. He served as Director of Corporate Quality for GTx, Inc. from 2003 until 2013 and was responsible for confirming all non-clinical (GLP), manufacturing (GMP) and clinical trial (GCP) activities were compliant with appropriate laws and regulations. He has held previous positions with Eli Lilly and the FDA. He represented both PhRMA and the FDA in the International Conference on Harmonization negotiations on four different agreed guidances. Dr. Bird holds a Ph.D. in Biochemistry/Entomology from Mississippi State University and is a Pharmaceutical Science Member of the Royal Pharmaceutical Society.

Dr Janet Woodcock will carry the titles of Director of CDER as well as the Director of the newly formed office for the immediate future while Dr Lawrence Yu, PhD, will be acting Deputy Director. Now, responsibility for all things quality; including chemistry, manufacturing, and controls (CMC) components of submissions, lifecycle management, investigations, etc. as related to new molecular entities (NMEs), i.e. new drug applications (NDAs) and biological license applications (BLAs), and non-NMEs (abbreviated new drug applications (ANDAs) and 505(b)2); will reside in the new office. The formation of the OPQ is over a decade in the making. In 2004, the FDA announced its good manufacturing practices (GMPs) for the 21st century initiative. This was followed in 2012 with the approval of the FDA Safety and Innovation Act (FDASIA) of 2012 which further enforced the direction the FDA was heading by stipulating, among other requirements, that the Agency improve its risk-based surveillance inspection schedule for

manufacturing facilities. To implement this approach, the FDA was to use performance measures to assess a facility's quality system to assure product quality. The FDASIA also required that a common language be established to gauge progress related to quality allowing the Agency "to identify and respond to quality issues at manufacturing facilities before those issues become major, systemic problems".

The stated purpose of the OPQ is to bring together all of the quality and CMC-related activities previously residing in multiple offices within the CDER. By consolidating them into a single super office, the FDA intends to establish a system for quality-related issues as robust as the Agency's current programs for drug safety and efficacy. The resulting organisation has responsibility for monitoring drug quality throughout the products lifecycle, including drug application review, post-approval improvements, and surveillance and inspections of

global manufacturing facilities. With this recent development, the FDA seems determined to achieve its more than 10-year goal of having "One Quality Voice".

## A refined focus

On 14 April 2015, the FDA published a white paper that describes the general expectations for this new organisation. The paper discusses the organisational structure, the expected processes that will be implemented, the mechanisms by which improvements will occur and provides significant context for the new organisation<sup>2</sup>. Since its primary focus is on patient safety and product quality, the Agency intends the new structure to encourage modernisation of manufacturing processes within the companies it regulates. This will necessarily require the FDA to modernise its own regulatory processes. The focus on quality goes beyond the traditional interpretation of the GMPs related to the manufacturing of the drug product. For the OPQ, this will include the following.

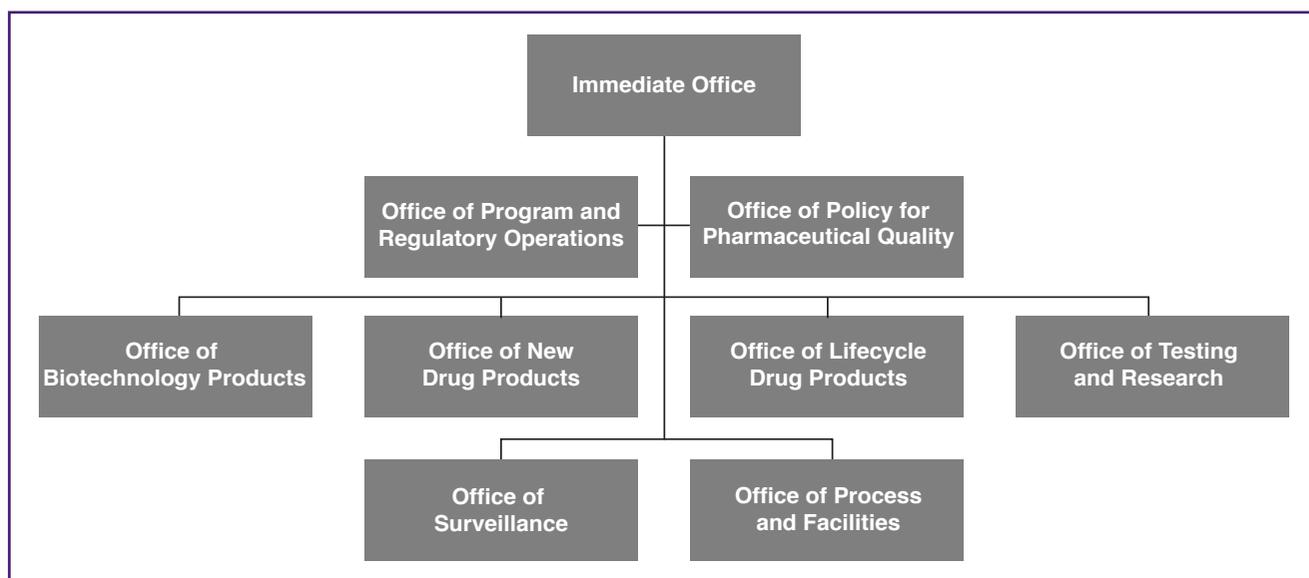
- The quality of products given to patients.
- The continuing improvement and modernisation of the manufacturing processes.
- Establishing clear review and investigational standards with clearly defined enforcement options.
- Establishing and implementing a patient-focus firmly linked to clinically relevant specifications.
- Confirming that risk-based decisions are linked to quality risk to confirm product availability.

## The new organisation

The OPQ was created to bear the brunt of the FDA CDER's Quality Initiative to achieve the following.

- Integrate regulatory reviews and inspectional activities.
- Establish standards and specifications that are clinically related and provide clear expectations for industry.
- Address the requirements for





**Figure 1: Organisation of the OPQ.**

drug products from early development through all stages of post-approval for innovator and generic drugs.

- Evaluate risks with clinical relevance that may impact the drug's safety and efficacy profiles.
- Encourage continuing manufacturing process and technology improvements.
- Encourage robust data and surveillance techniques to monitor the state of manufacturing in the pharmaceutical industry.

To achieve these goals, the OPQ has an "Immediate Office" that includes a Program Management Analysis Staff, providing administrative services, and a Science and Research Staff (SRS), coordinating scientific activities within the OPQ. Additionally, six other sub-offices, all charged with a significant component of the overall mission, were created as shown in Figure 1.

**The Office of Program and Regulatory Operations (OPRO)** takes on the formidable task of leading and coordinating the regulatory review processes of the new OPQ. It will facilitate the development and integration of a quality management

system by which all of the OPQ's staff and related FDA personnel will be able to exchange information. Further, as owner of the regulatory review processes, it is accountable for leading and coordinating the regulatory review processes and establishing the professional development programs required to harmonise review processes and to reinforce the use of the new systems.

**The Office of Policy for Pharmaceutical Quality (OPPOQ)** will assume responsibility for all scientific activities of the OPQ with respect to policies, standards, and guidance documents which include CMC guidances, review processes and inspectional standards, including current GMP regulations for all drugs, including large molecules. The OPPQ is intended to create an umbrella of consistency and collaboration under which the entirety of the OPQ will operate to promote a consistent interpretation and application of drug product quality policies and programs, including collaboration with international regulatory authorities.

**The Office of Biotechnology Products (OBP), Office of New Drug Products (ONDP) and Office of Lifecycle Drug Products (OLDP)** within the OPQ will assume primary

quality (CMC) review of drug substances, drug products, and biopharmaceutics. These three sub-offices will combine knowledge and experts to ensure that marketed drug products meet appropriate standards, provide the necessary data to support claims, and confirm that drug substance, drug product formulation and specifications for each maintain clinical relevance and data from exhibit or clinical batches are consistent and within acceptable limits. The depth of the combined knowledge will ensure that the approved drug products maintain their clinically defined efficacy and safety profiles and minimise risk to the patients. The offices will attempt to establish widely applicable evaluation and acceptance criteria for drug products in such related areas as impurity control, dissolution (where applicable), instead of using process capability or manufacturing controls as previous.

**The Office of Process and Facilities (OPF)** is assigned the responsibility of reviewing facility, process designs and controls to confirm that drug substances and drug products undergoing, for example, process scale-up and change activities, maintain their clinical safety, quality, and efficacy profiles throughout their lifecycles. Reviewers will participate in pre-approval

inspections, thereby linking the review process to the inspectional process. The restated job function of microbiology reviewers will include full evaluation of drug substances, drug products, and manufacturing processes to confirm they are sufficiently controlled for microbiological contamination to assure quality standards are met.

A key component of the new review paradigm will include a formalised communication process to share risk assessments with other reviewers and investigators to assist in pre-approval inspection, quality surveillance and decision-making. Additionally, a close relationship will be encouraged and fostered between the OPQ, the SRS and the FDA's research laboratories to further develop new manufacturing technologies and clarify regulatory expectations, process and facilities with implementation and regulatory requirements.

The Office of Surveillance will be responsible for the oversight of approved and marketed products to

enhance the Agency's ability to respond to identified process trends prior to occurrence of serious problems. Key to this proactive activity will be the establishment of a viable set of quality metrics, such as those that capture product, facility and process-related knowledge in a centralised database. This centralised data set will be at both the product-specific and site-specific level. It will allow rapid and thorough review of specific issues and circumstances that may affect product quality and the supply chain to strengthen the FDA's ability to both apply and make risk-based regulatory judgements related to, for example, inspection frequency, coverage, manufacturer reliability, and the need for greater oversight of a particular company or facility.

The Office of Testing and Research (OTR) and the OBP laboratory component, included in the OPQ's drug product quality laboratories, are tasked with performing the research required to develop

scientific standards and policies which are foundational for the quality, safety and effectiveness of human drug products. While it is recognised by the OTR and OBP that considerable information is already present, the key focus of the research efforts will be to understand new technologies, modernise current regulatory pathways and explore new regulatory pathways. These research functions will act as advisors, collaborators, trainers and researchers for review staff involved in pharmaceutical quality and bioavailability/bioequivalence issues, including formulation, analytical testing, manufacturing and modelling. Additionally, the laboratories will continue their "research on the development, manufacture, testing, and molecular mechanisms of therapeutic biotechnology products, assuring a scientific basis for establishing standards for safety, purity, potency, and effectiveness; they also anticipate emerging technologies and enable the timely provision of biotechnology products to meet patient needs".

**Teams: cornerstone to the OPQ and the new processes**

In the initial roll-out, the OPQ has chosen to devote considerable energy to confirm that the team concept becomes part of the new organisation's DNA. Because of the varied nature of the functions for which the OPQ will be assuming responsibility, the leadership team created the team-based structure to emphasise the cooperative relationships required to fulfil the lofty goals set for the organisation. In the white paper published on 14 April, the FDA includes a diagram to illustrate the intent of the team activities (see Figure 2).

