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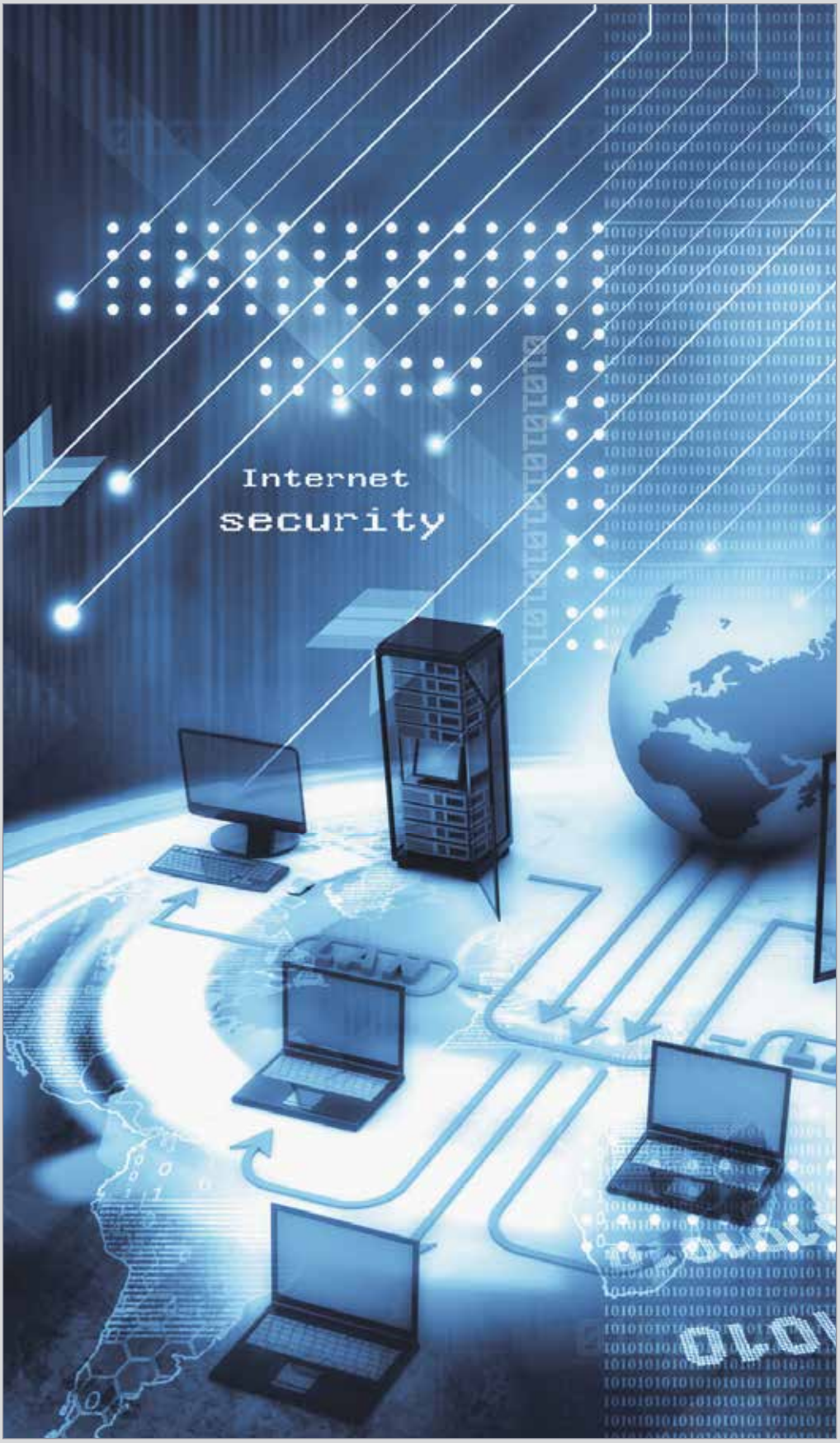

COVER STORY

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Editor‘s Note

Current GMP Trends

Today, modern pharmaceutical production is unthinkable without IT systems. They are involved in almost every GMP process, e.g. in quality control with LIMS systems and computerised systems controlling analytical instruments. The manufacturing area is a complex computerised environment involving PLC, DCS, MES, and even ERP for releasing batches.

