

europaean INDUSTRIAL PHARMACY

features

4 **ACHIEVING BIOSIMILAR PRODUCT APPROVAL - KEY SUCCESS FACTORS FOR DEVELOPMENT**

Biosimilars have attracted increasing attention over the past 10 years. This article describes key success factors for biosimilar development, such as understanding of regulatory requirements and the science of biological products.

by Hideaki Nomura and Gary Trewartha

10 **GAZING INTO THE CRYSTAL BALL: WHAT WILL THE EU-FMD SAFETY FEATURES DELEGATED ACT BRING?**

In 2018, far reaching changes will come into force across Europe that were introduced by the EU Falsified Medicines Directive (2011/62/EU). This article examines the details and impact of the provisions of the 'Safety Features' Delegated Act and how these will affect the pharma supply chain across Europe and beyond.

by Christoph Krähenbühl

14 **RECENT R&D BREAKTHROUGHS CONTINUE TO REVOLUTIONISE THE ALREADY DYNAMIC HEPATITIS C TREATMENT LANDSCAPE**

This article outlines the past and present hepatitis C virus treatment landscape, placing a particular emphasis on the most recent developments and industry trends.

by Christopher Pace

18 **QUALITY METRICS, QUALITY CULTURE, QUALITY MATTERS!**

This article examines measures to ensure quality throughout a medicine's lifecycle from product design to manufacturing and distribution, emphasising the pivotal roles of patient centricity and quality culture.

by Tom Sam and Henny Koch

regulars

3 **EDITORIAL COMMENT**

22 **REGULATORY REVIEW**

24 **LETTER TO EDITOR**

25 **BOTTLED BROWN**

26 **NEWS FROM THE EIPG**

27 **EVENTS**

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Cover photo: The Unique Identifier carried in the form of a 2D DataMatrix (see Gazing into the Crystal Ball: What Will the EU-FMD Safety Features Delegated Act Bring? on page 10)



Will they? Won't they?

Sir William Osler, Canadian physician and a founding professor of Johns Hopkins Hospital, stated "Medicine is a science of uncertainty and an art of probability". The same can easily be said of the pharmaceutical industry, as those of our colleagues involved in the research and development of new pharmacological molecules and new medicinal products will attest.



Lately, however, this element of uncertainty has been compounded beyond all expectations. Only as recently as my last message to you, talk was rife of an exceptional year of merger and acquisition activity in the sector. Fast forward a few months, and new financial rules across the Atlantic have disrupted the largest merger to emerge from the first half of the year, one that bore all the signs of a favourable union between two complimentary companies, whilst another merger that many were expecting to descend into an acerbic process of litigation has come to naught, upstaged by an amalgamation that will create one of the ten largest pharmaceutical companies worldwide. Thus, the attention now shifts to two other companies free to return to the bargaining table, as all ask the question:

Will they? Won't they?

Against this backdrop of merger activity, industrial pharmacists unfortunately continue to experience a different kind of uncertainty. The ink was hardly dry on media reports of the largest pharmaceutical merger of the year thus far, when – as always – statements of the need for cuts were reported, and in the eyes of friends, peers, colleagues who have given years of service to these players can be seen the concern, the doubt, the unuttered question:

Will they? Won't they?

This issue of *European Industrial Pharmacy* includes two topics that will define a new and emerging

pharmaceutical industry. The first of these is the issue of biosimilars. The years when these products will form the backbone of global healthcare loom just over the horizon, and whilst regulatory authorities have begun to issue guidelines for the industry, experience in biosimilar development and especially in the understanding of the mindset of different authorities when evaluating these products is still lacking. The second topic is that of the

Delegated Act on the detailed rules for a Unique Identifier for medicinal products, the publication of which, by all accounts, is expected soon. While the broader strokes of this legislation that will have far-reaching effects throughout the continent are by now fairly clear to many, the minutiae of the process remain largely unknown, leaving actors in the pharmaceutical supply chain in a state of uncertainty, asking largely unanswered questions and left to wonder:

Will they? Won't they?

Against this backdrop of uncertainty, however, one thing can be safely taken for granted – pharma is changing with time and the industrial pharmacist of the future will need new skill sets to continue to form the backbone of this industry – *tempora mutantur, nos et mutamur in illis*. Therefore, it is imperative that we look to the future, to be prepared for the challenges with which our profession will be faced. Meanwhile, however, I look to a more immediate future and extend to you all from EIPG the very best wishes for a serene festive season and a prosperous new year.

A handwritten signature in black ink, appearing to read 'Claude Farrugia'.

Professor Claude Farrugia
Vice-President Communications, EIPG

ACHIEVING BIOSIMILAR PRODUCT APPROVAL – KEY SUCCESS FACTORS FOR DEVELOPMENT

by Hideaki Nomura and Gary Trewartha

Biosimilars have attracted increasing attention over the past 10 years. As a growing number of biological medicinal products which have reached blockbuster levels in terms of sales will soon run out of patent protection, many pharmaceutical companies have initiated biosimilar development programs. Although many biological medicinal products provide remarkable efficacy in some diseases, these products concurrently cause a severe financial burden for payers because of their extremely high prices. This financial burden is coming under ever-increasing scrutiny and pressure. Therefore, biosimilars have been much awaited as a means of introducing affordable care to patients. On the other hand, biosimilar development cannot follow the established generic regulatory pathway, because biological medicinal products have extremely complicated structure and character, and to produce the exact same molecule as an original reference product is impossible.

Hideaki Nomura is the President and CEO of Fujifilm Kyowa Kirin Biologics (FKB), Tokyo, Japan. FKB was established in 2012 and simultaneously he took his current position. FKB is a joint venture company under FUJIFILM and Kyowa Hakko Kirin concentrating on the biosimilar business, and is developing a number of products for global markets.

Gary Trewartha is Regulatory Affairs Manager for Fujifilm Kyowa Kirin Biologics (FKB), EU Branch, based in the UK.

In many countries, specific guidelines for biosimilars have been issued by authorities to regulate the development and approval of these products. The companies involved in biosimilar development need to fully understand regulatory requirements, master the science of biological medicinal products, have the capability to manufacture these products in accordance with current good manufacturing practice (cGMP), and crucially to have sufficient budget to complete the development program.

Biosimilars guideline

The first biosimilar specific guideline

was issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in 2005¹. Subsequently, the CHMP released two further guidelines for biosimilars covering specific aspects^{2,3}. The constitution of the guidelines is described in **Table 1**. A distinguishing feature of the EMA guideline structure from that established by other countries is to have individual product-specific guidelines, such as those associated with erythropoietins, somatropin and monoclonal antibodies^{4–12}. Following a number of years of implementation, the CHMP is in the

process of revising some of the guidelines based on the experience gained over these years and current thinking on biosimilar development^{13–17}. Japanese biosimilar guidelines were issued in 2009¹⁸, whereas in the US the much-anticipated package of draft biosimilar guidance was initially released from the Food and Drug Administration (FDA) in 2012^{19–23}. Additionally, there are issued guidelines for biosimilars in several other countries, which, to varying degrees, follow the standards set by the EMA or the World Health Organization (WHO) guidelines²⁴ (WHO guidelines issued in 2009).

Though there are minor differences in the guidelines established within the ICH regions, the broad outline is the same, as shown in **Figure 1**. Broadly speaking, available guidelines recommend a risk-based stepwise approach to biosimilar development following the path of (1) a detailed physicochemical and analytical comparability between the biosimilar and reference product; (2) *in vitro* functional testing; (3) *in vivo* toxicity; and (4) clinical studies (pharmacokinetic (PK), pharmacodynamic (PD), efficacy, safety including immunogenicity).

The data which was collected for the original reference product should, wherever possible, be referred to during the development of its biosimilar, but this data are usually confidential and cannot be accessed. For example, the company aiming to develop the biosimilar cannot obtain the host cell and the information to manufacture the original reference biologic product. Thus, the biosimilar developer has to establish its own manufacturing process. In the next step of development, the characterisation of quality attributes should be studied and, moreover, the similarity in quality must be investigated. In these steps, far more data is needed when developing a biosimilar compared with the development procedure of the original reference product. On the other hand, some studies can be omitted in the non-clinical and clinical phases of biosimilar



Table 1: Construction of EU biosimilars guidelines

User guide		Guideline on Similar Biological Medicinal Products CHMP/437/04	Revision 1 adopted guideline CHMP/437/04 Rev. 1
General	Quality	Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues EMA/CHMP/BWP/247713/2012	Revision 1 adopted guideline
	Non-clinical and clinical	Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues EMA/CHMP/BWP/42832/2005	Revision 1 draft guideline EMA/CHMP/BWP/42832/2005 Rev. 1
Specific	Non-clinical and clinical	Insulin EMA/CHMP/BM WP/32775/2005	Revision 2 Draft guideline
		Somatropin EMA/CHMP/BM WP/94528/2005	
		Erythropoietin EMA/CHMP/BWP/3 01636/2008	
		G-CSF EMA/CHMP/BM WP/31329/2005	
		INF- α EMA/CHMP/BM WP/102046/2006	
		LMWH EMA/CHMP/BM WP/118264/2007	Revision 1 draft guideline
		Monoclonal antibody EMA/CHMP/BWP/40 3543/2010	
		INF- β EMA/CHMP/BMW P/652000/2010	
		FSH EMA/CHMP/BMW P/671292/2010	
Relevant		Comparability of Biotechnology-Derived Medicinal Products After a Change in the Manufacturing Process - Quality issues CPMP/ICH/5721/03 / - Non-Clinical and Clinical Issues EMA/CHMP/BWP/101695/2006	
		Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins EMA/CHMP/BWP/14327/2006	
		Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use EMA/CHMP/BWP/86289/2010	

development. Typically, in the non-clinical phase, safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity data are not required. The requirements for *in vivo* toxicology studies vary across the different regions, especially with regard to the requirement to conduct a repeat dose toxicology study in non-human primates. With a suitable risk-based

assessment of other non-clinical data, this study is generally omitted for biosimilar development in the EU, whereas a repeat dose toxicology study in non-human primates is still largely regarded as a prerequisite prior to a first-in-human study in the US.

In the clinical phase of biosimilar development, PK and PD study(ies) to show the similarity between

original reference product and its biosimilar is conducted as Phase 1. Generally, this is to show the bio-equivalency between the two products. In many cases, it is difficult to perform a PD study because there is no suitably robust and sensitive PD (surrogate marker) of efficacy. By definition, biosimilars will be administered using the same dose and dosing regimen to treat the same indications as the reference product, thus Phase 2 clinical studies are not required. Within Phase 3, safety and efficacy data should be collected to compare the biosimilar with the original reference product. Head-to-head immunogenicity studies between the reference and biosimilar product should be conducted throughout clinical development to ensure the biosimilar does not display any signals of increased immunogenicity.