For the OPQ, the use of team-based integrated quality assessments (IQAs) is the mechanism chosen by the Office to achieve its regulatory charge. It effectively places team members from each of the relevant sub-offices and the Office of Regulatory Affairs

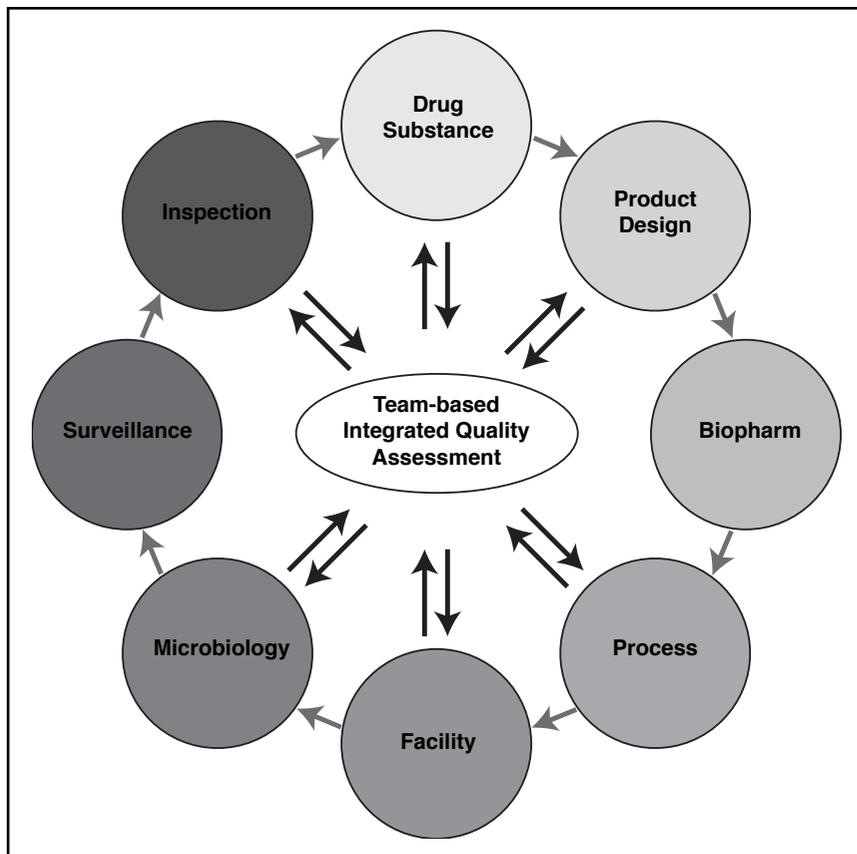


Figure 2: Team-based integrated quality assessment.

(ORA; the "field" investigators) into a formalised working relationship. In this arrangement, patient-focused and risk-based drug product quality assessments will be developed and communicated as the consensus review for the drug substance or drug product. The IQA teams will evaluate BLAs, NDAs and ANDAs and is inclusive of drug substance, drug product, manufacturing and facilities.

Formally, the make-up of the IQA teams will include the following.

- An application technical lead who oversees the scientific component of the review.
- A regulatory business process manager who manages the review process to confirm adherence to the established product-specific timelines.
- Discipline reviewers.
- Additional technical advisors as needed.

Review disciplines may include drug substance, drug product, process, facility, microbiology, biopharmaceutics and ORA investigators. The IQA teams will call upon technical advisors from OPQ laboratories, policy, surveillance and other offices as needed.

#### Finally

The effort to create the OPQ is challenging in both intent and outcome. By placing the motto of the organisation "One Quality Voice" into the forefront, the FDA is stating unequivocally that the OPQ will speak to industry on all issues of quality. As the OPQ matures, it is expected that its processes will impact all of the areas involved in quality-related activities. For example, CDER-OPQ reviewers will likely participate in inspections, just as the ORA investigators will be IQA team members. These stronger alliances and relationships between

the historic reviewer and "the field" are expected to enhance and speed up the quality assessment of product, ultimately leading to more effective and efficient regulatory decisions regarding facilities and the overall approvability of applications. Only time will tell if the effect will be worth the effort, but the initial response from industry has been generally hopeful that it will be.

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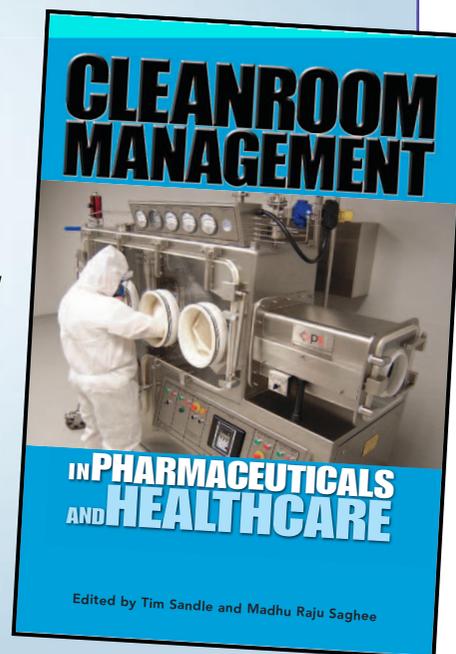
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# NEXT IN LINE: PERSONALISED HEALTHCARE

by Wouter Laroy

**Personalised medicine is considered the new model for an optimised healthcare system. Trial-and-error therapy approaches will make way for models where tailored diagnostics and fit-for-purpose therapy go hand in hand, providing clear advantages for both patients and social security systems. Innovative technologies will need to bridge the gap between biomarker discovery, and their commercialisation and use as 'syndromic' biomarker panels.**

Wouter Laroy (wlaroy@mycartis.net) is VP Scientific Marketing at MyCartis and has over 15 years of experience in biotech and life science research and industry. He held a management position at Pronota where he developed and applied state-of-the-art technologies for the discovery and validation of biomarkers in multiple disease areas. He has authored over 25 peer-reviewed publications during his academic research period, mainly on the involvement of carbohydrates in diseases.

## Introduction

Each person on this planet should be considered equal. However, all of us are unique from a molecular point of view. For sure, this has its influence on how humans should be medically treated. The era of 'one size fits all' medicine is over and an approach where tailored diagnostics and therapy go hand in hand should take that place<sup>1</sup>. Doctors have always taken into account the status of their patient. Hippocrates (460 BC) already mentioned the importance of balancing the four humours (black and yellow bile, phlegm and blood) for better health. In the modern concept of personalised medicine, prescription of therapy is based on actionable information on an individual, provided by different types of biomarkers. With today's advanced tools and technologies, most diseases are now considered multifactorial, meaning that multiple changes are at the origin of the disease itself or of the comorbidities associated with the disease. From a biomarker point of view this means that not one but rather a 'syndromic' panel of biomarkers will provide the clinician the information needed to

initiate or adapt proper therapy. To come to a truly personalised medicine, some hurdles still need to be overcome. For one, comprehensive technologies to measure these syndromic panels are crucial in making such models successful.

## The evolving healthcare model

Most healthcare models that are applied today are based on the treatment of the diseased. One could argue using the term *sickcare* rather than *healthcare* here. The ultimate goal of personalised medicine is to not only treat the sick people but to also take better care of the healthy and improve the overall wellness in life. The current trial-and-error strategy in therapy decision taking should make way for a more informed and timely treatment strategy where the information comes from a comprehensive syndromic panel (see **Figure 1**). Undoubtedly, this will have a positive influence on the patient's health and its environment. Besides that, the enormous current burden on social

security systems should be greatly relieved.

## The single biomarkers versus the syndromic panel

A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of specific biological processes or conditions. This information is considered actionable if a specific treatment can be linked to it. Different types of biomarkers exist, providing information on the genetic background (e.g. in targeted cancer therapy), the protein expression pattern (e.g. to assess the inflammation status), the metabolic content (e.g. in kidney function) or even the pathogenic content (e.g. human papilloma virus profiling in cervical cancer) of a person.

Rarely, one single biomarker provides the clinician sufficient information to treat his patient in the most optimal way. It is rather a syndromic biomarker panel that will provide the physician this information. The result of the panel can be interpreted in different ways. Through an algorithm, results from a multi-biomarker panel can be combined into one or multiple actionable outputs. On the other end of the spectrum, all biomarkers can be considered independently and guide the clinician through a therapy decision tree. In any case, to make syndromic panels work in practice, some major technological challenges still need to be overcome. Some examples are provided where the personalised approach has already proven its success or where a syndromic approach would show helpful.

Genetic profiles are becoming hugely important in anti-cancer therapy, where targeted therapy is taking a major position because of several advantages. Mutated pathways in cancer cells are the cause of uncontrolled growth into tumours. Targeted drugs specifically attack these mutated pathways. Assessing the genetic profile of a tumour is thus of prime importance in deciding on the right therapy<sup>2</sup>. Moreover, it has been shown that remission of tumour load after or during treatment is mostly due to an



altered genetic profile, making the tumour resistant against the drug used. Continued follow-up profiling is thus important to maximise therapy success. Tumour mutation profiles can be obtained from biopsy material. More recently, there has been a growing interest in getting the profile from tumour DNA shed in the blood. Especially for therapy monitoring, where the tumour was first removed, this is an important but challenging progression in this personalised approach.

