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Human error: don't blame people – fix the system because...if you don't the errors will happen again and again...

New EMA draft guideline on sterilisation of the medicinal product

Counterfeit drugs and product serialisation – an overview of serialisation requirements

Vol.15 No.2 July 2016

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Call for papers and articles

Dear Colleague,

We hope you find **gmp review** of interest and practical use in your specialty.

We are currently seeking new papers and articles for future issues of the journal and would like to invite you to contribute an article or review paper to the journal.

We would welcome papers on any aspects of regulations including pharmaceutical manufacturing and control.

We invite you and you colleagues to address any of the above suggestions and on any other topics that you think may be relevant and of interest to readers of **gmp review**.

Thank you for your continued support

Yours sincerely
Peter Savin

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Editorial comment

Welcome to this latest issue of GMP Review. As we go to print, the result of the UK referendum on our membership of the EU has just been announced and all the discussions on what it means have just started. While there are some seemingly obvious impacts on our world of pharmaceutical good manufacturing practice (GMP), such as the probable move of the European Medicines Agency out of its Canary Wharf London offices, it is difficult to see if there will be any significant impact on the GMP legislation or the UK inspectorate processes as we experience them. I guess that only time will tell, in the meantime, carry on regardless everyone.

Our Regulatory Update from Malcolm Holmes contains the usual comprehensive and informative summary of emerging requirements and news. One particularly interesting topic for all GMP professionals is the control of compounding pharmacies in the USA. Are the US FDA in control or are patients still at unacceptable risk?

So long after the Elixir of Death incident which resulted in approval of the Federal Food, Drug & Cosmetic Act, the FDA still doesn't appear to have the authority to demand recall or suspend manufacture in such circumstances. In the UK, the MHRA could (and would) suspend or withdraw a license. While the FDA regularly chases the money and imposes enormous fines on pharmaceutical companies, in cases like this it does not appear to be able to protect the patient. All it can do is to alert healthcare professionals not to use any drug products that are intended to be sterile and are produced and distributed nationwide by Pharmakon Pharmaceuticals Inc. This particular alert is due to a lack of sterility assurance and other quality issues, which are obviously very significant risks.

In this issue of GMP Review, we have a paper on human error prevention from Martin Lush. As a pharmaceutical consultant, 'human error' is a favourite topic of mine as I still see far too many companies citing it as the major cause of deviations, with the subsequent corrective and preventive action (CAPA) stating that 'the operator was retrained'. This raises so many questions about the quality of the initial investigations as well as the subsequent CAPA and the CAPA effectiveness review. All this is still happening despite the fact that the Eudralex EU Guidelines to Good Manufacturing Practice have clearly proscribed it since 2013 (just re-read Chapter 1 section 1.4). If this is the situation with human error in your organisation, then I thoroughly recommend that you read and share Martin's paper and his quiz. It is an excellent 'eye-opener'.

We also have papers from some of our regular contributors, Tim Sandle reviews the new EMA Draft Guideline on Sterilisation of the Medicinal Product and Andrew Love and Stephen McIndoe present their second paper in their series of four papers on anti-counterfeiting and the serialisation issue.

Peter Savin, Editor

Human error: don't blame people – fix the system because...if you don't the errors will happen again and again...

Martin Lush

Ever poured coffee into a tea pot, put petrol in a diesel car, written on a white board with a permanent marker, turned up at the wrong hotel for a conference or forgotten the name of your boss? Well, I've done them all. I even managed to get onto the wrong flight once. That took some doing. As they say 'To Error is Human'.

Well, if you're serious about error prevention, read on to get your error reduction questions answered, guidance on your 'Six to Fix', access to free 'error reduction' resources and additional support to help drive down errors.

Let's start with a 'top ten' error quiz to get the neurons firing. Answer with a simple 'Yes' or 'No'

1. Are a majority of your deviations or mistakes put down to 'human error'?
2. Do your preventive actions focus on things like 're-training', additional checks, adding more detail to instructions or, when all else has failed, disciplinary action? Who knows, even promotion (yep, I've seen this as well).
3. Do you think our regulators are happy with errors happening again and again?
4. Do most of your error investigations focus on your people, not the 'system' or working conditions they have to endure?
5. Do you believe there is no such thing as a single 'root cause' to any problem?
6. Does a culture of 'blame' increase the risk of errors and mistakes?
7. Does complexity increase error rates?
8. Do you think most errors are due to systems, procedures and the leadership who created them?
9. Is your training predicated on the belief in 'trained perfectibility'? In other words, once trained you're expected to get it right?
10. Do you think people are naturally error prone and will always make mistakes…and there is nothing you can do about it? I know what my long suffering wife would say.

Now the answers:

Q1. Lots of 'human error deviations'? Answer = Yes

I'm afraid so. In our experience, 'root cause – human error' is the conclusion of convenience for a good few incident reports. Why? Well, it's quick and easy for sure. It also satisfies those who believe in 'The Person Model' of human error. This is the most widely held view that places the origins of mistakes squarely between the ears of people at the sharp end. "The product of forgetfulness, inattention, distraction, ignorance and other wayward mental processes" (Prof. James Reason). The actions that follow usually involve retraining, naming, shaming and writing more procedures. This approach focuses on the person, not the system or environment. Although quick, easy and emotionally satisfying, it is also very wrong. The illusion of control it creates is false and potentially dangerous. More later…

Q2. Lots of checks, retraining and the like? Answer = in our experience Yes

If you focus prevention purely on 'The Person', a few things are guaranteed. The incident will happen again, risk will increase and culture of fear and blame will creep in (the biggest risk of all). Once blame becomes the norm, mistakes get hidden and go unreported. After all, who likes pain and

It is no longer acceptable to blame Human Error for deviations and incidents. For over 3 years the EU GMP regulations have made it very clear (in Chapter 1, 1.4 (xiv)) that an appropriate level of root cause analysis should be applied during the investigation of deviations, and that where human error is suspected or identified as the cause, this must be justified having ensured that system- based problems have not been overlooked.

The message is simple, do not blame human error for deviations and do not assign CAPAs that state "the operator was retrained" as you will have failed to identified the root cause and your CAPA will be totally ineffective. The regulatory inspectors know this, does your company?

In this paper Martin Lush provides a simple quiz that is a highly effective diagnostic to use in your organization to determine if it really understands the issues around 'Human Error' and if so, what to do about them.

embarrassment? As soon as 'error' becomes a dirty word, you're on the slippery slope to a potential crisis. It's not if, more like when. Few set out to create a blame culture (why would you?) but it can creep in unnoticed. Poor key performance indicators (KPIs), ineffective communication, invisible shop floor management all help 'blame' to sneak in.

Q3. Are regulators happy? Answer = emphatically No

Regulators, many of whom have attended our course Human Error Prevention, want you to fix problems and minimise risk. Not treat the symptoms and move on. An increasing number of companies have been cited for poor investigations and repeat incidents. If you've concluded 'root cause – human error', you had better have a good reason. If you have lots of human error deviations, you deserve the criticism and 483s coming your way. As one inspector said to me recently "it seems we're more concerned about the increased risk than they are".