A key current issue within biosimilar development is the question of extrapolation. In situations where the original

Figure 1: Required Data for Biosimilar Development

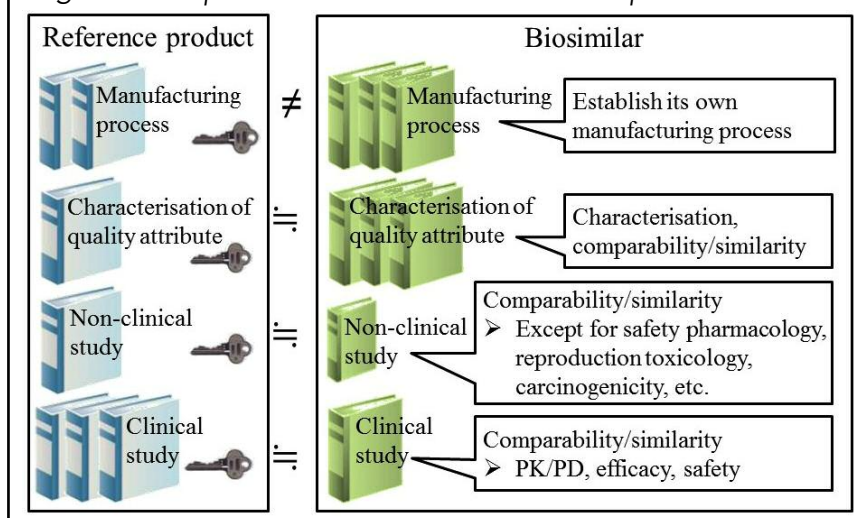


Table 2: Biosimilars in the EU

	Name (active substance)	Marketing authorisation holder	Status
1	Omnitrope (somatropin)	Sandoz	Authorised
2	Valtropin (somatropin)	Biopartners	Authorised→Withdrawn
3	Alpheon (interferon alfa)	Biopartners	Negative
4	Binocrit (epoetin alfa)	Sandoz	Authorised
5	Epoetin alfa Hexal (epoetin alfa)	Hexal	Authorised
6	Abseamed (epoetin alfa)	Medice	Authorised
7	Silapo (epoetin zeta)	Stada	Authorised
8	Retacrit (epoetin zeta)	Hospira	Authorised
9	Insulin Human Rapid Marvel (human insulin)	Marvel Life Sciences	Withdrawn
10	Insulin Human Long Marvel (human insulin)	Marvel Life Sciences	Withdrawn
11	Insulin Human 30/70 Mix Marvel (human insulin)	Marvel Life Sciences	Withdrawn
12	Filgrastim Ratiopharm (filgrastim)	Ratiopharm	Authorised→Withdrawn
13	Ratiograstim (filgrastim)	Ratiopharm	Authorised
14	Biograstim (filgrastim)	CT Arzneimittel → AbZ-Pharma	Authorised
15	Tevagrastim (filgrastim)	Teva	Authorised
16	Filgrastim Hexal (filgrastim)	Hexal	Authorised
17	Zarzio (filgrastim)	Sandoz	Authorised
18	Biferonex (interferon beta-1a)	Biopartners	Withdrawn
19	Nivestim (filgrastim)	Hospira	Authorised
20	Epostim (epoetin alfa)	Reliance GeneMedix	Withdrawn
21	Solumarv (human insulin)	Marvel Life Sciences	Withdrawn
22	Isomarv medium (human insulin)	Marvel Life Sciences	Withdrawn
23	Combimarv (human insulin)	Marvel Life Sciences	Withdrawn
24	Remsima (infliximab)	Celltrion	Authorised
25	Inflectra (infliximab)	Hospira	Authorised
26	Ovaleap (follitropin alfa)	Teva	Authorised
27	Grastofil (filgrastim)	Apotex	Authorised
28	Bemfola (follitropin alfa)	Finoc Biotech AG	Authorised
29	Abasria (insulin glargine)	Eli Lilly	Authorised
30	Accofil (filgrastim)	Accord Healthcare	Authorised

reference product has multiple approved indications with the same mode of action, a clinical study to show the similarity of safety and efficacy in each indication may not be required. The extrapolation of data obtained from one indication to allow approval in other indications is potentially accepted by authorities if the justification to support the extrapolation is fully demonstrated. However, where different modes of action exist in approved indications of the original reference product, additional clinical studies will usually have to be performed to pursue other indication approvals for the biosimilar. The level of acceptance by regulatory authorities of extrapolation justifications made in the licensing submissions for biosimilars has been shown to vary depending on the country/region involved, with assessment conducted on a case-by-case basis.

Developed biosimilars

Biosimilars are most firmly established in EU countries, with the EMA leading the way in establishing a formal regulatory pathway for the approval of biosimilars. **Table 2** provides a list of biosimilars approved in the EU, with central approval by the EMA rather than national approvals being a mandated requirement for biosimilars. Six types of biosimilars have been approved: somatropin, erythropoietin (epoetin alfa and zeta), granulocyte-colony stimulating factor (G-CSF; filgrastim), infliximab, insulin glargine, and follicle stimulating hormone (FSH; follitropin alfa). The first biosimilar, Omnitrope® (somatropin), was approved by the EU authorities in 2006 and more recently Remsima®/Inflectra® (infliximab) was approved in 2013 as the first biosimilar of a monoclonal antibody product (Remicade®). However, not all products could

obtain regulatory approval; with applications for human insulin, interferon alfa and interferon beta-1a being withdrawn because the available data did not sufficiently demonstrate similarity to the original reference product for the authority.

In Japan, somatropin, erythropoietin, G-CSF (filgrastim), and infliximab have already been launched as biosimilars, having met the requirements of the Japanese biosimilar regulatory pathway. In almost all cases, foreign clinical study data, which had been collected primarily for EU submission, was submitted to and reviewed by the Japanese regulatory authority, the Pharmaceutical and Medical Devices Agency. In every one of these cases, additional data was requested and a clinical study with Japanese subjects was required and the data from this study submitted to support the application.

In the US, there is currently no biosimilar product approved using the defined regulatory pathway (Section 351(k) of the Public Health Service Act). Although non-innovator biologic product versions of somatropin and G-CSF (filgrastim) have already been approved, somatropin was reviewed under an abbreviated new drug application pathway and G-CSF (filgrastim) was reviewed as a novel product under the 351(a) or biologics license application pathway. In 2014, infliximab and another G-CSF (filgrastim) were submitted under the specific biosimilar regulatory pathway (351(k)), and are thought to be the first products to do so.

Key success factors of biosimilars development

Firstly, knowledge and experience of biological sciences is necessary to develop biosimilars. A typical manufacturing procedure for biological medicinal products is described in **Figure 2** and discussed in more detail below. Biosimilar development starts from host cell clone selection. Screening for an adequate clone is very important because it significantly impacts the final character of the product. There is still an opportunity to adjust the character of the product in the

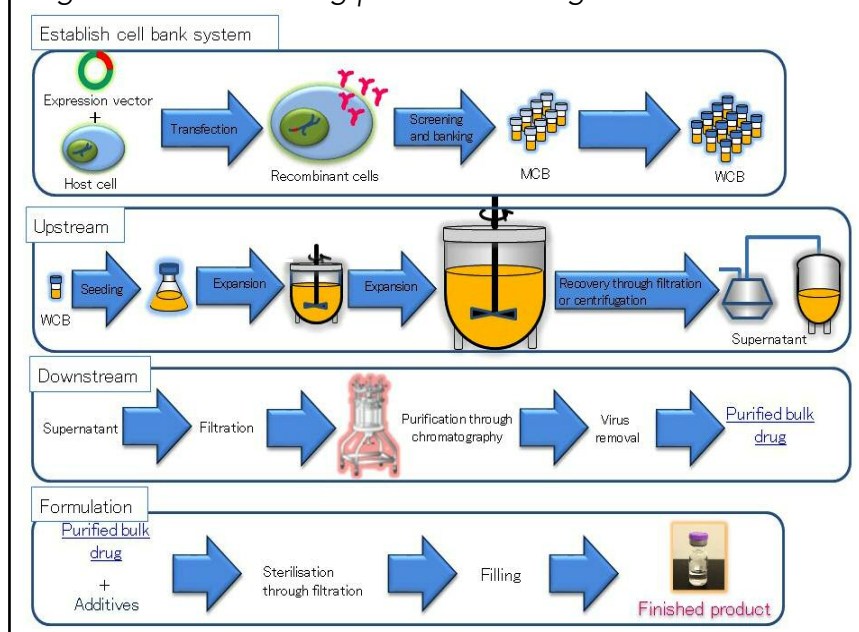
subsequent processes, but the range of possible adjustment is very narrow. Therefore, it is necessary to select a clone that produces a product as similar as possible to the original reference. Equally, consideration of the titer of the clone to produce the biosimilar product is also important, because it will influence the eventual manufacturing cost and market price of the biosimilar, which has implications for one of the most important aims of developing biosimilars that is to provide affordable product to benefit patients. In this early phase of biosimilar development, it is also important to establish an effective screening system to select a clone effectively. This requires the development of suitable and accurate analytical methods to investigate the clone characteristics. In the upstream processes, the selection of culture media and its additives will also influence the character and titer of the biosimilar product, and adequate culture conditions should be adopted to introduce similar characteristics to the original reference. In the downstream processes, the choice of resin and the combination and ordering of column purification also affect the character of the product.

In this step, consideration of the purification strategy to obtain the biosimilar product is important, where levels of variant contents should be reduced. However, this need is balanced by the fact that adoption of complicated purification processes would lead to lower purification yield and cause higher cost of the product. Prior to establishing the manufacturing processes of a finished biosimilar product, formulation studies need to be performed. Initially, a decision on whether to adopt the same formulation as the original reference product should be made. If the formulation of the original reference product is not to be used, another suitable formulation with the required stability and safety attributes must be developed. Additionally, the selection of container and closure system is also of high importance. In some cases, the original reference product is presented as a self-injection dosage form, therefore, the development of a pre-filled syringe and/or other devices, such as a pen or auto-injector, may be necessary.

Secondly, full understanding of the regulatory requirements for biosimilars is vital. A company wishing to develop biosimilars globally should understand not only the specific guidelines in every country or territory, but also the authorities' way of thinking. The communication with authorities, especially in the form of face-to-face advisory meetings, is very useful to understand this. To have a fruitful meeting, the data should be collected to the fullest extent possible and a plan of the total development package should be prepared and presented. Inevitably, in an area of evolving regulatory demands, a company planning to develop biosimilars globally will sometimes receive different opinions from one authority to another, but it should maintain communication with perseverance and attempt to introduce an acceptable plan for all authorities.