Hacker attacks on private individuals or even companies were a rare phenomenon in the past. Today, trojans, viruses and ransomware attack worldwide systems. The "WannaCry" and "NotPetya" cases have raised the threat to companies to a new level. Large pharmaceutical companies were affected. Production processes or batch releases became impossible!

Therefore, this time the cover story addresses the complex problem in detail. Every GMP responsible should ask the question: are my IT systems safe? Who has access to every single IT system? How up-to-date are the software versions? These are just a few questions to be addressed. Nowadays every company should have an action plan. Find out what an expert recommends – in the cover story.

In addition to this story you will find further valuable information regarding other GMP topics in this new issue. This includes the role of the Qualified Person in serialisation as well as technical and regulatory trends and their impact – like the revision of Annex 1 or the new requirements with regard to the production of WFI.

Yours sincerely,
Oliver Schmidt

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Publisher:
CONCEPT HEIDELBERG GmbH
Rischerstraße 8
69123 Heidelberg
HRB Mannheim Nr. 705125

General Manager:
Oliver Schmidt

Chief Editors:
Oliver Schmidt
Wolfgang Heimes

Editors:
Dr Gerhard Becker
Dr Günter Brendelberger
Dr Robert Eicher
Dr Andrea Kühn-Hebecker
Dr Andreas Mangel
Sven Pommeranz
Oliver Schmidt
Wolfgang Schmitt
Axel H. Schroeder

Editors of this Issue:
Dr Robert Eicher
Dr Markus Fido
Dr Afshin Hosseiny
Dr Andreas Mangel
Yves Samson
Axel Schroeder

Graphic Concept:
Wolfgang Heimes

Production:
abcdruck GmbH
Waldhofer Straße 19
69123 Heidelberg

Contact:
info@gmp-compliance.org

Photo on cover/back:
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ECA CORNER
NEWS FROM OUR ASSOCIATION

ECA Foundation www.eca-foundation.org

Foundation
Fostering harmonisation of GMP/GDP regulations

Every quarter the ECA's Interest and Working Groups inform about their accomplishments and current activities. Please read following their report for the third quarter 2017.

Richard M. Bonner (Chairman ECA Foundation & European QP Association)

UPDATES FROM ECA INTEREST GROUPS

Visual Inspection Group
Activities:
- The group meeting has been scheduled to take place from 10-12 October 2017 in Vienna.
- The group's chairman Tobias Posset is now official member of EDQM's Expert Group 12 (Dosage Forms & Methods). Expert Group 12 is responsible for developing the chapters of the European Pharmacopeia on Visual Inspection and Container-/Closure Integrity testing of parenterals.

www.visual-inspection.org

Validation Group
The number of group members rose to 800 in total – adding 71 members.
Activities:
- The new ECA Qualification and Validation Task Force met again in Frankfurt, where a first internal draft of ECA`s Good Practice Guide "Modern Qualification for fast track qualifications" was discussed. At the end of October section 4 "Qualification phases in a timeline" with a high-level model should be drafted by suppliers of the group. The next meeting is planned for 6th November again in Frankfurt.
- A week for a modern ECA Qualification Conference 2018 has been fixed. At this Conference the Good Practice Guide "Modern Qualification" is supposed to be published as official draft.