Q4. Investigations focus on people? Answer = in our experience Yes

A recent report from the highly respected Institute of Medicine endorsed the opposite approach to 'The Person Model'. Namely, 'The System Model' approach to error investigations. The premise here is that humans are fallible and that errors are to be expected. Even in the best organisations. Errors are seen as the consequence not the cause. The starting point of any investigation. Rarely its conclusion. The 'System' approach to investigations is adopted by those companies serious about removing the real 'error traps' that management unintentionally set by introducing complexity, poor communication, inappropriate KPIs, selecting suppliers on price alone…the list is endless. Ironically, many of these exist in your quality system which is meant to protect your patients and your legacy. Not increase error risk.

Q5. Root cause: Answer = there is no such thing as 'Root Cause'!

Every mistake, big and small, is always due to multiple contributing factors that all come together to form the 'error chain'. When investigating errors, you must dig below the surface to discover, and remove, the many contributing factors that exist. So, think error chain and multiple causes and ban the term 'root cause' for ever. It's a myth.

Q6. Does a blame culture make a difference? Answer = you bet

We humans are really quite simple creatures. Part of our makeup is to feel liked, respected and safe. When criticised, named, shamed and blamed we are conditioned to either fight or run away. Both career limiting. In a blame culture, there are a few other options to help avoid the pain and ignominy of criticism. Just say nothing or tell management only the good news or just hide problems that could be painful. All perfectly understandable really. Leaders are the architects of company culture and it is their job is to create one that allows problems to be raised, discussed and solved…without fear.

Q7. Do complexity and error go hand in hand? Answer = 100% Yes

Our 21st century brains are virtually identical to those of our ancestors. All they had to worry about was staying alive and reproducing. They didn't have to endure complex standard operating procedures (SOPs), overcomplicated batch records or operating processes that require multi-tasking which, by the way, is a neurological impossibility. As complexity increases, so does confusion, followed by errors. Want to reduce error rate? Just strip out complexity. Want to know how?...just carry on reading.

Q8. Do 'systems' create most errors? Answer: Yes

SOPs with just words, batch records with multiple checks, ineffective training, poor change control, overreliance on contractors, 12-hour shifts, a 20-page SOP for deviation investigations are all examples of 'error traps' set by leadership, albeit unintentionally. I could have gone on…my list of system 'error traps' reads like 'War and Peace'. Want to know how to find these and fix them? Read on…

Q9. Once trained, do you expect people to get it right? Answer = ermm…

We all know the correct answer is No. Training alone doesn't work. However, its effectiveness can be dramatically improved by taking the 10/20/70 approach and by focusing on the 'habit loop'. More later…

Q10. Should we just accept that people will always make mistakes? Answer = no, not really

We all make mistakes and there is little we can do to change the neurological processes that created them. However, we can change the environment, the error 'catalysts'. We can adopt good user centred design, wage war on complexity, put supervisors back on the line, fix the blame culture, remove the term 'root cause' and invest in education not training. The key to it all is to focus on the system not the person. Vital to error reduction is getting leadership connected and visible to the shop floor. Maybe, then, they wouldn't set so many 'error traps'.

Continued on page 8

New EMA draft guideline on sterilisation of the medicinal product

by Tim Sandle

Importance of sterile medicinal products

By 'sterile products', this is taken to include the preparation of terminally sterilised products and the aseptic preparation of products through sterile filling. The distinction here is that some products can be terminally sterilised in their final container while others cannot and need to rely on pre-sterilisation of the components and bulk product before being aseptically filled within a cleanroom.

Although the terms 'sterile manufacture' or 'aseptic manufacturing' are widespread, there is no generic approach to the manufacturing of sterile products. Each plant or process will differ in relation to the technologies, products and process steps. Some processes, for example, use terminal sterilisation which has one level of risk; other processes involve filling aseptic products which has an arguably higher level of risk. The new guidance attempts to contextualise these risks and provide the latest regulatory thinking in relation to product safety.

With the concept of sterility, this cannot be proven through testing (the weaknesses of the sterility test are well established); sterility assurance is a factor of a well-maintained and in-control manufacturing operation, including the following.

- The bioburden of the formulation components.
- The sterilisation procedure (or aseptic processing, using satisfactory aseptic techniques).
- The integrity of the container closure system.

European regulations

The existing European regulatory guidance for sterile products is based on European Commission Directive 2003/94/EC, which describes principles and guidelines of good manufacturing practice (GMP) with respect to medicinal products for human use and investigational medicinal products for human use. European GMP is set-out within EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4: EU Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use. Annex 1[2]. Annex 1 is currently under review – a process for which a concept paper has been produced[3].

In addition, to support Annex 1, there is a document pertaining to pre-sterilisation bioburden[4]; and one which provides the decision tree for selecting terminal sterilisation or aseptic filling[5]. The new draft document sets out to replace these two documents, unifying the content and adding additional material.

The difference between the new document and Annex 1 is that the new guideline focuses on actions to consider when establishing a new product, including what is required for licence submission, and for modifying processes; whereas Annex 1 focuses on maintaining compliance.

Given the importance of sterile products, in providing both a therapeutic medicine and with regards to the necessity of being free from viable microorganisms, pyrogenic substances and visible particulates, no new guidance has been issued by a regulatory authority in recent years. This has changed with a new draft guidance document from the European Medicines Agency. Issued in April 2016 for public comment, the document is titled *Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container*[1]. The key points are reviewed in this article.

Key points from the draft guidance

The most important points raised in the new guidance are as follows.

Sterilisation method

As with the previous guidance, terminal sterilisation remains the process of choice for sterile products. Aseptic processing should only be followed if it can be demonstrated that any conventional sterilisation process would destroy, or render ineffective, the medicinal product.

The guidance also reiterates that the sterility assurance level is applicable to terminally sterilised products, and that it is not applicable to aseptic processing.

Microbial control

The document stresses the importance of microbial control during processing. The main risk highlighted is levels of bacterial endotoxin in the finished product. With bioburden, emphasis is placed on filter validation and demonstration that the final filter used can remove a 'high' bioburden.

Steam sterilisation

With steam sterilisation, the draft guidance states that an F0 ≥8 minutes is required for all steam sterilisation processes. The F0 concept concerns equivalent lethality. An F0 of 8 minutes means that the process being conducted at whatever temperature (T°C) and time (minutes) is equivalent in terms of its lethality to 8 minutes at 121°C. This could be a higher

temperature than 121°C for a shorter time, or a lower temperature than 121°C for a longer time.

To support a case for steam sterilisation, the following data needs to be compiled.