Finally, it is necessary for biosimilar developers to establish a

Figure 2: Manufacturing process of biologics



suitable manufacturing facility, especially for bulk drug. The costs associated with commercial scale biomanufacturing are significant. It may require from \$150 million to \$250 million to develop a biosimilar globally (compared to an estimated \$2–3 million for small molecule generics), with the final cost depending on the specific target product. Also, the variation in the requirements to demonstrate clinical efficacy (and similarity) between different products/indications affects the number of patients required in the Phase 3 study and the price of reference product impacts these costs directly. Moreover, since antibody products generally require relatively high doses to produce clinical efficacy, large quantities of the biosimilar product needs to be manufactured for the development studies. To compound this issue, regulatory authorities require the biosimilar developer to show consistency in the batch to batch manufacturing, so many batches must be manufactured. As a result, the facility to manufacture the product is very important for biosimilar development. Within the typical biosimilar scenario, there is less opportunity to scale up the manufacturing capacity, due to limited time before starting a pivotal Phase 3 clinical trial, therefore, a substantial batch size is usually used for manufacture from the starting point of biosimilar development. If the company has no suitable facility, it needs to build a new one or request support from a contract manufacturing organisation to supply the product. Both ways are costly.

Conclusions

When considering biosimilars development, you should confirm whether enough budget is available, you have sufficient technology and know-how to develop biological medicinal products, and you can establish or identify a suitable facility for manufacturing. Furthermore, you should be ready to meet the guidelines and regulatory authority requirements. Biosimilars

development is different from innovative biologics development and during the course of product approval regulatory authorities will make additional requests which have never been required in the case of innovative biological product development.

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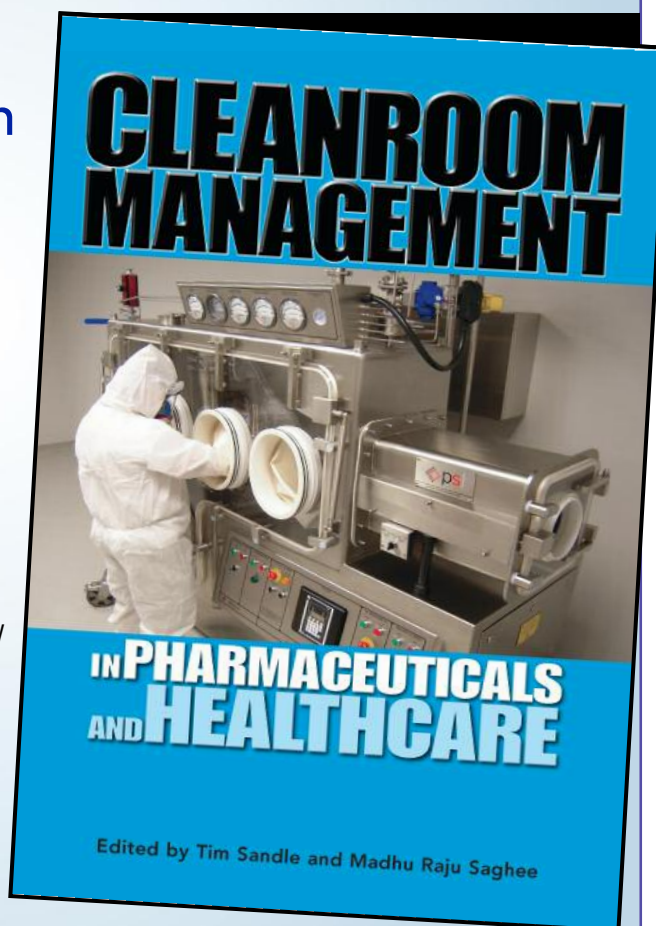
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GAZING INTO THE CRYSTAL BALL: WHAT WILL THE EU-FMD SAFETY FEATURES DELEGATED ACT BRING?

by Christoph Krähenbühl

This paper investigates the technical aspects of the anticipated 'Safety Features' Delegated Act and gives a personal view on how key stakeholders, in particular pharmaceutical manufacturers supplying products to the European market, will be affected.

Christoph Krähenbühl is a respected serialisation expert and thought leader in coding and serialisation for the pharmaceutical industry. Along with partner Ian Haynes, he runs 3C Integrity (www.3cintegrity.com), a specialist consulting firm which also offers comprehensive 2-day training programmes to fully prepare pharma companies of all sizes for the implementation of their serialisation/traceability readiness programme.

"Prediction is very difficult, especially about the future"

As the Danish physicist Niels Bohr said, "prediction is very difficult, especially about the future". It might, therefore, seem unwise to discuss the technical details of the European Falsified Medicines Directive (FMD) 'Safety Features' Delegated Act before this act has been published and when, in fact, even the date of publication is not certain.

The reasonable approach would seem to be 'wait-and-see' rather than second-guessing what prescriptions the Delegated Act may contain and how to prepare for these. Indeed, it may seem foolish to start a readiness implementation programme before the legislation has been published. It would rather seem sensible to delay any investment decisions until the details of the legislative requirements are fully known and understood. Particularly so, since reports from early adopters all suggest that serialisation and traceability implementation projects are complex, costly and present a

major challenge to any pharma company. Even worse, companies that have completed their projects and moved into business-as-usual mode testify just how significantly implementing serialisation and aggregation has impacted their lines, reporting initial reduction in manufacturing output and efficiencies in excess of 10%, sometimes up to 20%, and lengthy recovery times to return to a level that is, at best, a few percentage points below current capabilities.

So why would any senior decision maker volunteer to expose their organisation to the risks and costs that a serialisation readiness programme brings unless the requirements are clearly defined and tied to a firm legal compliance deadline?

"Worried about the cost of compliance? - Try non-compliance..."

The answer is that to wait and see is an even riskier and most likely even costlier option: the learning from early adopters is that reaching the point where serialisation is a

business-as-usual capability can take anything in the order of 2 to 3 years. Some companies have proudly talked about implementation programmes completed in less than 2 years, but, in my practical experience, I have yet to see a pharma company that has successfully implemented all parts of their serialisation readiness program in less than 18 months, and then only in auspicious circumstances, with vigorous senior stakeholder support and a level of investment that few companies can afford.

The stark fact is that the 'wait-and-see' approach does not avoid risks. On the contrary, any costs and risks associated with implementing a serialisation readiness programme pale into insignificance when compared to the alternative: being unable to supply the European market once the EU-FMD compliance deadline comes into force and losing a – for a typical pharma manufacturer – huge chunk of sales.

"Uncertainty? - What uncertainty?"

But what about the argument that there is still too much uncertainty regarding timing, scope of affected markets and products as well as the technical details of the EU-FMD requirements to commit at this stage? A closer look shows quickly that this argument, though often quoted, can be dispelled without the reach for a Crystal Ball. First of all, on the timing of the Delegated Act publication: DG SANCO, the responsible Commission department, updated their plan on 20 November stating the intention to adopt the Delegated Act by Q2 2015; publication in the *Official Journal of the European Union* would then follow in the second half of 2015, due to Parliament, Council and World Trade Organization scrutiny rights. Given that the Directive sets out a clear timetable of 3 years from the Delegated Act publication date, it is a safe planning assumption that the 'Safety Features' provisions of the Delegated Act will come into force in the second half of 2018.

What about the scope, in



particular, which markets are in the scope of the FMD? After all, the law differentiates two sets of markets, those where compliance is required 3 years after the publication of the Delegated Act and the Member States where 'equivalent features' are in use and that are, therefore, given an additional 3 years for compliance? It is true that the Directive makes special provisions for markets where a comparable authentication system has been in place since 1 July 2011, but a quick look at the main 'Safety Features' provisions of the Directive shows that only a very small number of Member States would qualify for the extended deadline: in practical terms, 2018 will be the Europe-wide compliance deadline with the possible exception of Member States, such as Italy and Belgium, that might argue that the Bollini or Vignettes currently used for other purposes could qualify as 'Unique Identifiers' as defined by the FMD.

Another area of uncertainty raised regards the question, which medicines are in the scope of the Directive. The law specifies that its provisions would apply, by default, to all prescription-only medicines

while over-the-counter drugs would be excluded, but allows for exceptions subject to risk-based assessment that would allow for some prescription-only medicines to be white-listed and, conversely, some over-the-counter products to be black-listed. Before exploring the provisions of the Delegated Act in more detail, it is worth setting out what the implementation of the EU-FMD will mean in practice.

Europe-wide medicines verification process

For the European patient, the most far-reaching change to come into force in 2018 will be that their prescription medicines will be checked out at the point of dispense against a complex Europe-wide medicines verification infrastructure of systems. Not that they, as patients, will be aware of this; there are really only two small changes to their packs they may notice. One is that the pack of medicines they are given will be tamper-evidenced – a change that is unlikely to catch their attention as

it will bring the level of physical pack security up to the standard expected of everything else they purchase, from packs

of sweets to pots of yoghurt. The second change, equally unremarkable, is that the pack of medicine will carry a 2D DataMatrix code – different to, but not unlike, the QR codes that we are getting increasingly familiar with.

However, these two features are the hardly visible tip of an enormous iceberg, the results of a multi-year and multi-billion Euro effort by industry and all supply chain stakeholders of putting in place technical measures, systems and processes aimed at ensuring the supply of genuine medicinal products to patients in all 28 Member States.

The unique pack identification code carried in the 2D DataMatrix lies at the centre of these efforts; as the name says, this Unique Identifier will be globally unique and contain the product code (and where necessary national healthcare reimbursement number), the batch/lot number, the expiry date and a highly randomised serial number. It will be used to scan every single pack at the point of dispense to carry out a series of automatic checks – within a fraction of a second – against a complex set of database repositories deployed across Europe to feed back to dispensing pharmacists information

about the status of the product. Pharmacists will see instantaneously whether the pack number has been dispensed before and could, therefore, be a counterfeit product; they can ensure it's still within its expiration date, and check whether there is a recall or other notice against the batch.

Implementing this unique pack coding system presents a huge step forward in terms of patient safety. However, it will also require a tremendous amount of work – not simply in terms of the development and





deployment of the complex Europe-wide systems infrastructure, but also the implementation projects needed to achieve readiness for compliance by every pharmaceutical manufacturer supplying the 28 EU Member Countries, be they original brand owners, generics manufacturers, contract packers or repackagers/parallel importers.

Anticipating the details of the Delegated Act

So what will manufacturers need to put in place to achieve compliance readiness?

The Directive, adopted in July 2011, has clearly set out the key provisions: that medicinal products sold in the EU should carry safety features that allow verification of the authenticity and unique identification of individual packs (which will also need to be tamper-evidenced) and that this verification would entail the use of repository systems (which manufacturers will have to pay for).