www.validation-group.org

European QP Association
New record of the number of group members in Q3/2017: more than 2.600 in total.
Activities:
- As in the previous years, the EQPA has received an invitation for this year's IWG Meeting with Interest Groups. Tor Graberg will represent EQPA in London. Suggestions for topics to be covered during the meeting were sent to EMA.
- Update Good Practice Guide: The Good Practice Guide "Duties and Responsibilities for Qualified Persons in the EU" was first developed in 2006 already. It extracts the requirements a QP has to fulfil from the various relevant documents and summarizes them. However, as there are also responsibilities in daily processes as well as requirements for continuous training that are not defined there in detail, the Guide also wants to provide some guidance with recommendations. Now the Good Practice Guide has been updated and is available as Version 4.0 in the members' area on the EQPA website.

www.qp-association.eu

Analytical Quality Control Group
Activities:
- The 2nd AQCG Board Meeting was scheduled on 11 October, where the following main topics were discussed:
  - Further development of the Guideline for "Analytical Procedure Life Cycle".
  - Launch of the Workshop Conference on 23rd & 24th November in Vienna.
  - Update of the ECA AQCG website to be launched in Q4.

Pharmaceutical Microbiology Group
Activities:
- First reviews of the draft guidance document on deviation handling in non sterile manufacturing were received.
- The Annual Board Meeting has been scheduled on 6 November in Neuss, Germany.
- A Microbiology Newsletter was published in September.
- An article focusing on Cleaning and Disinfection Requirements was published in the trade magazine Cleanroom Technology.

www.pharmaceutical-microbiology.org

IT Compliance Group
By now there are 300 members in this Group.
Activities:
- The IT Compliance Group collaborates with the AQC Group (in a Data Integrity Task Force) for version 2 of the Data Integrity Guide. It is supposed to be issued in Q4 2017.
- The group is currently starting the "E-Compliance requirements initiative" and evaluating the subject IT security and potential documents on this subject.

www.it-compliance-group.org

GDP Association
New record of the number of group members end of Q3 2017: close to 1.300.
Activities:
- A new Board Member has been nominated on the industry side: Dr Laura Ribeiro, who is a Responsible Person at ID Logistics (formerly Logiters) in Portugal, has accepted her nomination as the fifth member of the GDP Association's Board.
- On the authority side the Advisory Board also nominated a new member: Emil Schwan accepted the invitation to join. He is Pharmaceutical Inspector at the Drug Inspectorate of the Swedish Medical Products Agency (MPA) and member of the PIC/S Working Group on GDP.
- There are a number of detailed WHO Guidelines on Storage and Transportation. A lot of "supplements" have been published in May 2015. These 16 supplements cover a

continued on back side

Author:

Yves Samson... *founder and director of the consultancy Kereon in Basle, Switzerland. He has over 25 years of experience in qualifying and validating GxP computer systems and IT infrastructure. He is also editor of the French GAMP®4 and GAMP®5. With the e-Compliance Requirements Initiative (ecri.kereon.ch) founded in March 2017 he wants to support the regulated pharmaceutical industry and suppliers in implementing and complying with the e-Compliance requirements.*

COVER STORY

CYBER SECURITY

Is it time to reconsider the IT landscape and the design of industrial computerised equipment?

For the last couple of years, ransomware has been representing a serious and poorly mastered threat for both firms as well as for private people. The recent issues with "WannaCry" showed how real such a menace could be, even if this first global attack[1] had a limited impact because of some malware "design failures". We should be aware, though, that the situation may become worse.

Beyond the particular case of "WannaCry", the current situation of the industrial IT landscape – especially for the computerised equipment like laboratory, manufacturing, and infrastructure equipment – should be seriously reconsidered. The deliberate intention to destroy systems, infrastructure, data, and companies shall be acknowledged rather than underestimated or ignored.

Taking a look at discussion forums, the general trend of the various comments related to "WannaCry" is that such attacks are only possible because of "system administrator laziness and the company stinginess avoiding investment in software updates". Even if, in some cases, this statement could be at least partially correct, the situation is far more complicated than these initial statements, in particular for the regulated pharmaceutical industry and the GxP environment.