- Load mapping distribution (cold spots) – summary or confirmation of performance.
- Physical and biological cycle effect confirmation summary of at least three autoclave runs ensuring:
  - Sufficient time at or above nominal temperature in the whole autoclave.
  - Acceptable temperature differences between thermocouples in the load.
  - Acceptable F0 variability within the load.
  - Relationship between physical and biological validation.

An assessment of pre-sterilisation bioburden is also required, up to a maximum of 100 colony forming units (CFU) per 100mL (or equivalent).

Dry heat sterilisation

The requirements for dry heat sterilisation are similar (in that both steam sterilisation and dry heat sterilisation require a sterility assurance level of 10-6). The requirements for process description and validation are also similar.

- Load mapping distribution (cold spots) – summary or confirmation of performance.
- Physical and biological cycle effect confirmation summary of at least three sterilisation runs ensuring:
  - Sufficient time at or above nominal temperature in the whole dry heat sterilisation cabinet.
  - Acceptable temperature differences between thermocouples in the load.
  - Acceptable lethality variability within the load.
  - Relationship between physical and biological validation.

Sterile filtration

With sterile filtration, the specification given is for a filter with a pore size of 0.22µm or less, which is consistent with previous guidance. New information is provided about the point of filtration being located as close as possible to filling and that this should take place at the end of any hold time (with the aim of ensuring the tested bulk is representative).

A further change is in the bioburden limit. Since the mid-1990s, the bioburden limit has been not more than 10 CFU/100mL. The draft text now reads "bioburden limit of higher than 10 CFU/100mL before pre-filtration may be acceptable". This is based on data relating to product bioburden.

The terminology for the bioburden test is now described as "Total Aerobic Microbial Count", which is consistent with the terminology used for testing non-sterile products in the European Pharmacopoeia. This replaces the "Total Viable Aerobic Count", which is sometimes used. Interestingly, a specific agar is referred to for the test: casein soya bean digest agar (which is the non-commercial name for tryptone soyabean agar).

A key point is made regarding filter validation. Here, it states that the filter validation must have considered the total filtration time, and demonstrate suitable bacterial retention.

Other forms of sterilisation

The draft guidance makes reference to ionising radiation, although this is short on detail and the reader is directed towards ISO standards (such as EN/ISO 11137: Sterilisation of Health Care Products – Radiation). More detail is provided in relation to gassing. Here, it is emphasised that sterilisation by gas is limited to surface sterilisation only. Key requisites are as follows.

- Understanding the product bioburden prior to sterilisation.
- The time of exposure to the gas.
- The temperature and humidity prior to and during each step of the sterilisation cycle.
- Conditions for the removal of any toxic gas residues.

With the latter point, a caution is made about the toxicity of ethylene oxide.

For any other type of sterilisation method, not described in the draft guidance, these can be considered. However, scientific advice must be sought.

Depyrogenation

The guidance references the minimum temperature for depyrogenation by dry heat as at or above 220oC, with the requirement to demonstrate a three-log reduction of endotoxin. This is different from earlier descriptions of depyrogenation, which place the threshold at 180oC (albeit for a longer run time).

Aseptic processing

With aseptic processing, the draft guidance highlights two points of contamination concern: product hold time and process run time. Concerns are raised about processes

running for 24 hours or more, and there is a requirement that process simulations (media trials) are used to justify aseptic filling run times.

Other points covered

The guidance provides a revised series of decision trees for the sterilisation of aqueous products and non-aqueous liquid, semi-solid or dry powder products. These are designed to help the pharmaceutical manufacturer select between terminal sterilisation methods and aseptic processing.

Summary

The new document provides greater clarification on European regulatory thinking in relation to sterile products manufacture and simplifies access through bringing two existing documents together.

Overall, there is little of controversy; although the issue with the pre-final filtration bioburden being extended to a value about 10 CFU/100mL (when justified) may lead to a debate about microbial controls during manufacturing. A second point of discussion could revolve around media fills and run times. It is often unclear how long media fills should be. With things not covered, environmental monitoring – the key measure of environmental control for aseptic processing – is consciously absent, along with cleanrooms and manufacturing environments.

Nevertheless, the document does help to clarify the licence submission requirements in relation to sterilisation methods. Comments close in October 2016 and the finalised document is expected early into 2017.

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Human error: don't blame people

continued from page 5

Now for your 'Six to Fix'

- Ban the term 'root cause'. It's a myth. Focus on removing the multiple factors that accompany every error or mistake. Break the error chain.
- Make sure your investigation focuses on 'The System', not 'The Person'.
- Remove blame and you will be fine. Don't and you won't.
- If you haven't started your war on complexity already, start now. You can't afford to lose it.
- Get your leadership on the shop floor. You can't afford anymore error traps.

Martin Lush is the President of NSF Pharma Biotech Consulting. He has over 30 years' experience in the pharmaceutical and healthcare industry. He has held senior management positions in quality assurance, manufacturing, quality control and supply chain auditing and has conducted audits and education programs for many hundreds of companies in over 25 countries.

Counterfeit drugs and product serialisation – an overview of serialisation requirements

by Andrew Love and Stephen McIndoe

Serialisation legislation requires that every product pack is uniquely identified and registered in an external agency database, together with information about the product contained in the pack. Depending on the particular legislation, it may also be necessary to update the external agency database with product movement and change of ownership information, a significantly more complex requirement.

Whilst some pharmaceutical companies understand this legislation and have a clear strategy and program of capability implementation under way, others do not.

As discussed in our previous article on the threat of counterfeit drugs, pharmaceutical product serialisation legislation is being developed and approved across the world to ensure patient safety and prevent fraud. Achieving this across the supply chain is a major and very costly undertaking. Failure to comply with these legislative requirements will mean that pharmaceutical companies will not be able to sell products in the affected markets.

Unique identification

Firstly, let's look at the basics of serialisation. To help explain this, we will break serialisation legislative requirements down into four elements.

1. Unique identification.
2. Product information notification.
3. Authentication.
4. Track & trace.

1. Unique identification

All serialisation legislation requires one or more levels of packaging to be uniquely identified with some form of "licence plate" or serial number. Furthermore, in all recent legislation, this identification must be applied to packaging using some form of machine-readable carrier.

In current legislation, the lowest level of packaging requiring serialisation is the smallest saleable unit, typically the secondary pack. As will be discussed later, some legislation also requires higher levels of packaging and shippers to be serialised as well.

Ultimately, serialisation of primary packaging (e.g. blister pockets, vials) and in some cases (e.g. tablets) the product itself may be required, as many would argue that this provides the best protection to the patient. Whist some regulators are discussing this, few are indicating imminent legislation.

There are broadly two approaches to ensuring that serial numbers are unique that are currently adopted by legislation, market uniqueness and product uniqueness.

Market uniqueness

In this model, an external agency manages all serial numbers for a particular market or region. They issue serial number blocks to manufacturers (and potentially other supply chain partners), who would then manage the application of those numbers to product packaging.