The technical details of how this is to be achieved will be spelled out in the Delegated Act, but that does not mean that manufacturers – and other stakeholders – are left in the dark as to what measures they will have to implement to achieve compliance with the EU-FMD. After all, the provisions of the Delegated Act will have been arrived at through extensive consultation and continuous engagement with all stakeholders since the publication of the Directive. In fact, as will be shown, all the core technical requirements that manufacturers have to comply with are known and understood well enough for any manufacturer – brand owner,

contract manufacturing organisation, generics manufacturer or repackager – to be able to specify, plan and implement their EU-FMD readiness project today. Let us examine, then, the key components of such a manufacturer readiness programme and the provisions that have been set out so far through the Delegated Act consultations and stakeholder updates.

The proposed **technical specifications of the Unique Identifier** confirming the use of a machine-readable 4- (or 5-) element code expressed as an ISO-standard 2D DataMatrix barcode that will include the key data elements that are, by now, familiar from coding requirements that are already in place in other parts of the world, for example Turkey and Argentina. The DataMatrix will contain: 1) the product identification code (usually the global trade item number (GTIN)/national trade item number (NTIN), 2) expiry date, 3) batch/lot number, and 4) the unique and randomised serial number.

There is also the recognition that there may be a need to include a national product code, for example for reimbursement purposes (where that code is not part of the product code, such as the NTIN); this would then be included as a fifth element in the barcode, an approach that has been discussed extensively and is also supported by the GS1 General Specifications.

It goes without saying that these unique identifiers that have been applied to every pharmaceutical pack will need to be collected in order to upload them to the Europe-wide verification system. In practical terms, this means manufacturers have to establish their own serialised data repository. At the same time, there is a data retention requirement on all

stakeholders, including the requirement to make the information available to the authorities when requested. The timeframe is set, as widely expected, for the duration of expiry date plus 1 year. Note that, in the case of manufacturers, the **data retention requirement** also includes retaining a record of the anti-tampering device used.

Not directly relevant to manufacturers are the provisions regarding the **modalities of verification of the safety features**, but indirectly these are, in fact, of great interest as the Directive obliges manufacturers to pay for the repository systems and infrastructure. The good news here is that the Delegated Act describes the **establishment and management of the repositories system** in terms that fully support a stakeholder model approach, such as that being implemented by the European Federation of Pharmaceutical Industries and Associations (EFPIA)-led European Stakeholder Model coalition. This means that a model is finding support that has been developed with the aim of fulfilling the EU-FMD requirements in a cost-effective way and that the involvement of the industry stakeholders who are most directly impacted by the system is endorsed by the European Commission.

What this also means is that any manufacturer who is still uncertain about how to prepare for EU-FMD compliance would be well-advised to engage, through their industry associations, with the European Stakeholder Model and access the technical guidance documents that are available to any interested party. EFPIA and partner organisations, Pharmaceutical Group of the European Union, the European Association of Pharmaceutical Full-line Wholesalers and European Association of Euro-Pharmaceutical Companies, have invested a great deal of effort into preparing an industry-wide response that any affected stakeholder will benefit from.

Conclusion

The perception that there is still much uncertainty around the requirements of the EU-FMD is a fallacy, but, in combination with a lack of understanding of just how large a challenge the implementation of a compliance-ready solution will be for most companies and how long this work will take, can – and in some instances will – prove fatal for some pharma manufacturers. Companies that have not yet started their implementation programme and may not even have budgeted for any implementation activity in 2015, are running the very real risk that

they will be losing their European sales from 2018 onward.

Looking at a best-case implementation timeline for the first pilot line to repository installation taking at least 18 months, it becomes obvious that the task of implementing the serialisation capability and operating it reliably and without a significant hit on productivity across the majority of a company's packing lines is a multi-year endeavour that now clearly pushes hard against the 2018 compliance deadline.

The conclusion is clear: the sooner companies start their implementation programme, the better.

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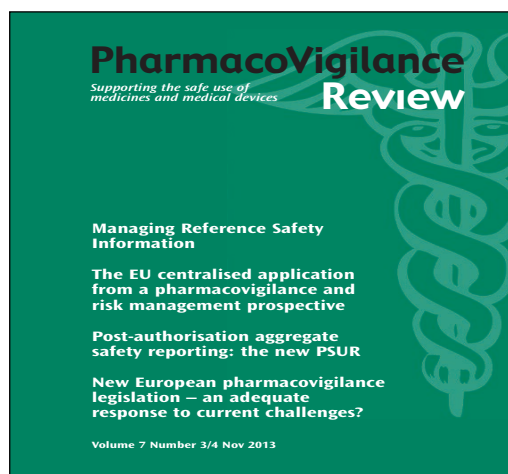
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RECENT R&D BREAKTHROUGHS CONTINUE TO REVOLUTIONISE THE ALREADY DYNAMIC HEPATITIS C TREATMENT LANDSCAPE

by Christopher J. Pace

The recent influx of late-stage pipeline candidates and newly-approved regimens has stimulated an unprecedented level of interest in the management and treatment of hepatitis C virus (HCV). Notable breakthroughs in the last few years, especially the emergence of all-oral, direct-acting antiviral (DAA) combinations, have revolutionised the treatment algorithm and forced pharmaceutical companies to reassess their portfolios in order to adapt to a rapidly changing competitive landscape.

Christopher J Pace, PhD, is a Senior Analyst covering Infectious Diseases at research and consulting firm GlobalData. He extensively researches and provides in-depth analysis on a wide range of topics in the infectious diseases space, in particular, hepatitis C therapeutics; vaccine research, development, and immunisation policy; and market access strategies for antibiotics. Email: pr@globaldata.com; www.healthcare.globaldata.com

In October, the US Food and Drug Administration (FDA) approved Gilead Science's Harvoni (ledipasvir/sofosbuvir), the world's first single-tablet, once-daily therapy for the treatment of chronic HCV genotype 1 (GT1) infection in adults. The decision, which came less than 12 months after the approval of Gilead's blockbuster NS5B nucleotide polymerase inhibitor, Sovaldi (sofosbuvir), represents the latest in a long line of momentous developments in the management of HCV, a disease that was effectively unknown just 25 years ago.

This article outlines the past and present HCV treatment landscape, with a particular emphasis on the most recent developments and

industry trends. It begins with a historical overview of the evolution of HCV management, from the use of interferon + ribavirin (1990s) to peginterferon + ribavirin (2000s), and concludes with a discussion of the arrival of the first-generation DAAs (2011–2013) and the present-day interferon-sparing and interferon-free DAA regimens. It also provides an overview of the current late-stage pipeline, the latest trends in research and development (R&D) and commercialisation strategies across the traditional seven major pharmaceutical markets (7MM; US, France, Germany, Italy, Spain, UK and Japan), and future considerations for industry stakeholders.

From interferon to the advent of DAAs: a brief history of the HCV treatment landscape

The history of HCV is a remarkable story that highlights the power of scientific and medical innovation. For decades prior to the identification of HCV in 1989, clinicians had been aware of an unknown pathogen that caused similar clinical outcomes to hepatitis A virus (HAV) and hepatitis B virus (HBV) infections. These cases confounded physicians because they consistently tested negative for HAV and HBV during the differential diagnosis, yet they had signs and symptoms that were suggestive of hepatitis. As a result, what later became known as HCV was referred to as "non-A, non-B hepatitis" in the years leading up to the identification of the virus.

Since the discovery of HCV roughly 25 years ago, the treatment algorithm has evolved rapidly, which is primarily a direct consequence of the pharmaceutical industry's commitment to developing safer and more efficacious treatment options for patients. The earliest therapies, interferon and ribavirin (see **Figure 1**), were initially used empirically, and rely chiefly on the patient's immune response to eliminate the virus. However, their effectiveness is hampered by debilitating side effects (severe flu-like symptoms for interferon and anaemia for ribavirin), the inconvenience of the requirement for frequent administration of interferon by a healthcare professional, long treatment durations of up to 48 weeks, and a high propensity for viral resistance. Moreover, the interferon-based therapies are less effective in combatting GT1 infections, which today represent a substantial proportion of the prevalent HCV cases — over 70% of all cases in the US alone. Despite these limitations, interferon + ribavirin served as the standard of care for HCV throughout the 1990s.

The first breakthrough in the treatment of HCV occurred at the turn of the century, when researchers at Enzon Pharmaceuticals discovered that the



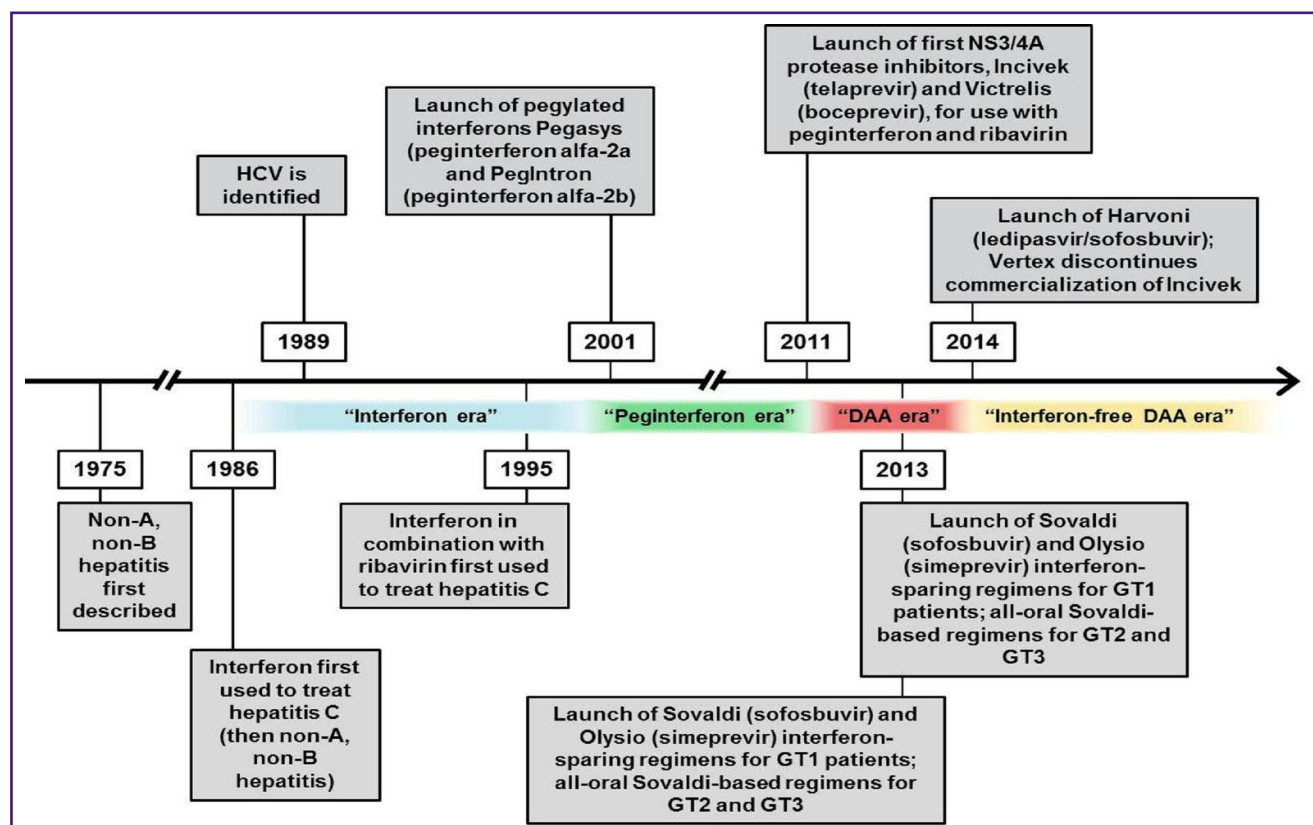


Figure 1: Timeline of significant events in the history of HCV treatment.