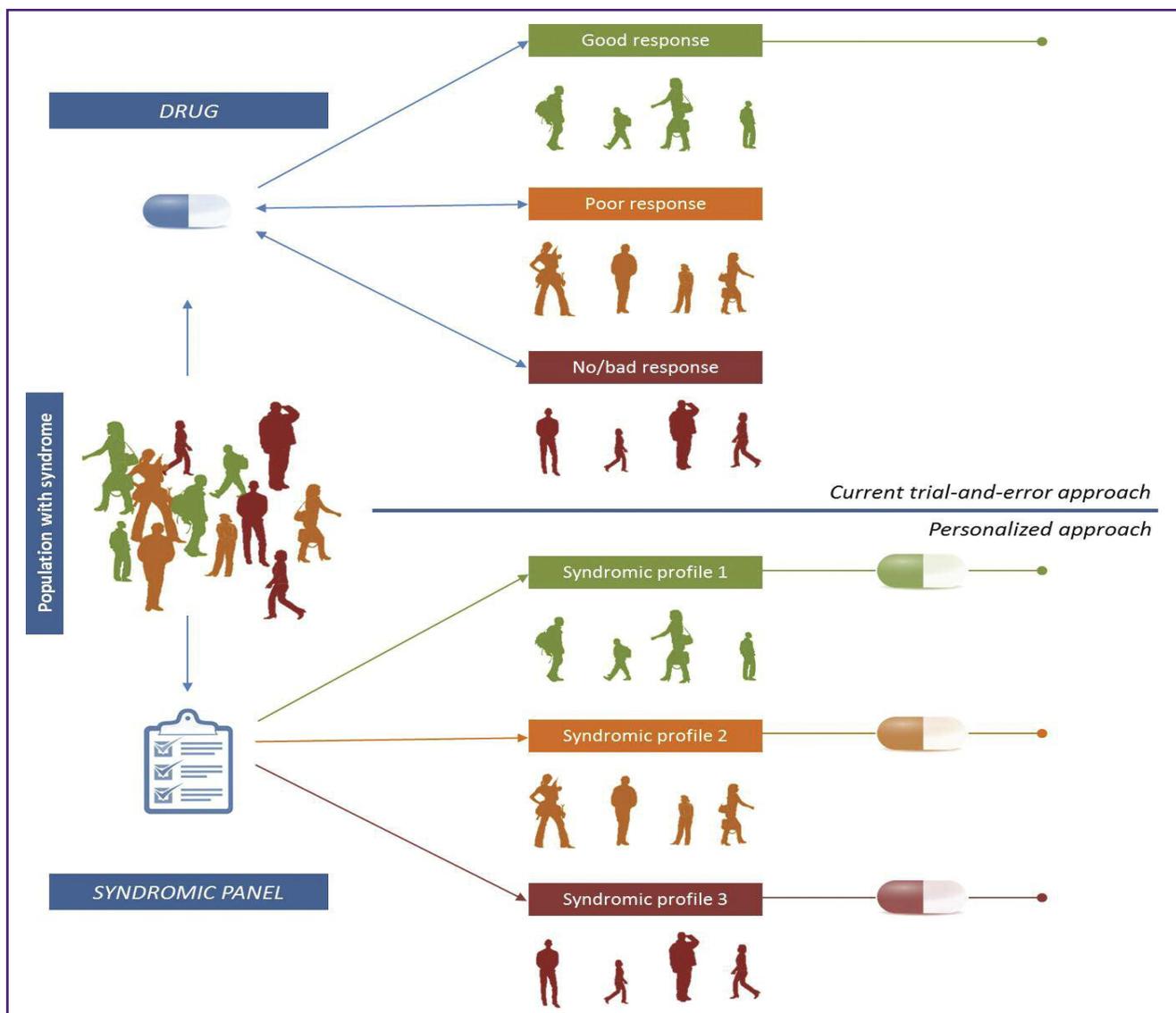
Cervical cancer is the fourth most common cancer in women. When diagnosed early, treatment has shown to be very successful. For that

reason, large screening campaigns have been set up, leading to much reduced mortality rates. The widely used Pap screening test (over 50 million of these cytology tests are run per year in the US alone) is limited by a high false-positive rate, leading to many unnecessary and expensive colposcopies and biopsies. The infection with certain high-risk strains of human papilloma virus is known to cause cervical cancer and a molecular test to identify these strains has, therefore, been added to most screening protocols.

However, this still results in a large over-diagnosis rate. Currently, new promising oncoprotein tests are

under development to solve this issue<sup>3</sup>. Clearly, a syndromic panel for screening and diagnosis of cervical cancer will cover different types of biomarkers.

Heart failure, a condition in which the heart is unable to pump enough blood to support physiological circulation, is one of the major causes of hospitalisation worldwide, only beaten by normal baby delivery. Disease cures are not yet available but correct disease management helps in improving quality of life of the patients<sup>4</sup>. Heart failure is truly considered a syndrome as it can be triggered by different conditions, such as



**Figure 1:** The current 'trial-end-error' approach to medical practice will make place for personalised medicine where tailored diagnostics and fit-for-purpose therapy go hand in hand. In the former approach, the drug is central. In the latter, the syndromic panel outcome provides the information for the clinician to make an informed decision on therapy.

damaged heart tissue, lung disease, infections or even life style. Moreover, the disease is typically associated with major comorbidities like kidney dysfunction. Disease management is mainly focused on reducing symptoms and treating comorbidities. Although the blockbuster biomarker b-type natriuretic peptide is used for diagnosing patients presenting in the emergency department with shortness of breath, it provides no or limited information on other important aspects of the disease. Again, in this area, a syndromic panel approach would dramatically improve patient wellness and reduce healthcare cost.

### Technological challenges and solutions

The understanding that personalised medicine is the future of healthcare has driven the biomarker market lately. Market reports differ a bit on their predictions, but with an expected compound annual growth rate of 12–18% through 2018, the global biomarker market is expected to reach \$40–50 billion by then. Nevertheless, only few new biomarkers hit the market yearly, despite the ever growing number of scientific publications describing new ones. Commercialising biomarkers is not only a long, tedious and costly process, technological limitations have also slowed down or halted their path through regulations at different stages of validation and assay development. Besides, most biomarker *in vitro* diagnostics technologies allow the measurement of only one biomarker per analysis or, at most, a panel of biomarkers of the same type. Within the concept of the syndromic panels, these established technologies have serious limitations. Both examples illustrate the current need for innovative technology to bridge the gap between discovery, commercialisation and use in a personalised clinical setting. Robust and reliable results as well as easy workflows are some of the major key features for such technology.

Ideally, a 'one technology fits all' solution enables researchers and assay developers to validate all their biomarkers, to utilise and to commercialise them, all in an accurate and robust way. Today, recording syndromic biomarker panels is still a time-consuming and labour-intensive process, putting additional pressure on the technology developers to make them fast and easy to operate. No technology that fits all criteria is yet available, but several are trying to take their share in the research and clinical market. Some advanced technologies allow the simultaneous measurement of different biomarkers of the same kind. The Idylla platform (Biocartis, Belgium), for example, seamlessly integrates sample work-up and measurement of molecular biomarker panels to enable rapid and high-quality care of cancer patients. To measure syndromic protein panels, automated multiplex immunoassay approaches like the MESO QuickPlex (Mesoscale, USA) have been developed. Rarely, multiple biomarker types can be measured using the same technology. Examples that can measure multiple biomolecules are the bead array approaches (Luminex, USA) or the recently launched microfluidics Evaluation (MyCartis, Belgium) platform<sup>5–6</sup>. Different chemistries and assay concepts enable the real-time measurement of proteins, nucleic acids and other (bio)molecules on a single device, which is a clear advantage within the syndromic panel idea. Moreover, the latter systems have an open design also allowing researchers to build custom assays, enabling them to validate their biomarkers.

### Conclusions

For a lot of diseases, good prevention methods or appropriate therapies are still lacking. Looking at these diseases as being a multifactorial syndrome and finding out the underlying biology is of key importance to finding solutions. In his latest State of the Union, US president Obama announced his Precision Medicine Initiative which

should pioneer this new patient-centred healthcare concept<sup>7</sup>. The initiative is associated with an initial \$215 million investment, clearly demonstrating its importance. One can argue the benefit of introducing a new term or discussing their meaning and differences, but 'personalised' and 'precision' medicine are essentially the same. Both put the patient in a central position and from there science drives decision taking. Finding, validating and commercialising new and powerful biomarkers and bringing these together in syndromic panels should be the major focus of future research, research that will be driven by new and innovating technologies.

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# TECHNOLOGICAL ADVANCES IN RATIONAL DRUG DESIGN

by Andreas Förster and Clemens Schulze-Briese

**R**ational drug design depends on structural information of the biological target to model ligands and optimise interactions. Recent advances in detector design, exemplified by the EIGER family of X-ray detectors, have dramatically improved the quality of data that can be obtained from protein crystals.

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Rational drug design depends on the quality of protein structures that serve as the basis for fragment searches. Protein structures are usually obtained by X-ray crystallography, which involves crystallising purified proteins-of-interest and then exposing the obtained crystals to X-rays. Crystals diffract X-rays, and if the protein crystals are of sufficient quality, a diffraction pattern can be obtained that will permit the determination of the three-dimensional structure of the protein, at atomic resolution in best cases.

The availability of high-resolution

structures allows the interpretation of biochemical experiments, like activity assays and binding studies. At the end of this process, an active site is described and chemically understood, which can then be used for fragment screening or ligand optimisation (Figures 1A and B)<sup>1,2</sup>. In this way, inhibitors are being developed against oncogenes<sup>3</sup>, G protein-coupled receptors<sup>4</sup> and  $\beta$ -lactamase<sup>5</sup>, to name just a few.

Structural information helps during the prioritisation of targets, potentially increasing the efficiency of targeting itself. Embarking on a drug design process is most promising and

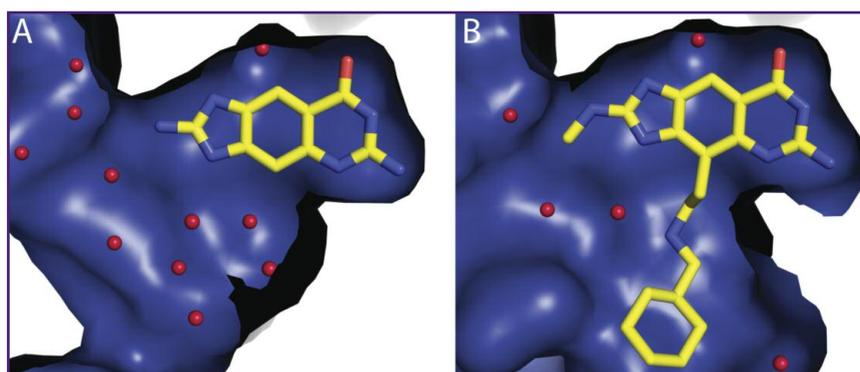
should be pursued preferentially if the active site forms a deep pocket with multiple contact points on the surface of the target protein that a drug could bind to with high avidity. The level of detail provided by a crystal structure is often beyond what other experiments allow one to see. For example, the crystal structure of the human P2Y1 receptor, an important target for antithrombotic drugs, showed not just one but two ligand-binding sites<sup>6</sup>. Without a crystal structure as a starting point, designing a drug is like building a house with closed eyes. One might arrive at something useable, but it will, in many respects, be deeply flawed.

To obtain a crystal structure, one critical step is protein crystallisation, which is poorly understood and largely random in its success. Most effort in industry and academia goes into growing better crystals – or getting crystals at all, but the approach is entirely stochastic. Specialised robots perform high-throughput crystallisation experiments in ways that minimise sample input and time expended, while maximising chemical space. Once conditions that yield crystals of sufficient quality have been found, these can usually be reproduced and scaled to whatever quantities are needed for structure determination or ligand-binding studies.