UNIQUE IDENTIFICATION = UNIQUE NUMBER ISSUED BY EXTERNAL AGENCY

In this model, a manufacturer will typically require a serial number [request and allocation management system] to ensure that enough serial numbers are available in the right locations to enable manufacture.

Product uniqueness

An alternative model uses a combination of product code and serial number to achieve uniqueness.

UNIQUE IDENTIFICATION = PRODUCT CODE + SERIAL NUMBER

Product codes, such as the internationally recognised Global Trade Identifier Number (GTIN) are unique. Therefore, in this type of scheme, the uniqueness of serial numbers need only be managed across all product of the same product code.

Given that product codes are normally unique to a single manufacturer, the management of serial numbers for a product can then become the entire responsibility of the individual manufacturer. Typically this simplifies matters as it is not necessary to ask an external agency for groups of serial numbers and it offers the opportunity for simpler rules-based serial number allocation and management to individual manufacturing facilities.

Having established which packaging levels need to be serialised and the method of creating and managing unique identifiers or serial numbers, we will now discuss the information that needs to be applied to the packaging and the mechanism by which this is achieved.

Information applied to packaging

Often, the information required to be applied to the packaging is not limited to the unique identifier or serial number described above. Frequently, additional information,

such as [Batch/Lot Identifier] and [Expiry Date] are also required to be included in the machine readable carrier. Often, if not already present, text describing this information must also be applied to the packaging.

This additional information allows people in the downstream supply chain to make use of the information to improve the efficiency and effectiveness of their processes without the need to obtain information from any other source.

As an example, dispensaries can scan the machine readable carrier, obtain information about the product contained within the carrier and compare this electronically with the prescription to help reduce dispensing errors.

Machine-readable carriers

There are many different ways in which information can be placed on a pack in order that it is machine readable.

Where serialisation legislation is concerned, two methods are typically currently mandated: linear barcodes and/or 2D/Datamatrix barcodes. Radio Frequency Identification (RFID) tags have also been extensively discussed, but at the time of writing had not been mandated.

2. Product information notification

Typically, once product packaging of one or more levels has been uniquely identified, this information, together with other information related to the product and manufacturer is passed to an external agency database.

The information in this database is then used by the downstream supply chain and other agencies as described later in this series.

The triggers and grouping of the information transfers will vary according to the specific requirements of the legislation and the local business processes. In the simplest of models, the information can be transferred at, or around the time when the product packaging batch has been completed.

3. Authentication

Authentication is a term often used to describe the following process of checking the legitimacy of a product using its serialisation.

One of the primary purposes of serialisation is to enable individuals in the downstream supply chain to scan a product and compare the information on the product packaging with the information stored in the external agency's database. If the two sets of information match and it is evident that the product has not been tampered with, then it will be highly likely that that the product is legitimate.

As an example, a patient might scan a product pack with a smart phone using its in-built camera. Using an application, the smart phone would then request information related to the unique identifier contained in the machine readable code and display it to the patient. The patient would then compare this information to the information contained on the packaging. If everything matched and the tamper evident sealing was still intact, the patient could have greater confidence that the product was legitimate.

A number of serialisation legislative models stop at the requirement for a means of authentication. It appears that the recent European Union falsified medicines legislation 2011/62/EU is one such example. Many would argue that this level of serialisation provides an improved level of protection against falsified products and fraud that is sufficient, at least for the current round of legislation.

4. Track & trace

Track and trace legislative models attempt to further improve the protection against the entry of falsified medicines into the legitimate supply chain.

Typically, this is achieved by also requiring every change of ownership (and potentially location) of product to be recorded in the external agency database. Such legislation then also requires purchasers to verify the legitimacy of the product they are receiving by ensuring that the external agency database confirms that the seller had legitimate ownership of the product prior to sale. Rules are also required in the external agency database to ensure that the same product was not introduced illegitimately into the supply chain, or sold more than once from any single owner.

This is a similar model to that used in many countries to control the legitimate buying and selling of motor vehicles, which also present a significant threat to the health and safety of the public if they are not legitimate. Many such models adhere to the following basic principles. Each car is identified by a unique licence plate. When a seller sells a motor vehicle, they have to complete a sales transaction which is registered in the transport agency's database stating which vehicle (licence plate) they have sold and to whom. When a buyer purchases the motor vehicle, they register their ownership with the same agency and indicate who they purchased the vehicle (licence plate) from. The external agency database also contains other information that helps confirm the identity of the vehicle to anyone concerned, such as make, model, colour. This information is also used by buyers and sellers to confirm the legitimate identity of individual vehicles. If the sale and purchase information matches then all is ok. If not, then investigation activity is triggered.

These additional track & trace requirements necessitate two very significant additional elements to be implemented over and above the authentication serialisation model.

1. Many, if not all, supply chain nodes handling product will need to be equipped to scan product and relate the unique identifier information to purchase, sales and other transactions and then communicate it to the external agency database. If they break product shippers down, they may also be required to serialise new shippers.
2. To make (1) practical, many if not all levels of packaging shippers (e.g. bundles, cases and pallets) need to be serialised, and the physical relationship between a shipper and its serialised contents built, communicated and maintained in the external agency's database.

Element (1) is required to track the purchase and sales transactions down to the individual uniquely identified pack. For example, whenever a sale is made, all products which are physically changing ownership would need to be identified and the associated sale information updated in the external agency database. This requires the location in the supply chain handling the product at the point of sale to physically identify all the product being sold, down to its unique identifier. This is normally achieved by incorporating serialisation technology into the order processing and picking activities at a distribution location.

Element (2) is required to avoid the need for every such distribution location to break open all shippers and identify all uniquely identified packages within. A situation which would quickly bring the product supply chain to an effective halt.

This completes the second article in this series. In the next article we will look at standards, opportunities presented by serialisation beyond legislative compliance, and what you would need to do to comply with the legislation.

Stephen McIndoe is a Vice President at Be4ward and works with global healthcare companies to create award-winning world class packaging labelling and artwork capabilities. He is also co-author, with his colleague Andrew Love, of the book Developing and Sustaining Excellent Packaging Labelling and Artwork Capabilities .

Andrew Love is also a Vice President at Be4ward. He was previously Head of Global Packaging Design at GlaxoSmithKline.

by Malcolm Holmes

Introduction

Within this summary, readers will note an example of a USA compounding company refusing to cease steriles manufacture and perform a recall despite Food and drug administration (FDA) "advice" to do so. There is also a letter from the Medicines and Healthcare Products Regulatory agency (MHRA) to a UK newspaper indicating that a recently published article is misleading and could lead to an increase in concern amongst healthcare professionals and patients. Developments in the "regulation" of the pharmaceutical industry since our last review include the following.

Europe

European Medicines Agency (EMA)

Improving safety of first-in-human clinical trials

The EMA has started a review of the guidelines that describe first-in-human clinical trials and the data needed to enable their appropriate design and allow initiation. This is being done in cooperation with the European Commission and the Member States of the European Union (EU). The review will identify which areas may need to be revised in light of the tragic incident which took place during a Phase I first-in-human clincial trial in Rennes, France in January 2016. The trial led to the death of one participant and hospitalisation of five others.