Update management

"WannaCry" impacted at first "obsolete" and non-updated operating systems[2]. And the main reason for obsolete operating systems still being in use is the complexity of the computer systems controlling manufacturing and analytical processes and the limitation of software updates for those systems. It is not just the requalification/revalidation effort, but a further significant factor is the multiple compatibility issues between the application and operating system when updates are applied.

Since the early 1990s, Microsoft has been promoting the use of Windows® not only for office purpose but as being an appropriate controlling platform for industrial and process equipment. Various frameworks and services were made available for supporting the implementation of equipment control features.

Implemented natively since Windows® NT4, DCOM – Distributed Component Object Model – has been providing a communication framework supporting application server infrastructure. Such a framework supports, amongst others, the implementation of OPC – OLE[3] for Process Control – used for process automation. However, the "Lovsan" worm contamination during Summer 2003 already showed the vulnerability of process control systems relying on DCOM. The deployment of an operating system patch simply closing communication ports to limit the propagation of "Lovsan" worm caused malfunction of automation systems since these ports are also used by DCOM.

The careless application of Windows® XP Service Pack 2 on PCs controlling laboratory equipment caused multiple serious operation failures in the laboratory environment. The industry and its equipment suppliers had to learn the hard way that uncontrolled changes such as adding operating system patches and service packs could make process control systems and laboratory equipment inoperable.

Such cases caused equipment suppliers to become very restrictive in the way of supporting operating system updates, unfortunately including the virtualisation of applications controlling equipment. Additionally, the legitimate wish to limit support efforts and costs as well as to improve business figures causes that, too often, expensive equipment is not really supported on software level after a few years. Although hardware and mechanics are still supported – including spare parts – the operating system and control software updates are significantly limited. The industry faces the situation that expensive equipment actually representing

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an investment for one to two decades can be operated after few years only with an obsolete software configuration.

The poor maturity of Windows® operating systems since the release of Vista®, and the frequently changing operating system architecture and interface design cause significant development and update costs for each new operating system for the suppliers of equipment and process control applications. This situation explains (but cannot justify) why the industry stuck on Windows® XP so many years long after Microsoft announced support cancelation for Windows® XP. On the other side, the temptation is high for equipment suppliers to cover partially the additional development costs with the sale of new equipment hardware instead of supporting software updates for existing equipment.

The description above is not intended to justify poor business practices but aims to explain the current situation.

IT infrastructure design: robustness vs. bad practices

There are multiple reasons to apply good IT infrastructure and network design practices for ensuring the reliability and the robustness of IT infrastructure and for improving information security; e.g.:

- Network segregation
  - Office network, laboratory network(s), automation networks, administration networks, etc.
- Resilient security concept ensuring a strong protection and confinement of each operation environment
  - For instance, deploying internal firewalls between the laboratory networks or automation networks and the rest of the IT infrastructure.

Today, such design measures do not represent significant additional hardware and software costs. At first, the implementation of such measures requires available subject matter expertise as well as the elaboration of a robust IT infrastructure and IT security concept.

In addition to a robust IT infrastructure design, good IT operation practices must be implemented, e.g.:

- Active network and operation monitoring
  - Multiple monitoring solutions (open source as well as commercial) are available and make possible an active and reliable monitoring of network and IT infrastructure operation. There is no excuse today not to monitor actively IT operations, including active alarming in case of troubles.
  - Monitoring does not only provide a current picture of the IT infrastructure components and networks, but it enables, based on historical data, the comparison of the current situation against previous configuration, and, based on an accurate configuration management, to identify possible deviations and their root causes resulting from updates or scope changes.
- Reliable (and paranoid) data management strategy
  - Virus and ransomware can easily jeopardize the integrity of backup data if those are not adequately protected. It is not acceptable to maintain a permanent on-line access to backup volumes. If users or systems have access to backup data, in case of contamination, a ransomware will be able to access to such backup data as well. At least, backup volumes must be disconnected after the backup has been performed. Better, a central backup application should be deployed for performing backup activities and the backup data should be stored in a dedicated part of the IT infrastructure with limited access (e.g. over a dedicated backup network only accessible by central backup servers). Virtualisation enables the implementation of robust backup concepts on hypervisor level with a very limited impact to the running virtual machines.
  - Because of the criticality of today's situation, appropriate and defensive backup strategies must be elaborated and implemented as well as regularly verified, trained, and exercised. Generally, incremental backups must be limited to very short terms (less than 24 hours) purposes. Daily backups should be performed at least as differential backup. Full backups should be performed regularly in order to provide a reliable data baseline enabling a fast and reliable data reconstruction in case of a disaster. Finally, the critical question is: "how much data could I afford to lose?" Whose answer will define the RPO (Recovery Point Objective).
  - Do not underestimate the restore time (RTO: Recovery Time Objective)! Even if it is possible to back up regularly very large data sets, the currently available technology requires time for restoring large data collection. Depending on the used backup strategy, data restoration could take several days (or weeks) even on high performance IT infrastructure. Restore activities must be rehearsed regularly and their performance must be controlled.

The above listed measures are neither exhaustive nor comprehensive. The design of the IT infrastructure and the definition of the IT operation processes must be developed based on accurately (and truly) identified risks.

Improvement proposal

What operating platform for industrial and process control applications?

Does Windows® represent a reliable operating system for process control purpose?

Despite of Windows® XP being definitively an old – even if reliable – operating system, it is interesting to look back at the last 24 months.

Since Windows® XP, Microsoft made multiple significant architecture and interface changes, limiting the backward compatibility of applications and jeopardizing the development investment of software editors, as well as initiating and stopping operating system platforms.

Additionally, Microsoft tries to enforce[4] – with questionable ways – the adoption of the newest operating system release, jeopardizing the integrity of existing systems, overloading customer's IT infrastructures, and becoming really intrusive. At the same time, significant changes in the operating system update process caused multiple system crashes and increased dramatically the control effort for limiting and mastering update scope.

The result of such aggressive "enforcements" is that the system administrators were busier with rescuing daily IT operation and fighting against data privacy issues than with the implementation of prospective approaches for migrating applications to the next operating platforms.

With the "Patch Tuesday" on April 11th, 2017, a few weeks before the WannaCry attack, Microsoft confirmed[5] that applying Windows® 7 security patches will not be possible anymore on systems using the most recent microprocessor architecture based on AMD Zen or Intel Kaby Lake microprocessors, although this operating system is supposed to be supported until April 2020. This behaviour has been already announced during summer 2016[6]. It should be noticed at this point that there is no technical reason for such a limitation; this limitation achieves only a marketing objective: increasing Windows® 10 market share. If this strategy should be pursued by Microsoft in the future, the Windows® 7 based systems will become rapidly the "new XP systems", making vulnerable replacement systems based on recent microprocessor architectures.

The multiple architecture and strategy changes in Windows® make development work more and more difficult, increasing the costs and jeopardizing long term support for industrial and process control applications.

As an automation and system engineer, I never considered Microsoft Windows® as a really reliable industry platform. At first because of the poor transparency of this software platform, secondly because of the poor "real time" performance ("real time" means at least a deterministic temporal behaviour and an accurate and monotone time management), and thirdly because of the limited ability to plan and to achieve a long term development strategy.

Back to POSIX standard and to open (and real time) platforms

If a reasonable and reliable operating system alternative for long term purpose must be considered, the choice is both limited as well as very large:

- Limited because today the only alternative is represented by *nix based systems, in particular GNU/Linux and its embedded version eLinux, and for hard real time application VxWorks or QNX.
- Large because multiple flavours of the Linux kernel are available for both operating system and user interfaces (so called "Desktop Environment").

The purpose here is not to advocate for a particular GNU/Linux distribution but to make the reader aware that a real world exists besides Microsoft Windows® and that such operating environments could secure investment and development costs because of their openness and long term reliability.