The other critical step is data collection, which also depends heavily on technology. In recent years, equipment has been improved at all levels to ameliorate the quality of the data that can be obtained. At one end of the diffraction experiment, this meant upgrading the radiation sources. Synchrotron beams are now more brilliant, more tightly focused and more coherent than ever before. At the other end, detector technology has made it possible to count every diffracted photon with minimal noise and high accuracy.

## Hybrid Photon Counting detectors

The greatest step forward in detector technology was the introduction of Hybrid Photon Counting (HPC) detectors.



**Figure 1:** Structure-based drug design applied to tRNA-guanine-transglycosylase, a target for the treatment of shigellosis. (A) The X-ray structure of lin-benzoguanine bound to the active site of the enzyme<sup>2</sup> (binding affinity 58nM) was used to design ligands with higher affinity. (B) Addition of a cyclohexyl moiety designed to fill the active site increased the binding affinity of the ligand (2nM). The protein is shown cut open to reveal the deep binding pocket as a blue surface. The ligand is shown as a stick model, with yellow carbons, blue nitrogens and red oxygens. Ordered water molecules are shown as red spheres. The atomic coordinates for both complexes are available from the Protein Data Bank (pdb codes 2z7k and 3eos, respectively).



Traditional X-ray detectors (image plates and charge-coupled devices (CCDs)) first convert X-ray photons into visible light, which is then detected. The detection is indirect by design, with associated problems, like leakage and peak broadening. In addition, during integration of the photon intensities, readout noise and dark currents are added to the recorded data. Traditional X-ray detectors thus degrade the data that is collected from protein crystals, a state of affairs that was only acceptable because of the lack of alternative technologies.

HPC detectors count each absorbed photon directly and discretely. When a photon is absorbed by the sensor material, normally a layer of silicon, a large number of electron-hole pairs are created. The application of an electrical field across the sensor allows the collection of the charge by a readout chip. As each sensor pixel is directly bump-bonded to its own dedicated readout pixel (from which the term hybrid in the name of the detectors derives), extremely short readout times can be achieved. Where image plates took minutes to read out and CCDs seconds, HPC detectors can be read out in milliseconds or faster. Correspondingly, high frame rates are possible in experiments where a crystal is rotated while hundreds or even thousands of successive diffraction images are collected. These experiments can now be done without closing the shutter between measurements, which not only further accelerates the process but also averts shutter jitter as a source of error.

In the readout chip, a threshold energy is set to suppress any low-energy signal and, thus, any noise present in the electronics. This makes HPC detectors effectively noise-free and leads to excellent signal-to-noise ratios. The direct detection of photons results in a point spread function of one pixel. Peak broadening is non-existent with HPC detectors, and diffraction lattices can be resolved for even the

largest unit cells. Combined, the features of HPC detectors have allowed the formulation of novel data collection strategies that yield data in unprecedented quality<sup>7</sup>.

The primary practical consequence of HPC detectors is the improved data quality, which means that the pharmaceutical target can be described more accurately and, therefore, targeted more precisely. Ligands or inhibitors developed against a well-understood target are obviously more likely to bind *ex silico*. Furthermore, the high speed of data acquisition increases the efficiency with which limited and, for that reason, pricey beamtime at synchrotron radiation facilities can be used, and enhances the effectiveness of more readily available time at laboratory X-ray sources.

### HPC detectors in industrial laboratories

The technology of laboratory X-ray sources has been optimised over years, even decades. Commercially available systems are mature and reliable. The strength of the beam approaches that of second-generation synchrotrons. The goniometer and the entire data acquisition process can be controlled by powerful software, even by an operator at a remote location (an office in the simplest case). Robotic sample changers have turned the cumbersome process of mounting samples into an efficient operation that does not require the presence of personnel onsite. Thanks to the stability of the beam and the automation of sample mounting and experimental control, laboratory X-ray sources can provide unattended operation overnight and collect data 24/7 with minimal downtime.

The only class of laboratory X-ray equipment that has not experienced a comparable degree of technological progress has, until recently, been detectors. Image plates and CCDs prevail and – arguably – hinder rather than help scientific research. This is now changing with the arrival of fast and

noise-free HPC detectors specifically designed for the requirements of industrial applications. These detectors benefit from affordability, small footprints, low maintenance, and operation at room temperature, while exhibiting all the attractive properties of their larger cousins at the synchrotron. It is likely that laboratory X-ray crystallography is about to enjoy a period of renaissance now that fully developed equipment is available.

In the long and unpredictable process of designing a drug and bringing it to the market, every step is under constant scrutiny. Fragment search algorithms, the prediction of binding affinity from structural complementarity, the bioavailability of the designed ligand, the exclusion of cross-reactivity, and clinical trials with all their uncertainties – all need to be persistently monitored and improved. With latest-generation HPC detectors, the pharmaceutical industry now has the option to optimise the quality of the structure of the underlying biological target as well.

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# THE PHARMACEUTICAL PIPELINE FOR NON-SMALL CELL LUNG CANCER

by Joshua Libberton

**The non-small cell lung cancer (NSCLC) pipeline is showing great diversity and innovation, in an effort to solve some of the most pressing issues facing NSCLC treatment. Following improvements to tumour characterisation and classification, treatment is still trying to meet the needs of an increasingly segmented market. The pipeline has a large first-in-class component, meaning that there are many therapies with inventive and interesting methods of treating this malignancy.**

Joshua Libberton is an Analyst at GBI Research. He is part of a team developing the Frontier Pharma module of market forecast reports, which focus on promising first-in-class, early-stage products in various disease markets. In recent years, he has specialised in oncology markets.

NSCLC has the second highest incidence of all cancers globally and is associated with a very poor prognosis and a 5-year survival rate of 14%, making it the leading cause of cancer-related mortality worldwide. Approximately 70% of patients are ineligible for surgery at the point of diagnosis, necessitating pharmaceutical intervention to delay disease progression<sup>1</sup>.

The NSCLC market is large, comprising 458 products; however, most lack diversity in terms of molecular target and active pharmaceutical ingredient (API). As a result, the market predominantly comprises generic chemotherapies that often have serious side-effects and that offer only minor improvements to overall survival. Targeted therapies are slowly emerging onto the NSCLC market and are having a significant impact, although generic chemotherapies retain dominance.

The NSCLC pipeline provides a drastic contrast to the market, with a much greater diversity and a plethora of novel therapies in development that are aligned to known disease-causing pathways. Furthermore, a significant portion of this pipeline diversity has emerged from high levels of first-in-class

innovation within this indication, defined as products acting on molecular targets not yet present in any market industry-wide.

A major driving force behind innovation and increased diversity in NSCLC drug development is the increasingly segmented market, which is beginning to alter the therapeutic landscape. Over recent decades, NSCLC has transitioned from a singular entity into a disease that encompasses multiple distinct subtypes. It is currently predominantly differentiated by histology, with adenocarcinoma, squamous cell carcinoma and large cell carcinoma being the most frequently occurring subtypes. Due to differing characteristics, certain targeted therapies, such as Avastin (bevacizumab) have been approved only in particular subtypes, thereby altering the treatment algorithm for patients depending on their histological subtype<sup>2,3</sup>.

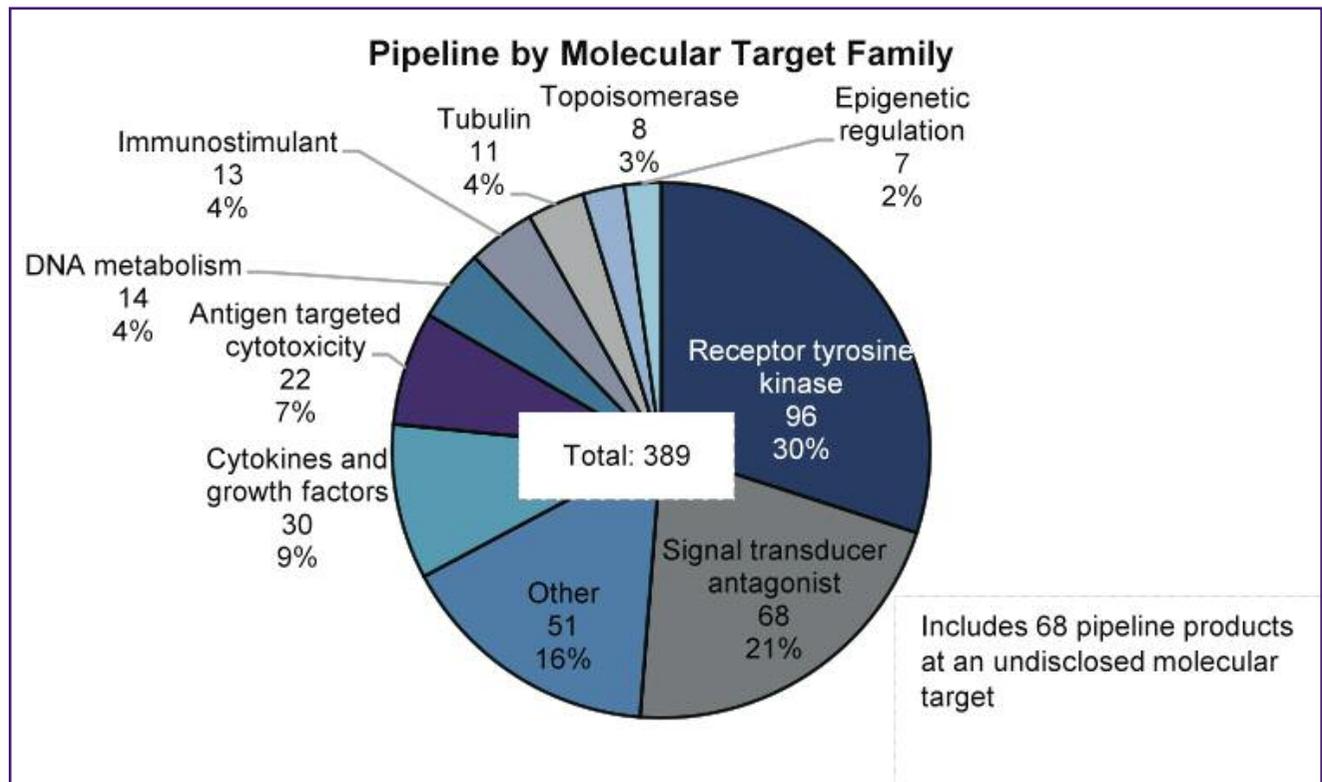
In addition to histological characterisation, recent advances in the understanding of NSCLC tumour pathophysiology have allowed tumours to be characterised based on molecular aberrations<sup>4</sup>. The identification of mutated, amplified or overexpressed proteins in NSCLC tissue is one of the

primary reasons that the pipeline is so diverse, as new and novel targets have been identified that drug developers are now aiming to convert into clinically and commercially viable therapeutics. The launch of mutation-specific therapies commonly targeting mutations to epidermal growth factor receptor (EGFR) further exacerbated the difference between NSCLC subpopulations and their treatment algorithms. As the mutation frequency of key proteins differs significantly between histological subtypes, treatment options will become more personalised in the future, providing the industry continues to develop therapies that target these molecular aberrations.