The aim of the review is to agree a concept paper by July 2016 identifying areas for change and proposals to further minimise the risk of similar accidents. The concept paper will form the basis for an EU-wide review of the guidelines. This process will include targeted discussions with stakeholders and a public consultation on proposed changes later in 2016.

EU Good Manufacturing Practice (GMP) Q&A – data required for sterilisation processes of primary packaging materials subsequently used in an aseptic manufacturing process.

Terminal sterilisation of the primary packaging, used subsequently during aseptic processing of the finished product, is a critical process and the sterility of the primary container is a critical quality attribute to ensure the sterility of the finished product. Both need to be assured for compliance with relevant pharmacopoeial requirements for the finished product and product approval.

The site where sterilisation of the packaging materials takes place may not have undergone inspection by an EU authority and consequently may not hold an EU GMP certificate in relation to this activity.

When GMP certification is not available, certification that the sterilisation has been conducted and validated in accordance with specific International Organization for Standardization (ISO) standards would be considered to provide an acceptable level of sterility assurance for the empty primary container.

Eudralex Volume 3 Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container

This draft guideline, which is open for comment until 13 October 2016, provides guidance on the documentation expected for sterile products in the quality dossier for a marketing authorisation application or a variation application for a medicinal product (called quality dossier throughout the guideline), and the selection of appropriate methods of sterilisation for sterile products.

Although, terminal sterilisation using a reference condition of the European Pharmacopoeia (Ph. Eur.) is the method of choice whenever possible, this guideline provides information on when other terminal sterilisation processes, sterilising filtration or aseptic processing (either alone or when combined with an additional terminal microbial reduction process), could be accepted as an alternative to a reference terminal sterilisation process.

This guideline replaces the previous Annexes to pharmaceutical development decision trees for the selection of sterilisation methods (human and veterinary). In addition, the information on methods of sterilisation previously described in note for guidance on manufacture of the finished dosage form (human and veterinary) has been revised and included in this guideline.

Implementation plan for the introduction of the safety features on the packaging of centrally authorised medicinal products for human use

Certain aspects of the implementation of the Falsified Medicines Directive (Directive 2011/62/EU FMD) and the new delegated act on the safety features (Commission Delegated Regulation (EU) 2016/161 – "the Delegated Regulation") may impact on the product information and the marketing authorisation dossier; in particular, the placing of safety features, a unique identifier (UI) carried by a 2-D barcode and an anti-tampering device (ATD), on the packaging of prescription medicines and certain non-prescription medicines for the purposes of authentication and identification.

The EMA and the European Commission have prepared this implementation plan to guide applicants and Marketing Authorisation Holders (MAHs) through the regulatory changes necessary to accommodate the new legislative requirements. The EMA and the Quality Review of Documents

Group (QRD) have revised the Human Product Information templates. The updated QRD template will facilitate the implementation of the relevant standard statements on the UI and its carrier under Sections 17 and 18 of Annex IIIA, in order for the MAHs to implement the safety features by 9 February 2019 as required by the Delegated Regulation.

The inclusion of the safety features standard statements under Sections 17 and 18 of Annex IIIA does not indicate that the safety features have been actually implemented on the packaging placed on the market, but rather that the product information has been updated to confirm that the safety features will be implemented on the marketed packaging in line with the provisions of the Delegated Regulation (i.e. by 9 February 2019). The implementation of the ATD is not expected to impact the product information. However, when the ATD is placed on the immediate packaging because there is no outer packaging, certain section(s) of the marketing authorisation dossier may be impacted.

European Directorate for the Quality of Medicines (EDQM)

Potential presence of mutagenic alkyl sulfonates in active substances

The last of five general methods, elaborated by the European Pharmacopoeia's Mesilate Working Party, were implemented on 1 April 2016 (Supplement 8.7). This working party had been appointed by the Ph. Eur. Commission in 2008 to assist users in determining mutagenic impurities potentially present in mesilate-, besilate- or tosilate-salts of active substances. In addition to the elaboration of these methods, the Ph. Eur. Commission had also decided to revise the production section of the monographs to inform users of the risk related to the potential presence of such mutagenic impurities.

New Ph. Eur. general chapter on host-cell protein assays

This general chapter provides guidance on the selection, development and validation of a host-cell protein assay and describes specific considerations for process-specific, platform and generic assays.

Survey on microbiological control of tissues

The aim of the survey is to gather information from relevant stakeholders to enable the Ph. Eur. experts in charge of the elaboration of this chapter to have a clear vision on the current situation regarding the characteristics of tissue preparations used in Europe and how they are monitored with regard to microbiological control. *Completing the survey should only take 5–10 minutes and should be done by 2 September 2016.*

MHRA

MHRA Blog

The latest edition of the MHRA Blog covers the following topics.

- Qualification of customers, what wholesalers need to know.
- Manufacture of investigational medicinal products – frequently asked questions.
- Enforcement Group – tackling the illegal trade in medicines.
- Refrigerated medicinal products, part 2: Transportation, packing, temperature management, the use of third party couriers and returns – some things to consider.

(Note: previous topics which may also be of interest are still available on the blog site – MH).

Good Manufacturing Practice and Good Distribution Practice

The MHRA has updated its December 2014 guidance on GMP and GDP and how to prepare for an inspection, which forms part of its guidance on manufacturing, wholesaling, importing and exporting medicines good practice, inspections and enforcement and patient safety.

GDP – Qualification of suppliers – the 3 steps needed to assure supply chain integrity

Recently, the MHRA has had a number of situations where companies have not understood the obligations placed on them by the Human Medicines Regulations 2012 Regulation 44 (2) and (3) and Good Distribution Practice in relation to qualification of suppliers. It has, therefore, published on its blog a reminder to companies of the requirements and gives tips on ways to ensure the system of qualification is robust.

USA

FDA

Manual of Policies and Procedures (MAPP) – Applying ICH Q8(R2), Q9 and Q10 principles to chemistry, manufacturing, and controls (CMC) review

The number of new drug applications (NDAs), investigational new drug applications (INDs), abbreviated new drug applications (ANDAs) and biologics license applications (BLAs) and their supplements containing quality-by-design (QbD) approaches has increased. Because of this increase, the Center recognises the need for reviewers to consistently implement the International Conference on Harmonisation (ICH) guidances in their reviews. As a result Office of

Pharmaceutical Quality (OPQ) product quality reviewers will consider ICH Q8(R2), Q9, and Q10 recommendations when reviewing applications that may or may not include QbD approaches.

Review of grouped product quality supplements

This MAPP outlines the policies and procedures for grouping supplements submitted concurrently that provide for the same CMC changes to multiple approved NDAs, ANDAs and BLAs and are submitted by the same applicant. The goal is to improve efficiency and provide consistency when reviewing these grouped supplements.