The best way to secure the portability of applications is to rely on widely accepted and supported standards. POSIX – Portable Operating System Interface – is one of such standards elaborated in the late 1980s and early 1990s for ensuring a "smooth" and reliable portability of a developed application between different operating systems and operating system versions.

Together with an appropriate development environment (including portable and open programming languages) and with clean and robust software development practices POSIX provides a stable and portable software development platform.

Even if the Linux kernel has been ex-

Learning from Automotive Industry

Within the last 25 years, the automotive sector has been experiencing a significant revolution in terms of embedded electronic for both security and control devices as well as for infotainment and comfort. Like for any other technology changes, the automotive sector defined at first clear requirements in terms of environmental conditions, robustness, reliability, and long term support. New standards have been elaborated, manufacturer consortiums have been built for supporting application platforms.

Although the automotive sector represents a field of stronger and harder competitiveness than ever been in the pharmaceutical sector, those firms – manufacturers as well as suppliers – work together for ensuring investment protection and development reliability.

Such collaboration regarding platform development does not prevent in any way the development of supplier specific applications, supporting the implementation of value added services.

It is to notice that some medical device manufacturers rely already on such standards for diagnostics equipment. Why could such an approach not be preferred for manufacturing and analytical equipment used in GxP environment?

periencing evolutions and some significant changes over the years, well developed software applications are still portable to the newest Linux platform with limited effort, securing long term support.

Platform independent application user interface

Two main different approaches could be basically followed for developing and implementing application user interfaces:

- Web-based user interfaces
- Multi-platform user interfaces based on application frameworks.

W3C conform web-based user interfaces

Since the last 20 years, web-based user interfaces have been efficiently replacing more and more so called "fat-client" applications, i.e. specifically developed applications for interacting with equipment or server applications.

For equipment suppliers, web-based user interfaces allow to avoid having to develop and to maintain, for each operating system type and version, fat client applications for interacting with equipment. Such an approach represents a real efficiency improvement in terms of long term and security support. However, such a design requires to implement accurately W3C specifications in order to provide a seamless support of W3C standards, enabling a neutral and consistent support of web browsers[7], ensuring the highest compatibility level. It is in particular crucial not to focus on proprietary browser technologies, but to prefer to simply comply with non-proprietary standards.

Qt-based user interfaces – Portability by design

Initially launched in 1995 by Trolltech AS, a Norwegian software company, Qt is a widely used cross-platform application framework for developing multi-platform applications and graphical user interfaces (GUIs). Adopted by multiple companies (including global players) in various sectors – from automotive to medical devices, including consumer electronic and mobile devices – Qt represents a reliable and stable application platform for limiting development effort, ensuring application portability, and for long term securing development and investment. Qt is available with both commercial and open source GPL licenses. Qt supports natively various platforms such as embedded Linux, VxWorks, QNX as well as Linux, macOS®, and Windows® on desktop level and mobile platforms based on Android or iOS.

It is to notice that Qt can be equally used for developing web-based user interfaces based on HTML5, hybrid user interfaces as well as native user interfaces based on widgets.

Robust IT infrastructure design

The industry challenges consist in preserving business operation and capability.

- Today only very few firms could survive without an operational IT infrastructure.
- Likewise a significant data loss in case of a disaster usually impacts or even jeopardizes the firm's future. Less than 10% of the organisations survive a complete data disaster[8].

Building a robust IT infrastructure is at first less a GxP requirement than a simple but strong and vital business requirement. The effort to secure the IT infrastructure represents an investment with a direct impact on the business capability of the organisation. The question is not "if" but "when" an attack will occur. Likewise it should be clear that IT security is like a war where we are only able to win a fight, but never the war definitively.

The above section already provides a couple of recommendations which must be supported by educated and well-trained system administrators. It is necessary to take a very defensive approach to design IT infrastructure and to deploy a reliable and accurate monitoring and operation approach. IT infrastructure reliability and security are not self-evident but the result of a systematic and defensive approach.