In terms of molecular targets, a small portion of the current market is devoted to receptor tyrosine kinase (RTK) inhibitors, which act on some of the most common molecular aberrations in the adenocarcinoma subtype, predominantly EGFR and anaplastic lymphoma kinase (ALK) mutations. In total, there are eight unique APIs on the market; however, there is a large generic presence for many chemotherapies. The remainder of the market is oriented around various DNA targets and tubulin, which are targets commonly associated with chemotherapies.

Analysis by GBI Research identified 389 products in active development for NSCLC<sup>5</sup>. In a drastic contrast to the market, there is a much wider range of products and target families in the pipeline, as shown in **Figure 1**. The largest target family is now RTKs, with 30% of pipeline products modulating these receptors in some way. Forty percent of the RTK target family is devoted to the ErbB family of receptors. Following on from the achievements of therapeutics, such as Tarceva (erlotinib) which targets EGFR, drug developers are seeking to build on the established success of this molecular target and provide treatment options that overcome resistance to current treatments or that improve upon the safety and efficacy profile. EGFR remains the favoured target of the ErbB family;





**Figure 1: Pipeline molecular targets.** Source: GBI Research, Proprietary Pipeline Products Database.

however, targeting other receptors has shown promise as combination therapies or methods of overcoming EGFR inhibitor resistance.

A significant number of combination inhibitors have a relatively broad-acting effect by inhibiting multiple RTKs. This can induce a larger response and can be safer in some instances as they require a lower dose of each specific inhibitor. ALK, hepatocyte growth factor and Axl-targeted therapies all occupy approximately 7% of the RTK target family. Both ALK and hepatocyte growth factor receptor are methods of targeting underlying molecular aberrations in NSCLC, whereas targeting Axl may have implications in overcoming EGFR inhibitor resistance.

The second largest category is signal transduction antagonists, which is a category that is absent from the market and comprises 21% of pipeline products. Products targeting signal transduction predominantly interfere with intermediates in common signalling cascades associated with cancer progression. The mitogen-activated

protein kinases/extracellular signal-regulated kinases and phosphatidylinositol 3-kinases signalling pathways are the most frequently targeted, at 28% and 17% of this particular target family, respectively. They are also well established in cancer pathology and often promote aberrant cell survival, proliferation, growth and migration in NSCLC cells. Such signalling pathways are often dysfunctional in NSCLC cells due to overexpression of pathway components or upstream mutations. Other target families that appear in the pipeline but not in the market include cytokines and growth factors, tumour-associated antigens, immune signalling, and epigenetic regulation.

The diversity in the NSCLC pipeline outlined above is a promising sign, as new therapies will offer opportunities to treat specific histological and molecular subtypes with higher safety or efficacy than offered by current therapeutic options. Innovation is an important aspect of drug development, with the industry constantly seeking to

improve on marketed products with addition-to-class or advance-in-class products. However, first-in-class drug development can be a sign of true innovation in a developmental pipeline and is associated with a greater chance of yielding breakthrough therapies, despite the riskier development strategy. GBI Research's analysis also revealed that, on average, first-in-class products generate higher annual revenue 4 years after market launch compared to non-first-in-class products. First-in-class development is especially apt in NSCLC, where advances in molecular characterisation of tumours have provided ample molecular targets.

Of the 389 pipeline products, 122 are first-in-class products, comprising 96 first-in-class targets<sup>5</sup>. This represents 38% of the pipeline therapies with a disclosed molecular target: greater than the pharmaceutical industry average of 36% but smaller than the oncology average of 43%.

The greatest amount of first-in-class development was in the signal transducer antagonist target

category, with almost 40 first-in-class products, as shown in **Figure 2**. However, the number of established targets within this category is almost equal to the number of first-in-class targets. Therefore, antigen-targeted cytotoxicity could be considered the most innovative target family, having 18 first-in-class products and four with established products, equating to 82% of this category being focused on first-in-class development. Targets in this category are incredibly diverse, including Mucin-1 and cancer testis antigen.

Using an array of parameters, including mutation frequency and alignment to disease-causing pathways, GBI Research has determined the most promising first-in-class targets in the early stages of the pipeline and substantiated them by reviewing published literature.

Literature on each of the discussed targets has, for the most part, justified the pharmaceutical industry's pursuit. It is, therefore, highly likely that several of these targets, such as focal adhesion

kinase and human epidermal growth factor receptor 3, provide a glimpse into NSCLC's distant future.

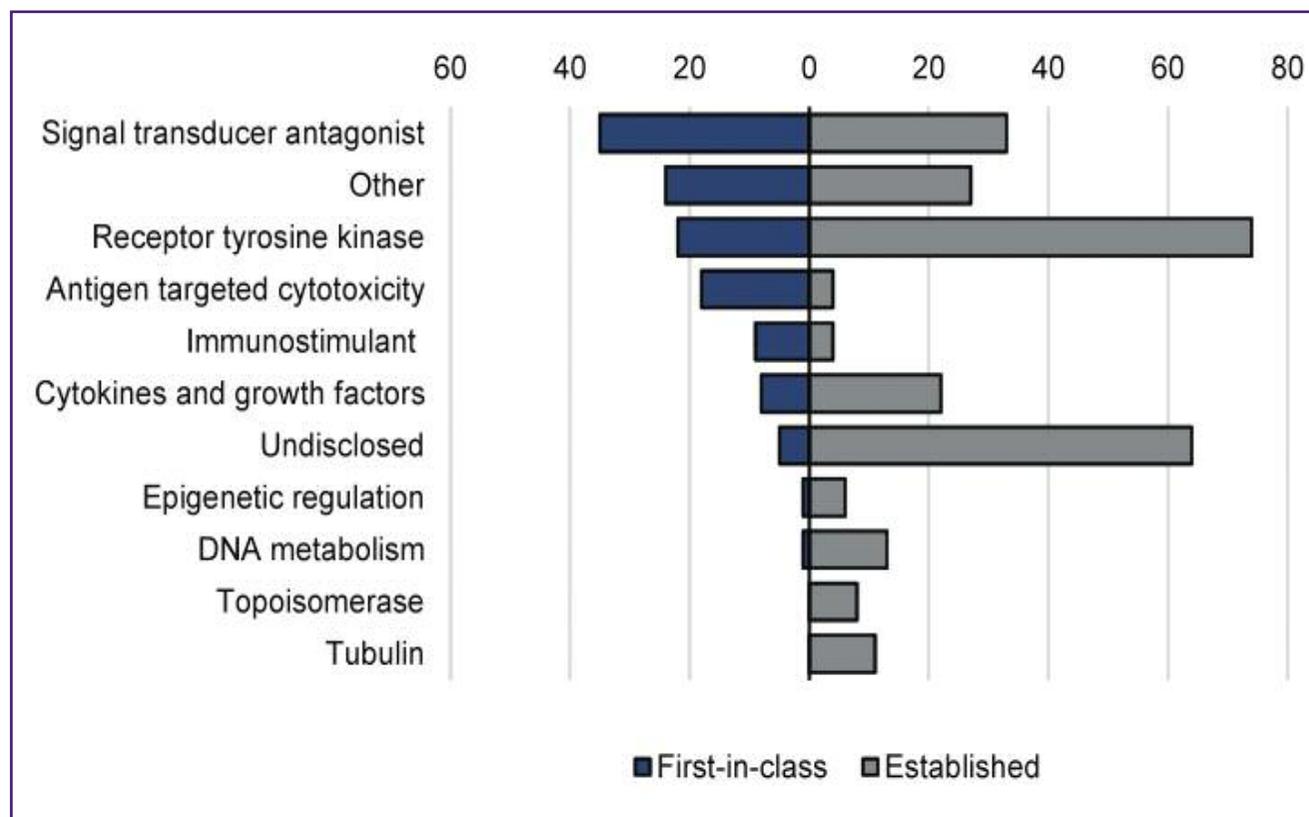
However, whether there is the potential for a blockbuster therapy to develop from these targets is a different matter. The benefit of many of the targets derives from them being able to enhance current therapeutic options, whether enhancing chemotherapy or combating resistance to the EGFR inhibitors. While these are undeniably important improvements, they are not revolutionary.

The NSCLC developmental pipeline comprises an array of molecular targets with variable alignment to disease-causing pathways. The importance placed on signal transduction and aberrant growth factor signalling pathways is seen across many oncology indications; however, this is of particular importance in NSCLC in terms of further segmenting the market based on histological and molecular tumour characterisation, with many of the therapies showing

greater efficacy in particular subpopulations. A large proportion of the NSCLC pipeline diversity is due to the high degree of first-in-class innovation. While a significant portion of these molecular targets has clinical potential, current evidence suggests that they will be most effective as adjuncts, rather than replacements, of chemotherapy.

**Further reading**

- <sup>1</sup> Daniels MG, Bowman RV, Yang IA et al. An emerging place for lung cancer genomics in 2013. *J Thorac Dis* 2013;5:S491-S497.
- <sup>2</sup> Forde PM, Ettinger DS. Targeted therapy for non-small cell lung cancer: past, present and future. *Expert Rev Anticancer Ther* 2013;13(6):745-758.
- <sup>3</sup> Perez-Moreno P, Brambilla E, Thomas R, Soria J-C. Squamous cell carcinoma of the lung: molecular subtypes and therapeutic opportunities. *Clin Cancer Res* 2012;18(9):2443-2451.
- <sup>4</sup> Shtivelman E, Hensing T, Simon GR et al. Molecular pathways and therapeutic targets in lung cancer. *Oncotarget* 2014;5(6):1392-1433.
- <sup>5</sup> GBI Research. Frontier pharma: non-small cell lung cancer – identifying and commercializing first-in-class innovation. Report code: GBIHC341MR. London, UK:



**Figure 2:** Distribution of first-in-class development in NSCLC. Source: GBI Research, Proprietary Pipeline Products Database.



# CURING THE AILING CLINICAL TRIAL

by Dirk Meijer

**Clinical trials are expensive and time consuming. It is often cited that only 50% of late stage and 25% of early stage trials succeed, so there is a very good chance that a clinical trial will be a waste of time and money. Fortunately, several early warning signs have been identified which can help to rescue them providing the intervention is swift.**

Dirk Meijer is the CEO and co-founder of Factory CRO, based in The Netherlands. Factory CRO is a Clinical Research Organisation that has been conducting medical device clinical trials for the FDA and CE Mark since 1994. With over 70 clinical trial specialists operating in 30 countries around the world, Factory CRO offers guidance and facilities to manufacturers of medical devices for preclinical and GCP clinical research.