- When applicants make identical CMC post-approval changes that affect multiple approved applications, the Center needs procedures for reviewing these groups of supplements. Implementing these procedures helps the OPQ manage the review of these changes in an efficient manner and ensures consistency.
- This MAPP has been revised to replace the term "bundled supplements" with "grouped supplements".
- The previous version of this MAPP applied only to supplements to NDAs/supplements to NDAs. A related MAPP applied only to supplements to ANDAs

Environmental Assessment: Question and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity – Guidance for Industry

This guidance is intended to supplement FDA's guidance for industry on Environmental Assessment of Human Drug and Biologics Applications, issued July 1998 (the EA Guidance), by addressing specific considerations for drugs that have potential estrogenic, androgenic, or thyroid hormone pathway activity (E, A, or T activity) in the environment.

FDA regulations at 21 CFR part 25 specify that EAs must be submitted as part of certain NDAs, ANDAs, BLAs, supplements to such applications, and INDs, as well as for various other actions, unless the action qualifies for a categorical exclusion. Failure to submit either an EA or a claim of categorical exclusion is sufficient grounds for the FDA to refuse to file or approve an application (21 CFR 25.15(a), 314.101(d)(4), and 601.2(a) and (c)).

This guidance focuses on the categorical exclusion for actions on NDAs and NDA supplements that would increase the use of an active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment would be below 1 part per billion. Although an action that qualifies for this exclusion ordinarily does not require an EA, the FDA will require "at least an EA" if "extraordinary circumstances" indicate that the specific proposed action (e.g. the approval of the NDA) may significantly affect the quality of the human environment.

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products

This draft guidance is intended to assist a potential applicant who plans to develop and submit an ANDA to seek approval of a generic version of a solid oral opioid drug product that has the potential for abuse and which references an opioid drug product with abuse-deterrent properties described in its labelling. The guidance recommends studies, including comparative in vitro studies, should be conducted by the potential ANDA applicant and submitted to the FDA in an ANDA to demonstrate that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug with respect to all potential routes of abuse.

Labeling for Biosimilar Products

This draft guidance is intended to assist applicants in developing draft labelling for submission in applications for proposed biosimilar products under Section 351(k) of the PHS Act (42 U.S.C. 262(k)). The recommendations for prescription drug labelling in this guidance pertain only to the prescribing information (commonly referred to as the package insert), except for recommendations in Section V pertaining to FDA-approved patient labelling (e.g. Patient Information, Medication Guide, and Instructions for Use). Specific labelling recommendations for interchangeable biological products are not provided.

To meet the standard for interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see Section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider (see Section 351(i)(3) of the PHS Act). An application submitted under Section 351(k) of the PHS Act must contain, among other things, information demonstrating that "the biological product is biosimilar to a reference product" based upon data derived from the following.

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.
- Animal studies (including the assessment of toxicity).
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

The FDA has the discretion to determine that an element described above is unnecessary in a 351(k) 72 application. Under FDA regulations, prescription drug labelling must provide adequate information to enable healthcare practitioners to use the drug safely and for the purposes for which it is intended, and to this end the approved prescribing information summarises the essential scientific information needed by healthcare practitioners for the safe and effective use of a drug. This labelling reflects the FDA's finding of safety and effectiveness for the drug under the labelled conditions of use and facilitates prescribing decisions, thereby enabling the safe and effective use of drugs (including biological products) and reducing the likelihood of medication errors.

Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products – Guidance for Industry

The FDA has issued new guidance for immediate implementation providing recommendations to reduce the potential transmission risk of Zika virus from human cells, tissues, and cellular and tissue-based products (HCT/Ps). The guidance addresses donation of HCT/Ps from both living and deceased donors, including donors of umbilical cord blood, placenta, or other gestational tissues.

Safety Considerations for Product Design to Minimize Medication Errors – Guidance for Industry

This guidance focuses on minimising risks associated with the design of the drug product and its container closure system, and is the first in a series of three planned guidances to minimise or eliminate hazards contributing to medication errors at the product design stage. The second guidance focuses on minimising risks associated with the design of drug product container labels and carton labelling, and the third focuses on minimising risks when developing and selecting proposed proprietary names.

To avoid safety issues and costly redesigns after a product enters the market, it is important to consider the end user(s) in their environments of use early in the development and design of a drug product. The FDA recommends the use of risk assessments early and throughout the development and design of a drug product. Identification of clinically relevant characteristics of the drug product during development will highlight potential areas for risk assessment. Risk assessments also are valuable for identifying potential medication errors that may result from post-marketing changes or additions to an already marketed drug product throughout its lifecycle.

Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information

This draft guidance provides recommendations to holders of applications for human drugs and biologics on implementing a CMC post-approval change through the use of a comparability protocol. It replaces the draft guidance that was published in February 2003. This guidance is intended to establish a framework to promote continuous improvement in the manufacturing of quality products by encouraging applicants to employ the following.

- Effective use of knowledge and understanding of the product and manufacturing process.
- A robust control strategy.
- Risk management activities over a product's lifecycle.
- An effective pharmaceutical quality system.

Contents of a Complete Submission for the Evaluation of Proprietary Names – Guidance for Industry

This guidance describes for industry the information that the FDA uses to evaluate proposed proprietary names for certain drugs, including biological products, under the traditional review process within the time frames set out in the Prescription Drug User Fee Act (PDUFA IV) performance goals. The review clock for the performance review goals begins when the Agency receives a complete submission.

Accurate identification of medications is critical to preventing medication errors and potential harm to the public. This guidance is intended to assist industry in the submission of a complete package of information that the FDA will use in the assessment of:

- the safety aspects of a proposed proprietary name to reduce medication errors, and

- promotional implications of a proposed proprietary name, to ensure compliance with other requirements for labelling and promotion using the FDA's traditional review methods.

As part of its premarket review of products that are the subject of an NDA, BLA or ANDA, the FDA evaluates both safety and promotional aspects of the product's proposed proprietary name. For tools and methods the FDA uses for its analysis, see the FDA concept paper entitled "PDUFA Pilot Project Proprietary Name Review".

Data Integrity and Compliance with CGMP

The purpose of this draft guidance is to clarify the role of data integrity in current good manufacturing practice (CGMP) for drugs, as required n 21 CFR parts 210, 211, and 212.

In recent years, the FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of the industry's responsibility to ensure the safety, efficacy and quality of drugs. These data integrity-related CGMP violations have led to numerous regulatory actions, including warning letters, import alerts and consent decrees. This draft guidance contains a set of Q&As clarifying the FDAs requirements.

FDA alerts healthcare professionals not to use sterile drug products from Pharmakon Pharmaceuticals, Inc., Noblesville, Indiana

The FDA is alerting healthcare professionals not to use any drug products that are intended to be sterile and are produced and distributed nationwide by Pharmakon Pharmaceuticals, Inc. in Noblesville, Indiana, due to a lack of sterility assurance and other quality issues.