conjugation of polyethylene glycol (PEG) to interferon, a process known as pegylation, increases its half-life, thus reducing the dosing frequency compared with standard, non-pegylated interferon. Enzon licensed its proprietary PEG technology to Roche and Schering-Plough (now Merck) in 2001, and the use of peginterferon — consisting of Roche's Pegasys (peginterferon alfa-2a) and Schering-Plough's PegIntron (peginterferon alfa-2b) — in combination with ribavirin, soon became the new standard of care for HCV. Despite the improved convenience of peginterferon over standard interferon therapy, key drawbacks remained — namely, a serious lack of efficacy in GT1 patients, and the continued presence of highly undesirable side effects that hurt compliance.

Recognising the clear need for new drug classes to combat HCV, particularly GT1 infections and for patients who could not tolerate peginterferon-based regimens, pharmaceutical companies began investing more aggressively in the

development of drugs that directly inhibit the viral life cycle, known as DAAs. An improved understanding of the underlying molecular biology and pathophysiology of HCV infection were essential to the identification of these novel drug targets. In 2011, the first NS3/4A protease inhibitors, Vertex Pharmaceutical's Incivek (telaprevir) and Merck's Victrelis (boceprevir), were licensed for use in conjunction with peginterferon and ribavirin in GT1 patients. At the time, these first-generation DAAs revolutionised the HCV treatment algorithm due to their improved efficacy. However, in addition to their own troubling side effects, they still required the co-administration of peginterferon and ribavirin in order to prevent viral resistance. As a result, patients began foregoing treatment, a phenomenon known as the "warehousing effect", in anticipation of the approval of novel DAA regimens with reduced side effects, higher cure rates, and shorter treatment durations looming on the horizon.

The Sovaldi era and the current HCV pipeline

The launch of the first next-generation DAAs in late 2013, Gilead's Sovaldi and Johnson & Johnson's (J&J's) Olysio (simeprevir), fundamentally altered the HCV treatment landscape yet again, with cure rates of over 90% achieved for most patients. These drugs offered the first peginterferon-based regimens with treatment durations as short as 12 weeks, termed "interferon-sparing", for GT1 patients, and Sovaldi in combination with ribavirin became the first all-oral regimen for GT2/3 patients. For certain interferon-ineligible GT1 patients, Sovaldi and Olysio were administered in combination with weight-based ribavirin. Warehoused patients rapidly sought treatment with Sovaldi-based regimens, resulting in over \$5 billion in sales by June 2014 in the US alone, despite payers having decried Sovaldi's \$84,000 price tag. Given the unprecedented success of Sovaldi and Olysio, key industry players are attempting to capitalise on the clear

demand for interferon-free, all-oral regimens, with this trend being reflected in the current late-stage DAA pipeline for HCV (see **Table 1**).

The late-stage HCV pipeline is highly diverse and is dominated by a variety of DAAs with distinct mechanisms of action, including NS3/4A protease inhibitors, NS5A inhibitors, NS5B nucleotide polymerase inhibitors, and NS5B non-nucleotide polymerase inhibitors. The efficacies of numerous DAA combinations, both interferon-sparing and interferon-free, are being assessed against different HCV genotypes (chiefly, GT1, 2, 3 and 4) and patient populations, which further enhances the overall diversity of the pipeline. The majority of these pipeline candidates have demonstrated cure rates of over 80% in clinical trials, with many topping 90% in their targeted cohorts.

For the past few years, the prevailing R&D strategy has been to advance interferon-sparing and interferon-free DAA regimens for the treatment of HCV GT1, which, as noted earlier, represents the largest HCV patient population across the 7MM. However, most drug developers, in recognition of the limitations of interferon and the rapid success of Sovaldi and Olysio, have shifted their efforts almost entirely towards the advancement of all-oral, single-tablet DAA regimens

in order to compete with market leader, Gilead. Firms, such as Merck, have also begun evaluating the potential of ribavirin-free, single-tablet DAA regimens to compete with Harvoni.

With cure rates no longer a key differentiator, treatment simplicity and clever commercialisation strategies will drive competition in the HCV market

The recent approval of Gilead's Harvoni signalled the beginning of a new era in the treatment of HCV. As pharmaceutical companies continue to revolutionise the treatment algorithm through the development of novel drugs, they must recognise that efficacy and tolerability may no longer represent an effective means of product differentiation. Because the next-generation, all-oral DAA combinations boast cure rates of over 90%, along with minimal side effects, in most patients, companies have already begun exploring alternative tactics for seizing market share, with one noteworthy approach being the use of aggressively competitive pricing strategies.

For example, to counter the moves of Bristol Myers Squibb (BMS), J&J, and other competitors, Gilead has employed a shrewd pricing strategy for Harvoni — a wholesale acquisition cost (WAC) of

\$94,500 for a 12-week course of therapy — with the hope of facilitating its rapid uptake, particularly in the US. This approach has easily positioned Harvoni as the more cost-effective option compared with the interferon-sparing Sovaldi regimens (WAC of \$94,726 for a 12-week course of Sovaldi in combination with Pegasys and ribavirin) for most GT1 patients, especially those who can be cured in 8 weeks (WAC of \$63,000), which could be up to 40% of all patients. In fact, 12-week courses of Harvoni or Sovaldi in combination with peginterferon and ribavirin cost less than a 48-week regimen of the now-defunct Incivek in combination with peginterferon and ribavirin (WAC of \$109,060, not including the costs associated with managing side effects). Gilead, after enduring months of scrutiny from US payers and policymakers surrounding Sovaldi's \$84,000 price tag, will silence some of its critics by essentially pricing its novel NS5A inhibitor contained in Harvoni, ledipasvir, at \$10,500 for a 12-week course of therapy.

As a consequence of attributing the bulk of Harvoni's WAC to Sovaldi, Gilead will also discourage the off-label use of more expensive Sovaldi-containing DAA regimens, an opportunity that competing firms, such as BMS and J&J, have hoped to exploit in their efforts to

Table 1. The current late-stage DAA pipeline for HCV*

Drug name	Company	Therapy class	Most advanced development stage (region)
Sofosbuvir/ledipasvir (fixed-dose combination)	Gilead	NS5B nucleotide polymerase inhibitor; NS5A inhibitor	Marketed (US)
Daclatasvir, asunaprevir, beclabuvir	Bristol-Myers Squibb	NS5A inhibitor, NS3 inhibitor; NS5B non-nucleoside polymerase inhibitor	Marketed (EU and Japan; daclatasvir and asunaprevir regimens only) Phase III (US; daclatasvir, asunaprevir, and beclabuvir regimens)
Paritaprevir (ritonavir-boosted), ombitasvir, dasabuvir	AbbVie	NS3/4A protease inhibitor; NS5A inhibitor; NS5B polymerase inhibitor	Pre-registration (US and EU)
Vaniprevir	Merck	NS3/4A protease inhibitor	Pre-registration (Japan only)
Grazoprevir/elbasvir (fixed-dose combination)	Merck	NS3/4A protease inhibitor; NS5A inhibitor	Phase III (US)
Sofosbuvir/GS-5816 (fixed-dose combination)	Gilead	NS5B nucleotide polymerase inhibitor; NS5A inhibitor	Phase III (US)

* The late-stage pipeline is defined as active programs having reached Phase III of clinical development as of October 2014 (source: GlobalData, Pipeline Products Pharma eTrack, October 2014).



seize market share. As previously mentioned, an all-oral regimen of Sovaldi in combination with J&J's Olysio has been prescribed frequently to GT1 patients thus far in 2014, despite carrying a hefty WAC of \$150,360 (\$84,000 for Sovaldi and \$66,360 for Olysio) for 12 weeks of therapy. While Olysio's unexpected success in 2014 (global sales surpassing \$1 billion in only 6 months) has been primarily attributed to its off-label use in combination with Sovaldi, J&J has already acknowledged that it expects sales of Olysio to decline in 2015 due to the arrival of Harvoni as a cheaper and more convenient interferon-free option for GT1 patients. In recognition of the need to develop its own all-oral DAA regimen, the company recently purchased Alios BioPharma and its nucleotide-based antivirals portfolio for \$1.75 billion. Gilead's astute pricing strategy and lifecycle management of its sofosbuvir-based regimens (Sovaldi and Harvoni) should serve as a case study for how to achieve commercial success in a rapidly maturing, competitive marketplace.

What's next? - future outlook

The HCV treatment landscape has undergone a paradigm shift over the past few years, and the impending arrival of multiple interferon-free, fixed-dose combination regimens promises even more dramatic changes in the near future. In fact, the large number of effective next-generation therapies entering the market may even make it possible to virtually eradicate HCV in the next decade, although the jury is still out

on how payers will seek to regulate who receives these cutting-edge, yet expensive, therapies, particularly once the initial wave of warehoused patients have been successfully treated. From a public health perspective, an increasingly crowded and competitive HCV marketplace is likely to benefit patients, payers, and healthcare providers.