Figure 1 shows success rates of pharmaceutical clinical trials at each phase of drug development. For example, 64% of preclinical studies succeed and progress into Phase 1 trials, 44% of Phase 1 studies successfully proceed into Phase 2 trials and 22% of Phase 2 studies continue on into Phase 3 trials. Furthermore, it is estimated that just 3% of preclinical studies, 5% of Phase 1 studies, 12% of Phase 2 studies and 54% of Phase 3 studies lead to one new drug product.

There are a number of reasons why so few clinical trials make it to the next stage. Two of the more

frequent reasons are that the product actually isn't any good at doing what it was being tested for or that the product has unacceptable side effects. However, a clinical trial that proves that a product has not achieved what it was meant to is not necessarily a failure, but rather could be considered a success because it has fulfilled the purpose of the trial. Many clinical trials, however, fail in their purpose; according to one source<sup>1</sup>, almost 80% of clinical trials fail to meet enrolment timelines. This can result in high costs, for example, a study<sup>2</sup> published in 2011

found that at a leading academic medical centre in the US, one-third of all the studies terminated between 2005 and 2009 had either no or only one participant, which cost the centre almost US\$1 million annually.

The medical device sector is even more prone than the pharmaceutical industry to flawed studies. This is because the medical device industry attracts more start-up companies with novel device ideas. These studies are frequently poorly designed and managed or based on incorrect assumptions, thereby increasing the chances that the study will be rejected by regulatory authorities. As the companies conducting such trials are often small, the cost of a failed clinical trial can bankrupt them.

The question then arises as to what can be done about it; and the adage that prevention is better than cure is as applicable to clinical trials as it is to the conditions they are designed to treat. There are some established assumptions that can put a trial in jeopardy. For example, when recruiting the study team, it is obviously important to attempt to recruit the best team possible; but the "famous" investigator may not be the ideal investigator, because they could be involved in a number of projects which will restrict them from fully committing to the trial. This is a very common problem and can occur particularly in situations where the Chief Investigator is given the freedom to recruit the other Principal Investigators, who are often colleagues involved in their other trials. The sponsor or contract research organisation should, therefore, ensure that the processes illustrated in Figure 2 are conducted in evaluating potential investigators.

In preparing the study design, the first question to ask is "What is the goal of the clinical investigation?" For example, is it to prove safety and efficacy or superior effectiveness to competitive technologies? The relevant endpoints should then be identified, for example, is it necessary to demonstrate 90% revascularisation by a stent at 6

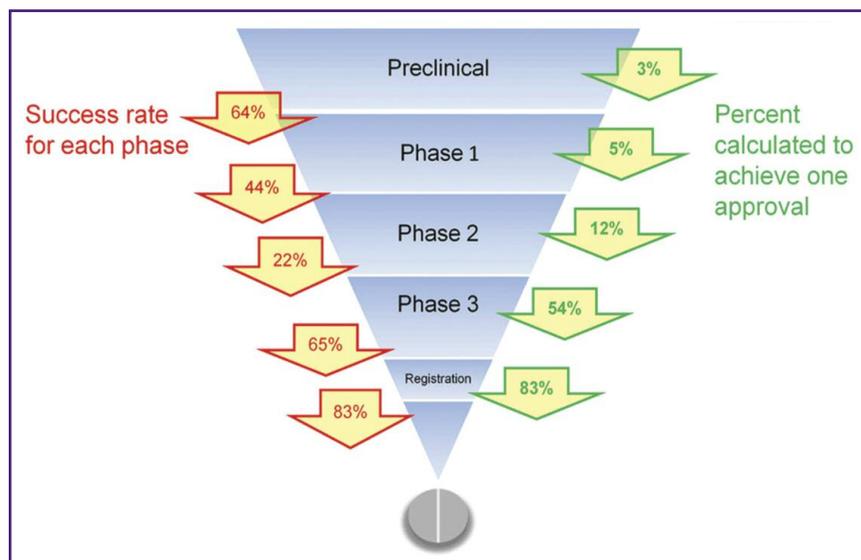
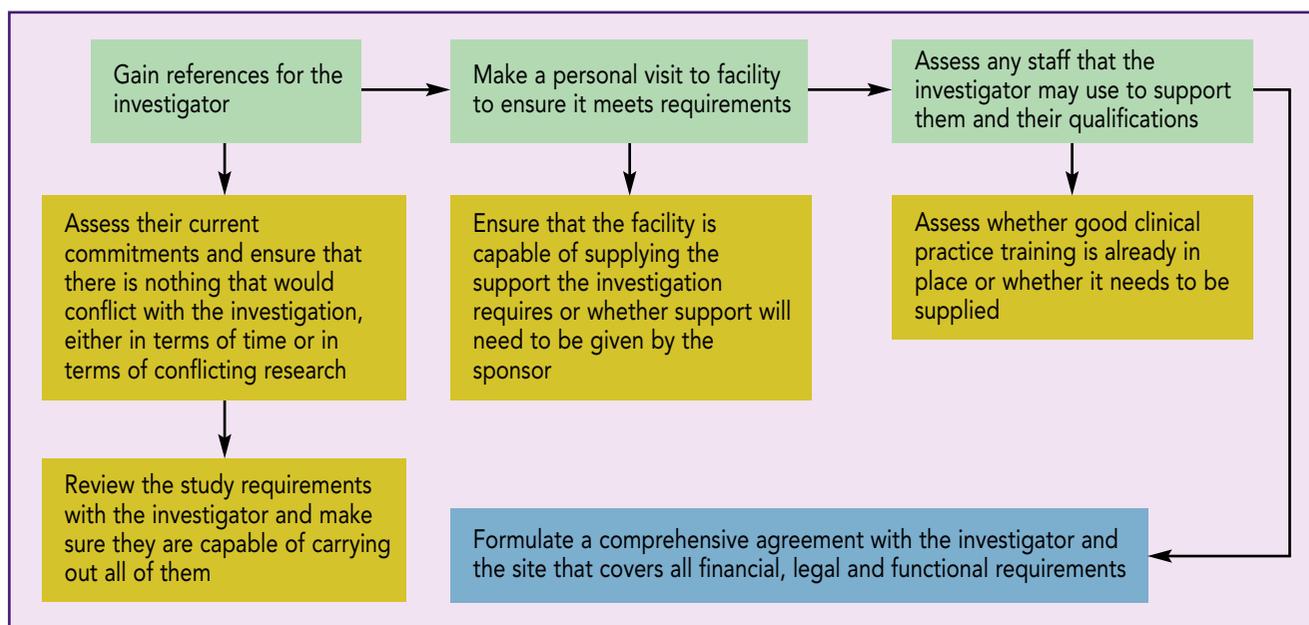


Figure 1: Drug development success rates.





**Figure 2: Feasibility checks on potential investigators and sites.**

months or a 50% decrease in readmission after 1 year? When deciding the goal and endpoints along with the rest of the trial design, information and opinions should be sought from a number of sources, including the manufacturer, the clinicians, and the users. Factors that should be covered include the following.

- The hypothesis behind the trial.
- The aims and objectives of the trial (endpoints).
- Randomised or comparative.
- Inclusion and exclusion criteria of patients – not only what are the physical requirements (concomitant treatments, etc.), but what are the ethical requirements (the use of terminally ill patients, etc.).
- Sample size of subjects to enable statistical significance to be calculated or to be clinically meaningful. Examining successful investigations of similar technologies/products is useful in this respect.
- Minimal data sets required per subject – both in budgetary terms and in terms of maintaining subject compliance. Fewer data points incurs less cost, but there needs to be

enough data points to allow for calculations of statistical significance. Procedures also have to be in place to follow when data points are missed.

- Duration of investigation – what is the minimum period needed for recruitment and follow up.
- Number of study sites – this has to be considered in terms of the rate of patient recruitment and the budget required to monitor different sites.
- Safety and performance criteria – these must be clearly defined and understood by all so that appropriate information can be disseminated as required throughout the trial.
- Data collection and monitoring procedures – again this should be well documented and understood and efficient dissemination of the information organised.

If the above procedures are not followed, the clinical trial can begin to fail and signs that sponsors should look out for are illustrated in **Figure 3**.

In circumstances where a failing study site has been identified, Factory CRO has developed a rescue assessment program, which

can be implemented in as little as 3 weeks, that effectively helps realign the failing study with best practice.

The process starts with an audit of the study that involves the cooperation of the sponsor and all of the investigation sites to examine such items as the screening logs, case report forms, enrolment logs, delegation logs and protocol. From this examination, many factors can be ascertained, including which centres are recruiting best, what factors are causing screening failures and which investigators are taking most personal responsibility for the study and are most proactive.

Site staff will also be contacted to discuss if they have noted any conflicts between the trial processes and the site's standard clinical practice, which could hinder the efficiency of the trial. On the basis of all these findings, the senior management of the clinical trial will be contacted to review the protocol; discuss problem areas, including those of enrolment and regulatory compliance; and develop a recovery plan. Although it may be unpalatable to some sponsors and Chief Investigators, such actions can include the following.

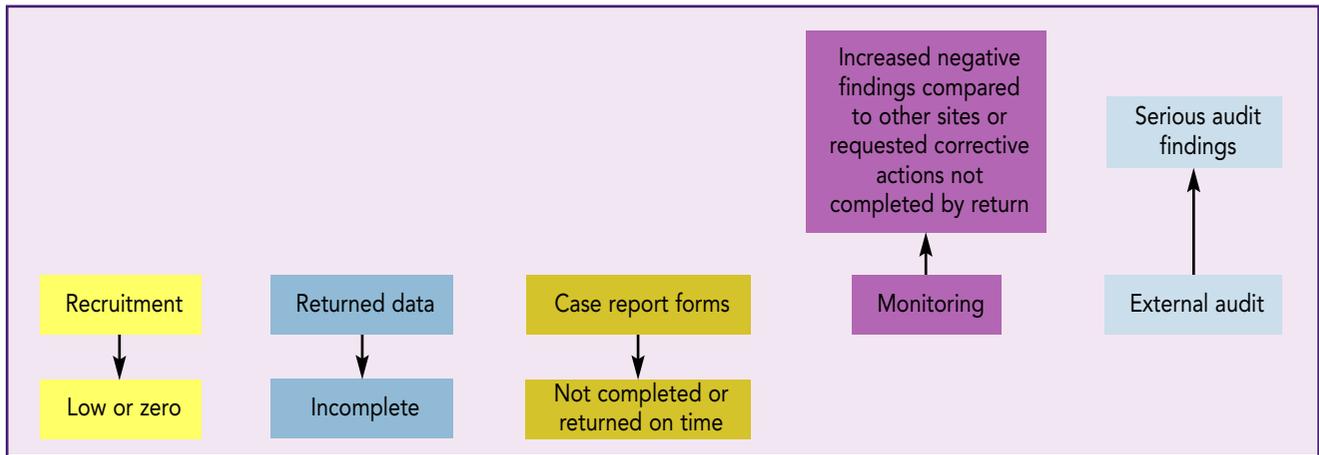


Figure 3: Signs of a failing site.