The FDA recently inspected Pharmakon's facility following the company's voluntary recall of super-potent morphine sulfate 0.5mg/mL preservative free in 0.9% sodium chloride, 1mL syringe, for intravenous use. The FDA test results showed the product to be nearly 2500 percent the labelled potency. During the inspection, investigators observed insanitary conditions, including poor sterile production practices, and other deficiencies, which raise concerns about Pharmakon's ability to assure the sterility and quality of drug products that it produces. Additionally, FDA testing confirmed environmental contamination on multiple sites within the cleanrooms, including the critical ISO-5 area.

The FDA recommended that Pharmakon cease sterile operations until appropriate corrective actions have been implemented by the facility and recall all non-expired drug products that are intended to be sterile. ***However, Pharmakon informed the FDA that it would neither initiate a recall nor cease sterile production.***

Pharmaceutical distribution supply chain pilot projects; request for information

The FDA is soliciting information regarding issues related to utilising the product identifier for product tracing, improving the technical capabilities of the supply chain, and identifying system attributes that are necessary to implement the requirements established under the Drug Supply Chain Security Act (DSCSA). The information gathered from public comments will assist with the design and development of the pilot project(s) that the FDA establishes under the DSCSA.

Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act

The FDA has received questions from outsourcing facilities and other stakeholders about the meaning of this term, such as whether multiple suites used for compounding human drugs at a single street address constitute one or multiple facilities, or whether a single location where human drugs are compounded can be subdivided into separate operations compounding under different standards. The FDA is issuing this draft guidance to answer these questions

Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act

This draft guidance describes the FDA's proposed policies concerning certain prescription requirements for compounding human drug products for identified individual patients under Section 503A of the FD&C Act. It addresses compounding after the receipt of a prescription for an identified individual patient, compounding before the receipt of a prescription for an identified individual patient (anticipatory compounding), and compounding for office use (or "office stock").

Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act

Pharmacies located within a hospital or standalone pharmacies that are part of a health system frequently provide compounded drug products for administration within the hospital or health system. Some of these compounders have registered with the FDA as outsourcing facilities under Section 503B of the FD&C Act and others are state-licensed pharmacies subject to Section 503A. This draft guidance describes how the FDA intends to apply Section 503A of the FD&C Act to drugs compounded in state-licensed hospital or health system pharmacies for use within the hospital or health system.

FDA approves a second biosimilar

The FDA has approved Inflectra (infliximab-dyyb) for multiple indications. Inflectra is administered by intravenous infusion. This is the second biosimilar approved by the FDA. Inflectra is biosimilar to Janssen Biotech, Inc.'s Remicade (infliximab), which was originally licensed in 1998.

International

Canada

Post-Notice of Compliance (NOC) Changes

This guidance document applies to sponsors intending to make changes to new drugs that have received a NOC pursuant to Section C.08.004 of the Food and Drug Regulations. This may include pharmaceuticals, biologics and radiopharmaceuticals for human use and pharmaceutical, radiopharmaceutical and certain biotechnological products for veterinary use. In the absence of a guidance specific to quality changes to drugs which were approved through a Drug Identification Application - Biologics (DIN-B drugs), the quality guidance document applies to those products. This guidance also applies to those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold.

China

China Food and Drug Administration requires generics to obtain brand-name drug quality

Pharmaceutical companies have been ordered to make sure the quality and efficacy of their drugs are on par with brand-name drugs, a move that aims to improve the nation's pharma industry.

According to a circular issued by the State Council General Office, generic drugs already available on the market should be assessed on whether they are consistent with brand-name drugs, and if they could be used clinically.

This circular strengthens the previous 2013 requirements for bioequivalence. It now requires bioequivalence to be determined against the brand name version of the generic drug or should this no longer be available then against an imported, globally recognised generic version.

India

Proposal to replace gelatine in capsules

India's Central Drugs Standard Control Organization is requesting comment on a proposal for the above.

Guidelines on similar biologics

The Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India, 2012 are in the process of revision. Stakeholders were requested to submit their suggestions or comments to the Office of Drugs Controller General (India) by 30 April 2016.

Pharmaceutical Inspection Cooperation Scheme (PIC/S)

2016 PIC/S Seminar, Manchester (July 2016)

This seminar *which is open only to member and non-member authorities* of the PIC/S will explore the current landscape with regard to inspection findings and trends, with a particular focus on data integrity issues and then look to see what changes Industry have on the horizon.

PIC/S–PDA API (Q7) Training, Puerto Rico (US), August 2016

Active pharmaceutical ingredient (API) suppliers are subject to regulatory oversight, and need to know what regulators are looking for. ICH Q7 is the international standard that many regulators use to define GMP requirements for APIs. This seminar *which is open to all* offers the opportunity to learn from regulatory and industry experts on how these requirements are being interpreted and enforced. Additionally, there is an evening session on "What is Data Integrity?".

World Health Organisation (WHO)

WHO Technical Report Series, No. 996

WHO Technical Report Series, No. 996 successfully passed the 139th session of the Executive Board on Tuesday 31 May 2016. The following guidelines, as contained in the Annexes to the Expert Committee's fiftieth report, are now recommended for use.

- Annex 1: Good pharmacopoeial practices (new)
- Annex 2: International Pharmaceutical Federation–WHO technical guidelines: points to consider in the provision by healthcare professionals of children-specific preparations that are not available as authorized products (new)
- Annex 3: Guidance on good manufacturing practices for biological products (revision), following its adoption by the Expert Committee on Biological Standardization on 16 October 2015
- Annex 4: Guidance on good manufacturing practices: inspection report, including a model report (revision)
- Annex 5: Guidance on good data and record management practices (new)
- Annex 6: Good trade and distribution practices for pharmaceutical starting materials (revision)
- Annex 7: Guidelines on the conduct of surveys of the quality of medicines (new)

- Annex 8: Collaborative procedure between WHO's Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO prequalified pharmaceutical products and vaccines (revision)
- Annex 9: Guidance for organizations performing in vivo bioequivalence studies (revision)
- Annex 10: WHO general guidance on variations to multisource pharmaceutical products (new).

Supplementary Guidelines on GMP for HVAC Systems for Non-sterile Pharmaceutical Dosage Forms QAS/15.639/rev.1

A copy of this document was released to a restricted audience for comment – MH.

Products

Proposed reduction of use in animals of "last resort antibiotic" colistin to manage risk of resistance

The EMA has launched a public consultation on the advice drafted by its Antimicrobial Advice Ad Hoc Expert Group (AMEG), and endorsed by the Committee for Medicinal Products for Veterinary Use and Committee for Medicinal Products for Human Use, to minimise sales of colistin for use in animals and restrict its use in animals to last resort treatment only. The deadline to provide comments is 26 June 2016.