Looking more closely at the future HCV competitive landscape, Gilead's strong pipeline, commercialisation strategies, and portfolio management have given it a key edge in the US over its competitors, but its position in the rest of the 7MM is less tenable. The same bold pricing strategy that has thus far succeeded in the US has only resulted in the delayed uptake of Sovaldi-based regimens in the EU due to cost-effectiveness concerns, particularly in the UK and France. Having received European approval for Daklinza (daclatasvir) in the treatment of GT1–4 infections in August, BMS is also looking to more aggressively commercialise Daklinza-based regimens there, as the proportion of non-GT1 patients is greater in the EU than in the US. Meanwhile, in Japan, BMS already has a leg up on its competitors, having become the first company to receive approval for an all-oral regimen (Daklinza and Sunvepra [asunaprevir]) for the treatment of GT1b infections, which account for roughly 70% of Japanese HCV patients, earlier this year. Nevertheless, Harvoni's once-daily, single-tablet dosing will be hard for clinicians and eligible patients to ignore once it launches in the European and Japanese markets,

especially if Gilead leverages a pricing strategy similar to the one it used in the US. For these reasons, Gilead, with its HCV portfolio of Sovaldi, Harvoni, and a promising next-generation pan-genotypic DAA regimen (sofosbuvir/GS-5816), has likely secured its leading position in the HCV marketplace for the foreseeable future.

Stay tuned in 2015 for an update on the next wave of innovation in the treatment of HCV.

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QUALITY METRICS, QUALITY CULTURE, QUALITY MATTERS!

by Tom Sam and Henny Koch

For quality medicines to deliver optimal therapy to the patient, it is critical to select and develop a patient-centric drug product design, and to subsequently control product and process development, the manufacturing processes, and the external supply chain. Quality metrics are seen as a tool to evaluate and optimise the manufacturing process, and an enhanced quality culture mindset is needed to sustainably deliver quality medicines throughout their lifecycles.

Tom Sam, PhD, MBM (tomsamphd@gmail.com) was, until his retirement in July 2014, Director Regulatory Affairs CMC of Merck Sharp & Dohme, managing four regulatory teams at its site in Oss, the Netherlands, covering the entire spectrum from active pharmaceutical ingredients to new and existing pharmaceutical products, medical devices and combinations thereof. He is the current chair of the AAPS Manufacturing Science & Engineering section and past president of the Industrial Pharmacy Section of the International Pharmaceutical Federation (FIP). His new area of interest is the impact of the new economy on pharmaceutical industry business management.

Henny Koch (hmpkoch@qimp.nl) is owner of Qimp Management Systems, a quality consultancy company for effective support to strongly regulated quality and management systems. His specialties are medicinal product and medical devices regulatory and compliance control and quality systems. Henny is a certified ISO 9001:2008 and GxP lead auditor and member of the Medical Devices Committee of the Research Quality Association in the UK.

Quality matters, but to most of us it is a rather intangible property. Quality is hard to grasp and may mean different things to different people in different circumstances. In most cases, we sense the importance of quality only when we see defects or clearly suffer from the fact that we cannot use the product properly. In a

similar way, the impact of poor-quality medicines is experienced when we encounter drug shortages and product recalls. The quality of a medicine is the degree to which the product is capable of consistently delivering its safety and clinical attributes to the patient. To obtain such a quality product, quality

ingredients and quality manufacturing processes should be in place. However, it starts with selecting the appropriate dosage form to optimally use the therapeutic potential of the medicine.

Patient-centric drug product design

How can one reduce the risk of developing a product that does not exhibit the required quality? It is important to start the development process by defining a target product profile summarising the quality characteristics of a drug product that should be achieved to ensure the desired quality, taking into account its safety and efficacy. Even for a single drug, there are many combinations of drug substance form (e.g. specific salt, ester, prodrug or probiological compound), excipients and packaging materials. The goal should be to create the optimal drug product with the highest therapeutic value for the specific patient target population that is appropriate for these patients¹. It is also important to ensure the drug can and will be used as intended, which could lead to modifications to prevent misuse or abuse.

The same active pharmaceutical ingredient (API) can be used as drug substance in various routes of drug delivery, requiring different formulations with different excipients and packaging. Optimal development of the drug product should be patient-centred². Choosing the most suitable dosage form is not straightforward since industrial factors like manufacturability, cost and speed of development need to be taken into

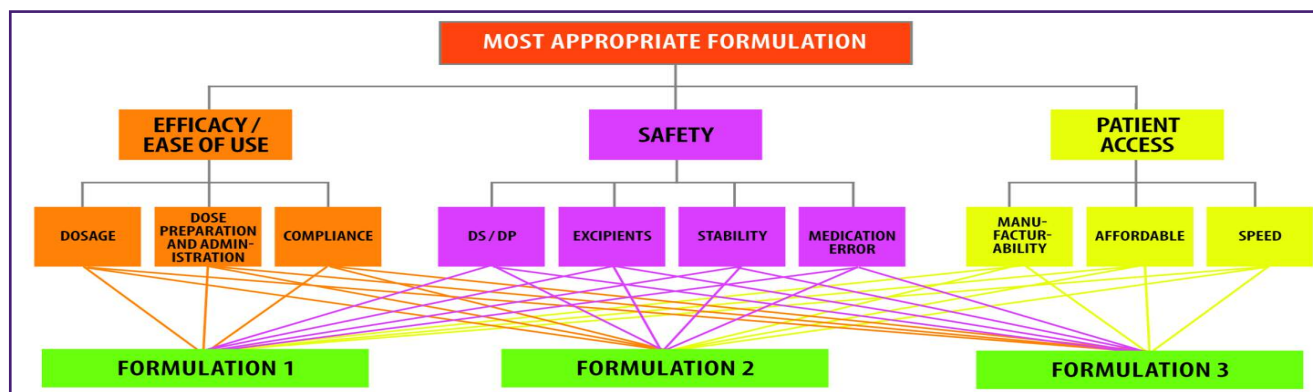


Figure 1: Use of an analytical hierarchy process to decide on the most appropriate formulation for a specific setting. In this example, the most appropriate formulation is selected from three alternative formulations based on the efficacy, safety and patient access.



account apart from safety and efficacy. In the current development paradigm, a risk-based approach should be used to select the optimal patient-centric formulation. A procedure employed by several major companies uses three sets of composite criteria to arrive at the formulation of choice: efficacy/ease of use, safety and patient access (Figure 1).

Designing quality into the product during development

For innovative medicines, we should consider the clinical target product profile (CTPP) and the interplay between clinical and pharmaceutical development. The CTPP not only provides guidance to the clinical phase 1–3 studies, but also serves as an input for the quality target product profile (QTPP; see Figure 2, step 1), which is the starting point for the pharmaceutical development cycle. For generic drugs or biosimilars, the pharmaceutical development cycle holds, but the clinical development cycle is reduced to bioequivalence studies or demonstration of biosimilarity. Pharmaceutical development guidance on quality by design and control strategy is obtained through the International Conference on Harmonization (ICH) series of Quality Guidelines Q8–Q11^{3,4}. The emphasis is on managing quality throughout the product life-cycle, covering development, manufacturing and distribution through the end-to-end supply chain, including the discontinuation of the marketing authorisation.

At the beginning of the pharmaceutical development cycle (step 2a), the desired quality of the drug product is derived from the QTPP and laid down as a set of potential critical quality attributes (COAs), quantitatively describing its intended physical, chemical, biological or microbiological characteristics. The commercial formulation and the commercial manufacturing process need to be defined in parallel (step 2b) using the same considerations as discussed for patient-centric drug product design. Emphasis in the development cycle is

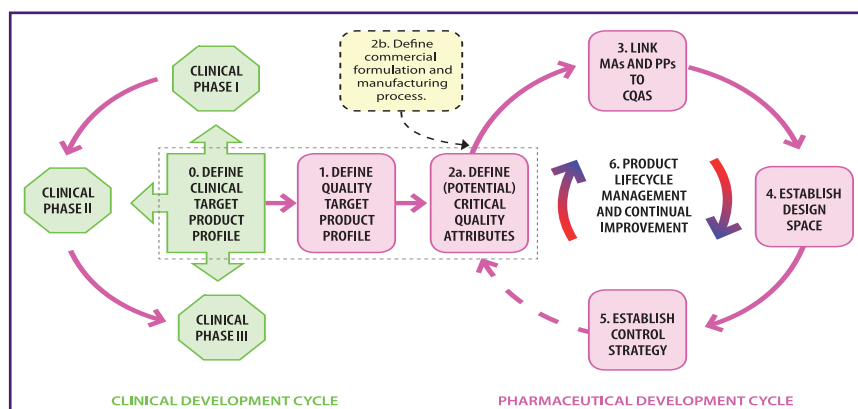


Figure 2: Science- and risk-based development of a drug product integrating the clinical and quality-by-design cycle. MA: material attribute; PP: process parameter).

on product life-cycle management and continual improvement (step 6). At the end of the process, the quality attributes are established as truly critical to ensure product quality and hence its safety and efficacy. These COAs can be considered final as long as no new insights are obtained or changes occur in the formulation or manufacturing process.

Quality in the manufacturing process

There is a strong recognition that a quality product requires not only a defined quality of ingredients, but also quality of the manufacturing process. Quality products can only be developed by understanding and appropriately controlling the linkage (step 3 in Figure 2) of the ingredient attributes and the process parameters of the various process steps in relation to their criticality for obtaining a quality product.

Traditionally, health authorities control the quality of the products on their markets by requiring an approved marketing authorisation (e.g. new drug application) and a series of good practices (GXP) to be adhered to during the life-cycle of the product.

- Good laboratory practice for toxicology studies.
- Good clinical practice for clinical studies.
- Good manufacturing practice.
- Good distribution practice.
- Good pharmacovigilance practice.

Adherence to the GXP is subject to companies' auditing processes and regulatory inspections. This dual system of approvals and audits/inspections is intense, time consuming and costly and has appeared to be vulnerable, especially due to the globalisation of the supply chain. APIs, excipients and packaging, and their corresponding starting materials are now sourced from all over the globe, and the processes used and quality systems applied may not always be known and may not be up to Food and Drug Administration (FDA) regulatory standards. Approximately 90% of the APIs of products on the US market and 50% of the drug products are now imported from outside the USA⁵. Medicines originate in factories all over the world, moving into the American marketplace through supply chains that can involve numerous processing plants, manufacturers, suppliers, brokers, packagers and distributors. This introduces additional vulnerability to the quality of the drug product (Figure 3)⁶. The new Drug Supply Chain and Security Act (Title II, Drug Quality and Security Act, 2013) addresses risks in the pharmaceutical distribution supply chain by establishing a national system that allows stakeholders and regulators to trace each package of product. The serialisation and traceability requirements will be phased in over the next 10 years. The act requires all sectors in the supply chain to participate, including the repackagers

and wholesale distributors.

With the increasing complexity of the supply chain, it is increasingly difficult to ensure quality via traditional organised audits and inspections. Many incidents influencing quality have been reported, leading to regulatory actions, recalls, drug shortages and counterfeit medicines on the market. It has become an even bigger challenge than ever to ensure public health. Therefore, health authorities have been evaluating ways to rationalise their inspection practices. FDA has announced that it will collect metrics on the quality of pharmaceutical products and their manufacturing sites. Quality metrics could ideally provide objective measures of the quality of the product or process, the quality of a site, and the effectiveness of quality systems associated with the manufacture of marketed pharmaceutical products.