- Closing down failing sites and creating feasibility forms to assess new sites.
- Removing and adding investigators to the delegation logs at sites.
- Reviewing delegated duties in the study as a whole and on a site-specific basis.
- Changing endpoints.
- Streamlining case report forms.
- Modifying overly strict inclusion and exclusion criteria.

- Conducting a statistical check to see if the sample size can be modified.
- Creating and submitting amendments to the protocol.

Although many companies may be concerned about the financial costs and time implications with modifying protocols and adjusting investigational site dynamics, such early-stage diagnosis and re-alignment can mean the difference

between success and failure of the clinical trial; a factor that is significant to both medical device and pharmaceutical companies.

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- 1 Hess J. Web-Based Patient Recruitment. North Carolina, USA: Cutting Edge information. <http://www.cuttingedgeinfo.com/process/?ref=122>
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# Expert Guidance on Industrial Pharma Microbiology

Edited by Geoff Hanlon and Tim Sandle

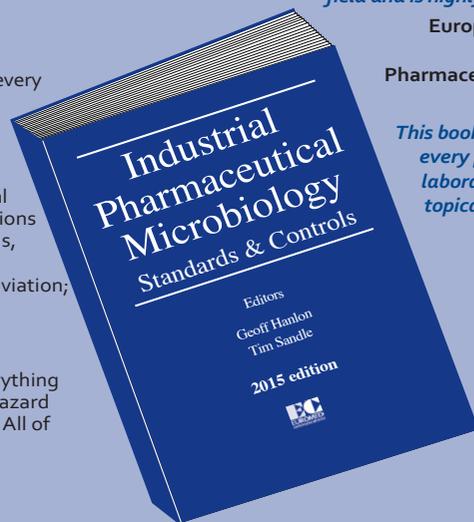
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**The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, international markets and the USA**

## USA

### **Development and Submission of Near Infrared Analytical Procedures**

This Draft Guidance provides recommendations to applicants regarding the development and submission of near infrared analytical procedures used during the manufacture and analysis of pharmaceuticals.

### **Final guidance on reprocessing of reusable medical devices**

The food and drug administration (FDA) has announced new actions to enhance the safety of reusable medical devices and address the possible spread of infectious agents between uses.

### **FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients**

This initiative is intended to reduce the serious risk of infection spread through sharing of multi-dose diabetes pen devices intended for single patient use only.

## Europe

### **Reverse osmosis in European Pharmacopoeia (Ph. Eur.) monograph for water for injections bulk**

This monograph has been revised to include, in addition to distillation, reverse osmosis coupled with suitable techniques for the production of water for injection; a requirement for regular total organic carbon monitoring has been added to emphasise further the specific test controls required in

the production section. As a result, the monograph water, highly purified (1927), will be made redundant and will be deleted from the Ph. Eur.

The European Directorate for the Quality of Medicines and Healthcare (EDQM) organised a free webinar explaining the context of the revision and the steps taken towards revising the water for injection monograph.

### **Identification of medicines: EU task force to implement new international standards**

The European Medicines Agency (EMA) is establishing this task force and has invited interested parties to express their interest in taking part.

### **Prospective pharmacopoeial harmonisation pilot project (US Pharmacopoeia and EDQM/Ph.Eur.)**

Four monographs were elaborated via this project and eleven reference standards established to support the monographs. Subsequently the US Pharmacopoeia and the EDQM decided to officially conclude the pilot project. Both remain fully committed to pharmacopoeial harmonisation and will continue to collaborate on prospectively harmonised monographs in a less formal manner.

### **Specification for sub-visible particles in eye drops and eye lotions**

The Ph. Eur. Commission is currently considering updating this monograph to add a specification for particulate contamination. Accordingly, it invites responses to the following questions.

- Is such a specification necessary?
- If not, why not?
- If so, why, and what should the specification be?

### **EU Good Manufacturing Practice (GMP) Guidelines Concept Paper on the**

### **Revision of Annex 1 of the Guidelines on Good Manufacturing Practice - Manufacture of Sterile Medicinal Products**

This Concept Paper (jointly issued by the Pharmaceutical Inspection Co-operation Scheme (PIC/S)) states that the revised guideline will clarify to what extent Q9 and Q10 should be followed in the design and implementation of facilities, equipment and processes for the manufacture of sterile medicinal products. Other changes that may require new GMP guidance include those for the revision to the Ph. Eur. monograph on methods other than distillation for the production of water for injection.

### **Annex 15 - Qualification and Validation**

This revision, effective 1 October 2015, is considerably longer than the previous version. Retrospective validation is no longer allowed. Newer (than 3 batch validation) approaches or hybrid approaches to validation are discussed. There will be significant impact in the area of cleaning validation where a toxicological approach is required. The revision takes into account changes to other sections of the EudraLex Volume 4, Part I, relationship to Part II, Annex 11, ICH Q8, Q9, Q10 and Q11, Quality Working Party guidance on process validation, and changes in manufacturing technology. The document has also been adopted by PIC/S with the same operational date.

### **Good distribution practice (GDP) of active substances for medicinal products for human use**

The European Commission (EC) has published new guidelines, effective 21 September 2015, on GDP for active substances for medicinal products for human use.

Distribution of active substances comprise activities of procuring, importing, holding, supplying or exporting active substances.



**MHRA****GMP Data Integrity Definitions and Guidance for Industry**

Following initial publication of this guidance in January 2015, the MHRA has responded to questions from stakeholders by providing additional clarifications to the text.

**Certificates of Free Sale to be issued by the MHRA**

The MHRA took over responsibility

for issuing Certificates of Free Sale for medicines from the Department of Health from 1 April 2015.

**International****Canada****Inspections database**

Health Canada has made available access to its inspection databases for both foreign and domestic facilities.

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@euromedcommunication.com](mailto:info@euromedcommunication.com)

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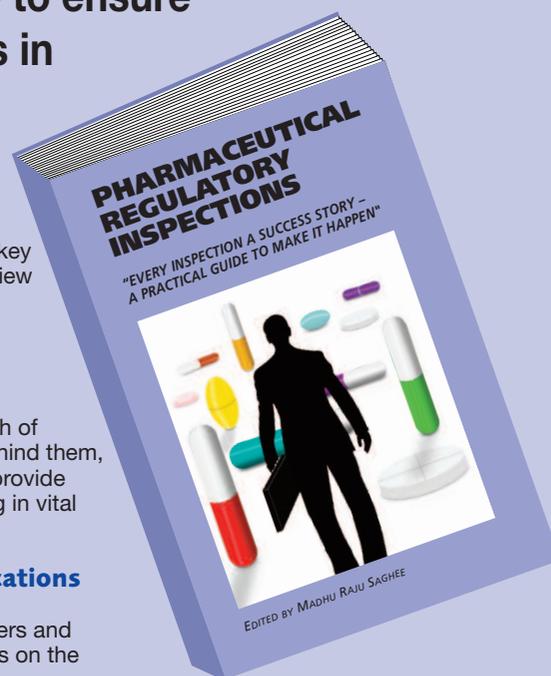
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## bottled brown

### The mother of all battles

The critical economic battle of the first half of the 21st century is nigh. It will hurt. At least, so argues Jeremy Rifkin in *"The Zero Marginal Cost Society the Internet of Things, the Collaborative Commons and the Eclipse of Capitalism"*. What is the connection with industrial pharmacy?

Three industrial revolutions each took (or are taking) 30 years to introduce and 20 to mature. The mid-19th century saw the first industrial revolution. Its power was coal, communication was the telegraph, and transport (logistics) was the railway. The early 20th century saw the second revolution. Power was from oil (e.g. petrol), communication the telephone, transport, vehicles on roads. The third revolution started in the late 20th century. Power is "green" (e.g. solar), communication, the internet, and the need for transport has almost vanished. Sustainable micro generators feed electricity into local co-operative networks; that avoids the high losses in long-distance transmission. Smart machines/robots communicate without humans. Most software is free; friendly, collaborative global "geeks" write. They despise intellectual property protection. "Prosumers" (consumers and producers) print most desired objects from, for example, glass, metal, plastic or proteins. Artefacts range from bulldozers to skin prosthetics to new printers. Many already are. Think *Star Trek* replicator.

### Death of capitalism?

However, capitalism works by producing things more efficiently, so

cheaper, so customers buy more, so profits increase. When marginal costs fall to near zero, capitalism dies. It will fight: that is the battleground.

It may not happen. It is crystal ball territory. Even future orbits of just three inanimate bodies cannot, in general, be accurately predicted. Add humans, cultures, global warming and cyber terrorism and anything *could* happen. But if the internet of things looks likely, brace yourself against three blows.

First, the pharmaceutical industry, as we know it, may vanish — no matter how gargantuan the efficient factories in the developing world. Goodbye mass production of meticulously quality-assured batches of medicines and associated expensive distribution. Hello 3-D printing of medicines, within health professionals' premises or even patients' homes, tailored for individual patients. Mass production continues but locally. The number of dose forms required is smaller because (assuming compatible) medicines are mixed into a single medicament. That increases compliance. Industrial pharmacists merely supply, for example, stable concentrated liquids. Arguably, a signature pharmaceutical material from the first ("smoke-stack") industrial revolution was paracetamol tablets; from the second (oil), plastic packaging. The third (replenishable energy, internet/computers, local fabrication), tailored, in exact dose — not one-size-fits-all — biopharmaceuticals for *that* patient's genetics. Already, the cost of gene-testing has tumbled to almost zero.

Secondly, patent protection,

however strong, may vanish. The reason is that the ideological passion of the internet, that open-source software programmers and 3-D modelling hobbyists inhabit, globally, firmly favours collaboration. The internet is increasingly a "commons" like other long-accepted shared public spaces, such as Swiss mountain pastures or public squares of cities. Clearly, some governance (e.g. pharmaceutical regulation) is necessary.

But discontented citizens will swarm. Tanks might prevail, short-term; long term, probably not. Ghandi said that the Earth provides enough for every (wo)man's need but not every (wo)man's greed.

### Industrial pharmacist as warrior

Finally, pharmaceutical capitalists may enlist you. Brainstorm: how can we stop this? How can our model of investing in research and development, claiming patent rights and recouping costs (plus a bit, including your salary) during patent life, continue? Brown suggests: turn threat into opportunity. Buy the "pipes": expensive web infrastructure and industrial printers. Lease out with your research/development expertise. Re-structure management from vertical to horizontal. *Co-operate*, not compete, with rival companies.