The new advice is an update to AMEG's 2013 opinion, which was requested by the European Commission following the recent discovery of a new mechanism of resistance in bacteria to colistin (caused by the *mcr*-1 gene), which has the potential for rapid spread. The gene can easily be transferred between different types of bacteria, potentially leading to rapid development of resistance.

Documents

The Responsible Person for GDP – Code of Practice

A Task Force initiated by the European Compliance Academy (ECA) Foundation has developed a guidance document which aims to support responsible persons for GDP. The Code of Practice Version 01 is available on the ECA GDP Group webpage. The document is available at no costs after registration.

Annex 16: Certification by a Qualified Person and Batch Release Q&A

The EU Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use Annex 16 Certification by a Qualified Person and Batch Release was published in October 2015, and came into effect on 15 April 2016. Maas & Peither have published in their GMP Logfile, eight Q&As from an interview by their editor Dr. Sabine Paris with GMP Inspector Dr. Rainer Gnibl of Regierung von Oberbayern, Munich (Government of Upper Bavaria , Munich). These Q&As make interesting reading, they cover topics relating to:

- clarity of the Annex,
- globalisation of the supply chain,
- third party audits,
- imports from third countries,
- parallel imports/distribution,
- unexpected deviations.

Can regulators influence the affordability of medicines?

The growing problem of high medicine prices and its impact on the sustainability of healthcare systems is getting more and more attention in many countries around the globe. Regulators are willing to play their part in solving the problem and in facilitating continued access to patients of safe and effective medicines. In an article recently published in the New England Journal of Medicine, two representatives of the EMA, i.e. the Executive Director and Senior Medical Officer, as well as heads of two national agencies discuss possible regulatory interventions. Even though the pricing of medicines is clearly out of their remit, medicine regulators cannot ignore the current debate on the cost of medicines and can make a contribution to affordable care, explain the authors.

Guide to Information on Human Medicines Evaluated by EMA

The EMA publishes information on human medicinal products at various stages of their life cycles, from the early developmental stages through to the EMA's evaluation of authorisation applications, post-authorisation changes, safety reviews and withdrawals of authorisation. This guide describes the different types of information the Agency currently publishes for both centrally and non-centrally authorised medicines, as well as publication times and location on the EMA's website. It aims to help stakeholders know what kind of information to expect on medicines undergoing evaluations and other regulatory procedures.

Further information on these and other topics can be found in recent versions of the "GMP Review News" circulated to subscribers by Euromed Communications and on the websites of the relevant regulatory bodies and international organisations. In addition a list of useful websites can be obtained from info@euromedcommunications.com

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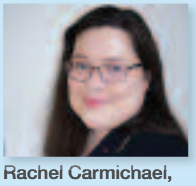
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Events

August 2016

4–6 August 2016 – Manchester, UK
2nd World Congress on Biopolymers
http://biopolymers.conferenceseries.com/

12–13 August 2016 – Toronto, Ontario, Canada
5th International Summit on GMP, GCP & Quality Control
http://gmp-gcp-quality-control.pharmaceuticalconferences.com/

15–16 August 2016 – Toronto, Ontario, Canada
5th International Summit on GMP, GCP & Quality Control
http://gmp-gcp-quality-control.pharmaceuticalconferences.com/

22–24 August 2016 – New Orleans, LA, USA
7th Annual Global Pharma Summit
http://american.pharmaceuticalconferences.com/

22–24 August 2016 – Vienna, Austria
Global Pharmaceutical Industry Summit
http://industry.pharmaceuticalconferences.com/

22–24 August 2016 – New Orleans, LA, USA
7th Annual Global Pharma Summit
http://american.pharmaceuticalconferences.com/

28 August–1 September 2016 – Buenos Aires, Argentina
76th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2016
www.fip.org

September 2016

5–7 September 2016 – Glasgow, UK
APS 7th International PharmSci Conference 2016
www.apsgb.co.uk

5–7 September 2016 – Beijing, China
Drug Formulation & Bioavailability Congress
http://drugformulation-bioavailability.pharmaceuticalconferences.com/

8–9 September 2016 – Washington, DC, USA
World Anti-Microbial Congress US 2016
www.terrapinn.com

12–14 September 2016 – Washington, DC, USA
2016 PDA/FDA Joint Regulatory Conference
www.pda.org

12–14 September 2016 – Berlin, Germany
6th International Conference on Genomics & Pharmacogenomics
http://genomics.conferenceseries.com/

18–21 September 2016 – Atlanta, GA, USA
2016 ISPE Annual Meeting
www.ispe.org

19–21 September 2016 – Vienna, Austria
Global Pharmaceutical Industry Summit
http://industry.pharmaceuticalconferences.com/

27–28 September 2016 – Strasbourg, France
Pharmaceutical Freeze Drying Technology
www.pda.org

28–30 September 2016 – Toronto, Ontario, Canada
6th Pharmacovigilance Congress
http://pharmacovigilancecongress.pharmaceuticalconferences.com/

October 2016

4–6 October 2016 – Barcelona, Spain
CPhI Worldwide
www.cphi.com

10–12 October 2016 – Barcelona, Spain
World Vaccine Congress Europe
www.terrapinn.com

11–12 October 2016 – Amsterdam, The Netherlands
2016 Pharmaceutical Cold & Supply Chain Logistics
www.pda.org

13 October 2016 – London, UK
Quality and stability in the distribution chain
www.jpag.org

13–15 October 2016 – Manchester, UK
2nd World Congress and Exhibition on Antibiotics and Antibiotic Resistance
http://antibiotics.omicsgroup.com/

17–18 October 2016 – Huntington Beach, CA, USA
2016 PDA Universe of Pre-filled Syringes and Injection Devices
www.pda.org

18–20 October 2016 – Berlin, Germany
Global Pharmaceutical Regulatory Affairs Summit
www.informa-ls.com

19–21 October 2016 – Houston,TX, USA
6th International Conference and Exhibition on Biologics and Biosimilars
http://biosimilars-biologics.pharmaceuticalconferences.com/

24–26 October 2016 – Arlington, VA
11th Annual PDA Global Conference on Pharmaceutical Microbiology
www.pda.org

25–26 October 2016 – Berlin, Germany
Visual Inspection Forum
www.pda.org

26–27 October 2016 – Cambridge, UK
BioData World Congress 2016
www.healthnetworkcommunications.com

27–28 October 2016 – Rome, Italy
2nd International Conference and Expo on Drug Discovery & Designing
http://drug-discovery.pharmaceuticalconferences.com/

November 2016

3–4 November 2016 – Washington, DC
2016 PDA Outsourcing/CMO Conference
www.pda.org

7–9 November 2016 – Istanbul, Turkey
2nd International Conference and Expo on Drug Discovery and Designing
http://drug-discovery.pharmaceuticalconferences.com/

7–9 November 2016 – Istanbul, Turkey
2nd International Conference and Expo on Parenterals and Injectables
http://drug-discovery.pharmaceuticalconferences.com/
http://parenterals-injectables.pharmaceuticalconferences.com/