Quality metrics

Quality metrics are an essential tool for quality improvement and have been successfully implemented in industry, with Six Sigma quality efforts being one example. The emphasis is on the quality improvement bottom line and cost reduction, building on the Cost of Poor Quality (COPQ) concept, where COPQ is defined as the cost incurred by the various non-value-added activities and inputs contributing to the non-conforming output. COPQ includes appraisal (inspection, audit), internal failure (defectives, rework, scrap, ineffective use of resources, derailed stocks), external failure

(repairs, service calls, warranty claims, write-offs, lost business, lost opportunities) and prevention (costs incurred trying to minimise the cost of appraisal and failures). Poor quality in the supply chain also contributes to these costs. COPQ typically accounts for up to 30% of sales and 40% of operating costs.

In addition to "lean"/Six Sigma type of improvement efforts, quality metrics should provide a standard language tool for health authorities to evaluate site quality as a measure of a site's ability to manufacture quality products. The FDA Safety and Innovation Act gives the FDA authority to request such data to allow for regulatory inspection flexibility. The idea is that appropriate utilisation of metrics would allow FDA inspectors to do more efficient and effective inspections or even use metrics to waive inspections at good performing sites. It would also allow companies to improve the quality in their manufacturing activities. However, the use of metrics is not straight forward. While FDA is looking for absolute measures of site quality to compare quality risk in the field, the industry is emphasising that metrics of manufacturing site quality would at best be semi-quantitative and not comparable across sites of the same company let alone across sites from different companies. Trend analysis for a specific site could be the most realistic outcome.

Some examples of metrics currently proposed by not-for-profit associations, such as the International Society for Pharmaceutical Engineering and the Parenteral Drug

Association, are batch rejection and out-of-specification rate. These are lagging metrics, but more effective metrics predict future quality performance, the so-called leading metrics. Examples of more advanced leading metrics are quality system effectiveness, process capability, and a measure of the degree of quality culture awareness in the company or on site^{7,8}. Agreement on suitable metrics across the pharmaceutical industry and with the health authorities will be a challenging goal, especially since companies vary greatly in processing activities. Experts warn that metric definitions should not be multi-interpretable and metrics should not become a goal in themselves, but a tool to achieve the companies' quality objectives.

Quality culture as an essential element

Why has quality culture received so much attention recently? In daily practice, existing GxPs led to a culture of complying with regulators' standards, but not necessarily with a quality environment resulting in reliable and consistent production of high-quality products. A change of awareness in our quality culture is necessary to create full awareness and understanding of the implementation and application of a properly functioning pharmaceutical quality system suitable for metrics-based surveillance.

The main challenge for creating and maintaining a quality culture is that organisations may not be sufficiently transparent where unidentified failures or threats may be

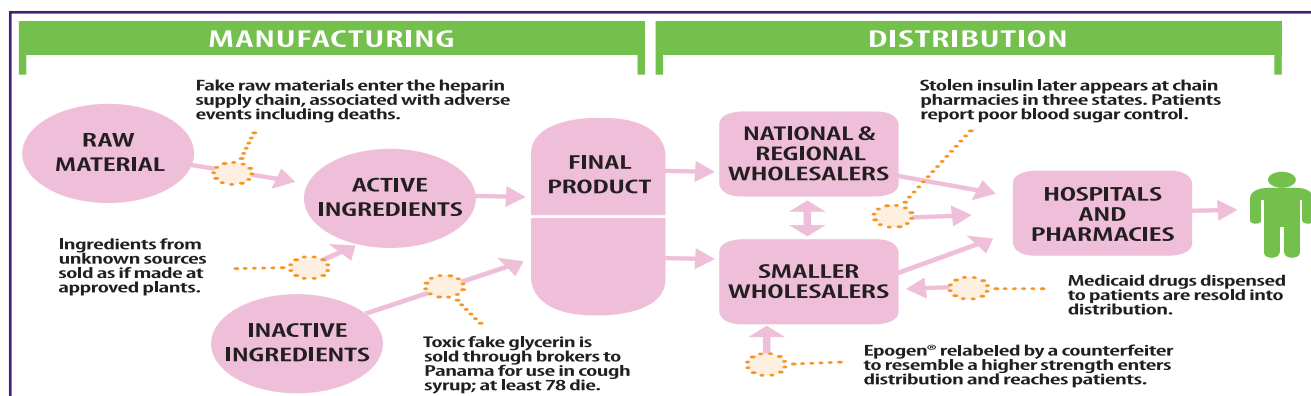


Figure 3: The pharmaceutical supply chain with examples of vulnerability/potential failure modes (figure adapted from PEW Health Group⁶).

at stake. Management goals might not be aligned with the quality culture. Under the force of legal pressure, unexpected failures may be stashed and not used to learn and improve. A more open attitude can be achieved by taking failures away from the individual and identifying the true cause as part of the established processes and systems. To achieve a more proactive attitude, a higher level of quality culture is needed. Realising that culture (shared values) is at the very heart of any organisation, its impact on day-to-day business cannot be underestimated. In a brief historic overview of the 7-S McKinsey management model, coinventor Tom Peters states that changing the attitude and behaviours of people is very, very hard and that culture is not just one aspect of the game—it is the game.

The Juran Institute defines quality culture as the capabilities of the organisation, its habits and beliefs, which enable it to design and deliver products and services that can meet customer needs and be successful in the marketplace over the long term. Quality will prevail only in an environment where every person in the company understands and embraces his or her responsibility for protecting product quality and patient safety. NASA, for instance, differentiates four levels of quality culture: absence of quality emphasis, error detection, error prevention and creative quality.

The proactive levels of a quality culture are associated with higher levels of organisational effectiveness. An advanced quality culture should be able to enhance continual improvement throughout the lifecycle by the following⁹.

1. Using risk- and science-based approaches.
2. Making decisions based on understanding of the manufacturing processes and the product's intended use (having the patient's needs in mind).
3. Properly identifying and controlling areas of potential process weakness (including raw materials).
4. Having responsive deviation

investigation systems in place that lead to timely remediation and preventive actions.

5. Applying sound methods and a variety of tools for assessing risk.
6. Having well-defined and designed manufacturing processes and products from development through the entire product life-cycle.
7. Having systems in place for building in and careful analyses of product quality.
8. Ensuring that senior management is supportive, both philosophically and financially.

A real commitment to quality and demonstration of the same by living the example is essential and should be practiced from both the top down and the bottom up. Quality oversight and governance must be implemented at every level both at the site and globally. Goals and quality metrics should be developed and progress communicated throughout the organisation. Evidence of upper management leadership and empowerment should be provided to employees. To create this culture of quality, the development, implementation and harmonisation of the quality systems should be supported by meaningful auditing. ICH Q10 describes the four major systems to support the life-cycle approach as follows.

1. Process performance and product quality monitoring system.
2. Corrective action and preventive action system.
3. Change management system.
4. Management review of process performance and product quality.

It would make sense to develop leading metrics consistent with at least these four systems. The process owner would have the information about the health of the respective system. This would allow optimisation and continual improvement of these systems. The assessment of quality culture could be done by preparing anonymous questionnaires for employees and/or by conducting focused discussions with groups of employees. Feedback

from these activities and implementing changes are crucial. By putting forth an extensive array of questions, companies can explore areas such as overall product quality, conformance to requirements, equipment use, supplier quality, management commitment, work group performance, employee participation and training.

Optimising the quality culture of an organisation requires long-term dedication and investment both from management and all other company employees on all levels throughout the organisation. However, the rewards for pharmaceutical companies, i.e. being able to deliver quality products to our patients by abolishing drug shortages and product recalls, will make the effort more than worthwhile. Quality matters!

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regulatory review

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

USA

Food and Drug Administration (FDA) Data Dashboard

This new tool shares inspectional, compliance and enforcement-related data in various, easily understood graphical formats. It allows users to drill down on elements within the graphical formats for a more detailed view and to export the graphs and underlying data.

Revocation of duplicative general safety test regulations

This proposal to amend the biologics regulations by removing the general safety test (GST) requirements for biological products arises because GST regulations are duplicative of requirements that are also specified in biologics licenses, or are no longer necessary/appropriate to help ensure the safety, purity, and potency of licensed biological products.

Electronic submission of lot distribution reports (LDRs)

This draft guidance provides recommendations to licensed manufacturers of products distributed under an approved Biologics License Application (BLA) on how to submit LDRs in an electronic format that the FDA can process, review, and archive.

Abbreviated new drug application (ANDA) submissions – refuse to receive for lack of proper justification of impurity limits

This draft guidance highlights deficiencies in relation to information about impurities that may cause FDA to refuse to receive an ANDA as it is not sufficiently complete to permit a substantive

review. Typical deficiencies are quoted.

Europe

European Medicines Agency (EMA)

Qualified person declaration template Q&A

The final template and guidance was published in June 2014. EMA has now published answers to the comments provided from industry groups on the original 2011 documents. These comments provide insight into EMA's expectations on active pharmaceutical ingredient supplier auditing and qualification.

Reflection paper – selection and justification of starting materials for the manufacture of chemical active substances

Disagreements between applicants and quality assessors on the suitability of proposed starting materials have become more frequent, suggesting that the current (intentionally high level) guidelines are open to interpretation. This document expands on some of the points in ICH (International Conference on Harmonization) Q11 in order to harmonise opinions between assessors and clarify the requirements for applicants.

EU GMP Guide

Chapter 3: Premise and Equipment

The only change from the previous draft is to section 6 as part of the improved risk-based guidance on prevention of cross-contamination. The Guidance indicates that dedicated facilities are required for manufacturing when a medicinal product presents a risk because of the following.

- The risk cannot be adequately controlled by operational and/or technical measures.
- Scientific data from the toxicological evaluation does not support a controllable risk.

- Relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

This guidance is effective from 1 March 2015

Chapter 5: Production

Changes have been made to sections 17 to 21, including adding a new section, to improve the guidance on prevention of cross-contamination and refers to toxicological assessment. (However, there is no longer mention as to how the toxicological assessment as part of the risk management process for deciding whether dedicated facilities are required has to be done, MH)

Changes were also introduced in sections 27 to 30, including adding a new section on the qualification of suppliers in order to reflect the legal obligation of marketing authorisation holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Sections 35 and 36 are inserted to clarify and harmonise expectations of manufacturers regarding the testing of starting materials. Section 71 introduces guidance on notification of restrictions in supply. This guidance is effective from 1 March 2015

Chapter 6: Quality Control

This revised chapter was effective from 1 October 2014. It involves a new section on technical transfer of testing methods and covers other items such as Out Of Specification results.