Diversify, preferably into pharmacies, but otherwise doctors'/dentists'/vetinarians' surgeries and/or patients' homes. I already hear howls.

Malcolm E Brown



## General Assembly 18-19 April

During the April General Assembly, Dr Piero Iamartino, AFI, Italy, was re-elected as Vice-President of Technical Affairs and Dr Maurizio Battistini, AFTI, Switzerland, was elected as Vice-President of European Affairs for the next 3 years. The chairman, Jean-Pierre Paccioni, described his vision for the EIPG, and the Bureau reported on the progress of the Road Map. A wide range of "hot topics" were presented by delegations. Annual reports of Member Associations can be found on the EIPG website under "Member States".

## Working Group on New Tasks and Responsibilities of the Qualified Person (QP) resulting from revised Annex 16

The aim of this group was to discuss the impact of revised Annex 16 on the professional duties of the industrial pharmacist, especially when acting as a QP. It was also the scope of this Working Group to identify any necessary actions to be taken by the EIPG to support industrial pharmacists in their role as QPs.

Tracy Lovatt, MHRA Inspectorate, joined the meeting and the main contents of the published revised Annex 16 were presented, focusing in particular on the responsibilities for batch certification and release, recalling difficulties due to the complexity of the supply chain and in case of conflicts within the company. It was observed that among the duties assigned to a QP, as reported in the Annex, 21 of them can be delegated. However, it was agreed that a QP needs to be very confident with an appropriate quality management system.

The auditing performed by third parties was highlighted as a critical issue as a QP has to count on reliable professionals in order to maintain his/her responsibility for this essential duty.

On the discretion in evaluating unexpected deviations from the Marketing Authorisation dossier, it was observed that there is still a large discrepancy in the position of local regulatory authorities, allowing a margin of interpretation on this issue.

After further discussion, the group pointed out that, apart from a few challenges (such as increased knowledge), opportunities can be found in the development and manufacture of biotechnology products and personalised medicines.

Among the actions the EIPG will take to support industrial pharmacists in their QP role, it was agreed to promote continuing professional development (CPD) initiatives, to keep on track with our Special Interest Group (SIG) initiative, to maintain the current prompt circulation of technical information via the website and to consider the introduction of a free forum for an open discussion on professional issues.

## Working Group on Shortages of Medicines

This group, which included community pharmacist Ash Soni, President of the Royal Pharmaceutical Society, and Patricia Munoz, Pharmaceutical Group of the European Union (PGEU), noted that there is an urgent need for improved communications. Products in the European Medicines Agency (EMA) drug shortages catalogue give an "ongoing" description with no reason for the shortage or re-supply date, and most national authority shortage lists do not indicate when supplies will be resumed.

The General Assembly agreed that it was appropriate to re-engage the Commission in discussion on this topic, emphasising that if the Commission truly believes that medicines are not ordinary items of commerce, then in current scenario it has a duty and responsibility to

intervene more effectively, and, amongst other actions, review tender-driven purchasing models and the improvement of standards in giving value to robust supply chains. The Assembly also recommended joining other partners in renewed public statements on shortages, and participating in the PGEU-driven stakeholder roundtable on drug shortages. It was also agreed that all organisations should work towards an integrated shortage information system to provide a pan-European picture and hence mitigate the impact on effects of potential and actual drug shortages.

## Communications Report

Professor Claude Farrugia presented the website improvements including the new Education Section with the PharmaConsult e-learning courses available on a wide range of topics. He discussed the wide choice of social media fora, a line-up which now includes Paper.li, Slideshare and YouTube, as well as the original fora Twitter, LinkedIn and Facebook. Amongst various items of interest, the sites cover regulatory round ups of Commission/EMA published guidelines, directives and regulations, their enforcement dates and the final dates for comment on drafts.

## EIPG SIGs

Once the revised Annex 16 is published, the Production SIG proposes to update the EIPG Code of Practice for Qualified Persons and incorporate the EIPG Guidance on CPD. The PHAR-IN courses on the manufacture of biopharmaceuticals, prepared in response to competencies requested by staff in the pharmaceutical industry, will be advertised on our website.

The Regulatory Affairs SIG aims to update the EIPG Guide to Good Regulatory Practice and the Guide to CPD for Regulatory Affairs. The

*Continued on page 28*

potential for webinars on hot topics in regulatory affairs was discussed.

### **EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations**

In his presentation on the European Federation of Pharmaceutical Industries and Associations (EFPIA) Disclosure Code, Andrew Powrie-Smith, Director of Communications, noted that nine EFPIA members will disclose information via a central website and the other 24 members will use their company websites.

Payments from industry to the medical profession must be disclosed to the public by the end of June 2016 for the first reporting period which is the calendar year 2015. The EFPIA guide explains what is to be disclosed whilst national bodies are responsible for implementation. Most companies

have sensible in-house minimum limits for disclosed monies which the EFPIA considers should be capped at about 75 Euros. Disclosure varies from one country to another and if there is no consent from the medical profession there can be no disclosure and no payments made. EFPIA company heads have all contributed to the production of the Code so that there should be consensus. Generic and medical device companies are lagging behind on disclosure but the requirements will be implemented by them.

### **European Commission**

The Commission's proposed update to Annex A of the Professional Qualifications Directive was referred to by the PGEU, as was the European Medicines Verification System resulting from the Falsified Medicines Directive. The Commission-funded survey on CPD

for health professionals providing a comparative account of CPD models in the European Free Trade Association and European Economic Area countries can be found on the following website  
[http://ec.europa.eu/health/workforce/docs/ev\\_20141124\\_co01\\_en.pdf](http://ec.europa.eu/health/workforce/docs/ev_20141124_co01_en.pdf)

### **Symposium**

A scientific symposium on "Technology Advances Impacting the Pharmaceutical Industry" was held at the University of Strathclyde on the day before the General Assembly. It was chaired by Professor Jayne Lawrence, Chief Scientist to the Royal Pharmaceutical Society, and was attended by about 75 participants, including EIPG delegates. Slides from the presentations are available on the EIPG website.

Jane Nicholson, Executive Director EIPG, [jane@nicholj.plus.com](mailto:jane@nicholj.plus.com)

# PharmacoVigilance Review

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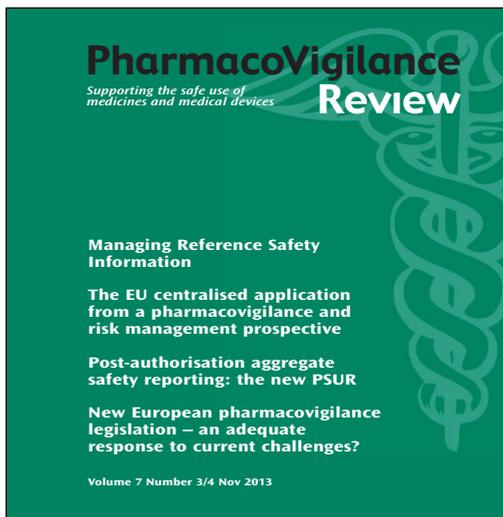
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[www.gmp-conference.org](http://www.gmp-conference.org)

10–12 June 2015 – Boston, MA, USA

### 14th Annual World Pharma Congress

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15–17 June 2015 – Geneva, Switzerland

### EUFEPS Annual Meeting 2015 – Systems Approaches for Better Medicines and Health

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10–12 August 2015 – Philadelphia, PA, USA

### Global Pharma Summit

<http://american.pharmaceuticalconferences.com/>

17–19 August 2015 – Washington, DC, USA

### 9th Annual Transparency Reporting Congress

[www.cbinet.com](http://www.cbinet.com)

## SEPTEMBER 2015

1–3 September 2015 – Nottingham, UK

### APS PharmaSci 2015

[www.ukpharmsci.org](http://www.ukpharmsci.org)

7–9 September 2015 – The Hague, The Netherlands

### 1st Annual GMP by the Sea – Europe

[www.pharmaconference.com](http://www.pharmaconference.com)

7–9 September 2015 – Nottingham, UK

### APS 5th International PharmSci Conference 2015

[www.apsgb.co.uk](http://www.apsgb.co.uk)

8–9 September 2015 – Berlin, Germany

### World Drug Safety Congress Europe 2015

[www.healthnetworkcommunications.com](http://www.healthnetworkcommunications.com)

13–14 September 2015 – Birmingham, UK

### Royal Pharmaceutical Society Annual Conference 2015

[www.rpharms.com](http://www.rpharms.com)

15–16 June 2015 – Munich, Germany

### Pharmaceutical Freeze Drying Technology

<https://europe.pda.org>

28–30 September 2015 – Las Vegas, NV, USA

### 2015 Pharma EXPO

[www.ispe.org](http://www.ispe.org)

29 September–3 October 2015 – Düsseldorf, Germany

### 75th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2015

[www.fip.org](http://www.fip.org)

## OCTOBER 2015

5 October 2015 – Loughborough, UK

### APS Pharmaceutical Photostability 2015

[www.apsgb.co.uk](http://www.apsgb.co.uk)

6–7 October 2015 – Amsterdam, The Netherlands

### Pharmaceutical Cold & Supply Chain Logistics

<https://europe.pda.org>

7–8 October 2015 – London, UK

### Pharma Compliance Europe 2015

[www.terrapinn.com](http://www.terrapinn.com)

8 October 2015 – London, UK

### What's New in the Approval and Conduct of Clinical Trials in Europe?

[www.jpag.org](http://www.jpag.org)

13–15 October 2015 – Madrid, Spain

### CPhI Worldwide

[www.cphi.com](http://www.cphi.com)

14–15 October 2015 – Dublin, Ireland

### BioProduction 2015

[www.informa-ls.com](http://www.informa-ls.com)

21–23 October 2015 – Washington, DC, USA

### 16th Annual Pharmaceutical Regulatory and Compliance Congress

<http://pharmacongress.com>

26–28 October 2015 – Hyderabad, India

### 4th International Summit on GMP, GCP & Quality Control

<http://gmp-gcp-quality-control.pharmaceuticalconferences.com>

## NOVEMBER 2015

4–6 November 2015 – Amsterdam, The Netherlands

### 18th APIC/CEFIC European Conference on Active Pharmaceutical Ingredients

[www.gmp-compliance.org](http://www.gmp-compliance.org)

8–11 November 2015 – Philadelphia, PA, USA

### 2015 ISPE Annual Meeting

[www.ispe.org](http://www.ispe.org)

9–10 November 2015 – Basel, Switzerland

### World Biosimilar Conference

[www.terrapinn.com](http://www.terrapinn.com)