Chapter 8: Complaints, Quality Defects and Product Recalls

Extensive changes reflect that quality risk management principles should be applied when investigating quality defects or complaints and when making decisions in relation to product recalls or other risk-mitigating actions. It emphasises the need for



the cause(s) of quality defects or complaints to be investigated and determined, and that appropriate preventative actions are put in place to guard against a recurrence of the issue and clarifies expectations and responsibilities in relation to the reporting of quality defects to the competent authorities. This guidance is effective from 1 March 2015.

Medicines and Healthcare products Regulatory Agency (MHRA)

Review of GMP inspection deficiencies 2013

The most frequently encountered defect categories raised over the previous 5 years have remained relatively consistent with the exception of 'contamination, chemical/physical (or potential for)' which has significantly increased. Deficiencies relating to 'quality systems' are by far the most prevalent observed during inspections.

New collaboration in the development of advanced therapies

The National Institute for Biological Standards and Control, a centre of MHRA, has signed an agreement with University College London to maximise and further promote scientific collaboration in the field of advanced therapies.

International

ICH

Final Concept Paper ICH Q12 Guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle

This topic was endorsed in September 2014 by the ICH Steering Committee. The proposed purpose is to provide guidance on a framework to facilitate the management of post-approval chemistry, manufacturing and controls (CMC) changes in a more

predictable and efficient manner across the product lifecycle.

Pharmaceutical Inspection Cooperation Scheme (PIC/S) Croatia applies for PIC/S membership

The Rapporteurs will be appointed soon.

2014 PIC/S Annual Seminar on "Dedicated Facilities or Not"

Unfortunately this Seminar held in Paris in October 2014 was limited to National Health Authorities only, despite the fact that it is likely to have a significant impact on industry.

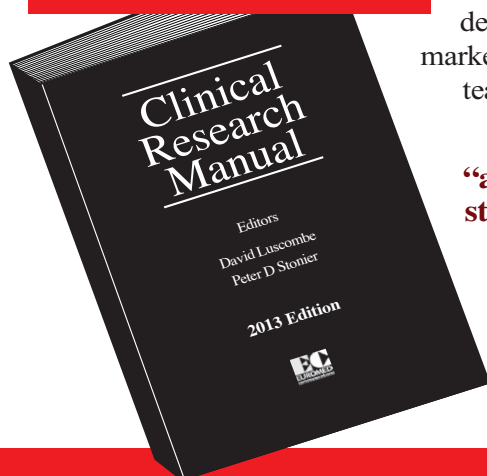
For further information on these and other topics we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications. To subscribe to this monthly news service contact info@euromedcommunication.com

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letter to the editor

Dear Editor

In the last edition of *European Industrial Pharmacy* (issue 22), Tony Cartwright wrote a very comprehensive article on the history of pharmacopoeial harmonisation as a rebuttal to my previous article in *European Industrial Pharmacy* titled "Unstandard Standards". While he has done an eminent job, and I do not dispute a single fact that he has raised, he has sadly not answered the several cogent questions I raised in my articles.

Namely, why are reference standards between pharmacopoeias not harmonised and interchangeable, why has the world's most common excipient – purified water – not been harmonised, and why has it taken over 140 years to only harmonise about 14% of the general methods and 17% of the excipient specifications listed in the US Pharmacopeia. At a recent conference, I asked, off-the-record, a

senior member of US Pharmacopeia staff as to why reference standards were not harmonised – to which the first response I received was "we make more money selling the standards than selling the book", a point I alluded to in my article.

My article was in no way meant as a denigration of the technical and scientifically fine work done by many hundreds of scientists worldwide, including Tony as a long-standing member of the British Pharmacopoeia Commission. However, I raised the question for industry discussion as to whether vested interests might be in the way of true pharmacopoeial harmonisation into a "Global Universal Pharmacopoeia" – a topic which Tony has yet to address.

Michael Anisfeld



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bottled brown

Thorn

In 1940, a garden rose thorn scratched Albert Alexander, 48, a policeman. A streptococcal/staphylococcal infection resulted. It was held at bay until the last supply of penicillin was given. Then he died. During the antibiotic era such fatalities have seldom occurred in the developed world.

But antibiotics have been overused; microbial resistance is increasing. Few novel antimicrobial agents have been marketed. Antibiotics, by definition, have short courses that are one-off; few people use. So antibiotic development has made little commercial sense for industry. It appears the "bad guy", only seeking profit, again. But read on.

Health professionals have warned for decades about the risk of antibiotic resistance. In the 1960s, I urged "complete the course"... "only give if essential." That plea is so old that it has grown whiskers. But professionals were only one voice, often ignored. The respected sociologist Elliot Freidson (1988) pointed out three groups: practitioners (e.g. medical practitioners, pharmacists), academics and administrators (e.g. managers, politicians). Each group thinks that they are "the best" and respect other groups less. Practitioners have expert power and some autonomy, such as choosing not to give antibiotics and pleading to use them wisely. But the administrators retain power where to invest and support with public relations expertise, behind

an opinion. It has taken the politicians about a generation to hear the practitioners' message: antibiotics have problems ahead.

Zeitgeist

But, at last, politicians have got it. David Cameron recently publicised that a return to pre-antibiotic days ("dark ages") is an "unthinkable scenario". At last the public zeitgeist is shifting. Something must be done. But what?

One action is the (UK) Longitude Prize 2014 developed and run by the innovation charity Nesta. It is for a cost-effective, accurate rapid and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotic at the right time. This is good because any new antibiotic will eventually suffer microbial resistance. The prize is worth £10 million: peanuts. It also ignores "the elephant in the room": veterinarians and farmers use "industrial" amounts of antibiotics, globally, on other animals, especially poultry.

But industry here has a chance to be the "good guy". Think of the tetracycline from allotment soil, the cephalosporin from Sardinian sewage. Many species have waged chemical warfare against another; those that adapt, survive. That cornucopia remains there for humans to harvest. One example is ants keeping fungus gardens over Darwinian time: gardens that humans may harvest for powerful antimicrobial agents. Dripping

within the rain forests, many goodies may await pharmacognostical explorers. They may not, of course. But there is a fighting chance and it is a simple-to-understand, powerful yet romantic story, a quest with (hopefully) a happy ending: a public relations dream.

Flux

Another perspective exists. Babies, during non-Caesarean births, are born face-first to their mother's anuses, and so smeared with faeces. The microbial gut colonisation resulting is important for the babies' survival. We need those "good" archaea, bacteria, fungi, etc. Indeed, of our total bodily cells, only 10% are mammalian and fully 90% are micro-organisms.

Within Earth's primordial soup, about 3.4 billion years ago, RNA/DNA developed. Welcome Lua (the Last universal ancestor), the mother of all mothers, the mother of us all. Early descendents were the archaea. Such extremophiles seldom cause disease. But some of their bacterial cousins do. Normally we all survive in "happy" equilibrium. Bacterial disease generally occurs when equilibrium is disturbed or they venture where they should not. Chemical (antibiotic) warfare between progeny, refined by trial-and-error "experiments" over billions of years, is part of that flux. That awes me.

Malcolm E Brown

Anti-counterfeiting measures

The Bureau has been keeping a watching brief on the progress of the Delegated Act which will implement the requirement for a Unique Identifier on packs of medicinal products. It appears that the Commission is behind schedule with publication which was due this quarter. Nevertheless, once published, there will be little time to input any concerns via Members of European Parliament and the Bureau would welcome your opinions on the practicalities of implementation as soon as the text is available.

European Medicines Agency

Piero Iamartino, EIPG Vice-President Technical and Professional Development, will represent EIPG at a meeting with the Inspectorate Working Group on 2 December. The main topic of discussion will be the initiatives in response to the EMA's reflection paper on shortages caused by manufacturing and quality/good manufacturing practice (GMP) problems.

On-line training

Several GMP e-learning courses aimed at process operators, courses on the Guide to Good Distribution Practice (including measures involving the falsification of medicines) and a guide to developing nanomedicines are being added to the Pharma Consult

website by the end of December. The Pharma Consult short courses are now under "Education" on the home page of the EIPG website (<http://eipg.eu/education/>)

EPSA Seminar and Autumn Assembly

Following an idea of Anni Svala, EIPG Vice-President Education and Training and the Executive of the European Pharmaceutical Students Association (EPSA), the first of what is expected to be a series of joint webinars has been arranged for 9 December. Speakers will be Claude Farrugia, EIPG Vice-President Communications on "The Subject(ion) of Pharma" and Georgina Gal, delegate to EIPG for the Hungarian Society for Pharmaceutical Sciences, who will speak on "Regulatory Affairs – the Coordination Centre of the Pharma Industry". For registration, see www.EPSA-online.org. Although aimed at students, members of EIPG are welcome to attend.

At the end of October, Amon Wafelman (EIPG Special Interest Group, Production Co-Chair) spoke at the EPSA Autumn Assembly in Hradec Kralove, Czech Republic. His presentation was entitled "Development of Biopharmaceuticals: Structure and Formulation Considerations". The slides can be found on the EIPG website under media library, presentations.

Proposed project for PhD students

EIPG has been invited to participate in a European Joint Doctorate project proposal which will be arranged by a consortium of four universities: Milan (Italy), Aberdeen (UK), Antwerp (Belgium) and Leiden (Netherlands). The scope of the project is to create, through a shared training programme, a common knowledge and language for PhD students working in the pharmaceutical sciences.

To improve student knowledge of the pharmaceutical industry, EIPG was identified as a non-academic consultant to assist with the training programme definition, the evaluation of students' experience in their internships and in networking. A representative of EIPG will attend the Project Management board meetings.

Special Interest Groups

Anyone interested in joining the "Regulatory Affairs" or "Production" groups should contact:

Regulatory Affairs: Georgina Gal (georginagal@gmail.com) or Marianne Andersson (marianne.andersson@astrazeneca.com)

Production: Piero Iamartino (pieroiamartino@gmail.com) or Amon Wafelman (amon.wafelman@pharmachemie.com)

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17–18 February 2015 – Berlin,
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Germany
Pharma Congress 2015
www.pharma-kongress.com

APRIL 2015

4–7 April 2015 – Glasgow, Scotland
**10th Pharmaceuticals,
Biopharmaceutics and
Pharmaceutical Technology
World Meeting**
www.worldmeeting.org

13–14 April 2015 – Reims, France
**1st European Conference on
Pharmaceutics – Drug Delivery**
www.apv-mainz.de

14–15 April 2015 – Berlin, Germany
Aseptic Manufacturing
www.pda.org

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