Even if, sometimes, the operational flexibility seems to decrease a little bit because of IT security measures, it should be clear that IT security cannot be negotiable (even for the senior management).

IT infrastructure robustness is only achievable by implementing a defensive design with a strong segregation of the multiple networks, with reliable and verified redundancies, with accurate operating processes. For instance, a dedicated and secured network has to be available for managing active IT infrastructure components and for connecting server console ports otherwise, in case of a security breach, it will be very easy (and efficient) for a cracker to modify the configuration of network and storage components causing an immediate and irrevocable data deletion.

The available time for evaluating security patches and for assessing changes depends directly on the degree of the IT infrastructure robustness.

Conclusion

The industry currently faces multiple and serious IT menaces[9] being able to destroy companies and to jeopardize business capability.

We have to recognize that this situation is the result of decisions

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taken years ago with insufficient care of – even deliberately ignoring – business capability and IT security. The technology, the design solutions, and the recommendation for building robust IT infrastructure and reliable process control systems have been available for more than 25 years (e.g. POSIX, VxWorks, QNX), including portable user interfaces (e.g. web-based, Qt-based).

The regulated industry and its equipment and solution suppliers must actively work together for supporting the design of better control systems for laboratory and manufacturing equipment as well as for process automation. The required expensive investment for new equipment does not fit anymore with the short term support (for only few years) on Windows® level[10].

Nevertheless, it is urgent to initiate and to require explicitly such paradigm change since architecture changes will need a couple of years – three to five years – until manufacturing and infrastructure equipment and analytical systems designed on the basis of such more reliable software architecture will be finally available on the market.

Appropriate requirements should be defined and enforced by the regulated customers for long term support and for long term data availability and readability. These requirements must be (prospectively) taken into account by the equipment suppliers.

Within the scope of data integrity and of the required system upgrades, it would be meaningful to equally address requirements for long term system support.

Such strategy changes are really demanding in terms of training and design efforts for the suppliers: new development platforms, new development environments, probably the use of different programming languages. However, if the "Industry 4.0" should become an effective and efficient reality, such paradigm changes are unavoidable.

In 2016, the first significant troubles caused by inappropriate design and the implementation of "Internet of Things" devices were already noticeable on a global level.

Now, it is the time to reconsider the IT landscape and the design of industrial computerised equipment and to require and to enforce more reliable system architectures.

Postface

Since the first draft of this article in May 2017, new cyberattacks (see "Petya" resp. "NotPetya", "GoldenEye") occurred, impacting various organisations (e.g. UK NHS), including larger firms (e.g. Renault, Maersk, Saint-Gobain, TNT Express (FedEx)) and global acting pharmaceutical companies (e.g. MSD and Reckitt Benckiser). About five weeks after the initial "WannaCry" attack, larger manufacturing facilities (e.g. Honda) have been impacted through "WannaCry aftershocks" disabling their business capability.

Like "WannaCry", the recent malware and malworms use weaknesses of previous versions of Windows® operating systems and network services (e.g. SMB). The same remarks regarding the followed update strategies are made, still ignoring the complexity – and the related limitations – of industrial and real time systems.

These recent events should not be considered as being a particular bad "season" for cybersecurity. Furthermore the industry should become aware that such attacks will surely become part of the daily business.

It is clearly impossible to win such a cyberwar; only single fights could be won, never presuming a successful future.

Acknowledgements

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References

1 In the meantime, in late June 2017, attacks based on (Not)Petya and GoldenEye inflicted sever damages to several organisations, including so called "global players".
2 See http://www.ubergizmo.com/2017/05/wannacry-victims-mostly-running-windows-7/
3 OLE: Object Linking and Embedding
4 See: Get Windows 10 "update"
5 https://support.microsoft.com/en-US/help/4012982/the-processor-is-not-supported-together-with-the-windows-version-that
6 In the meantime, the situation became more confusing, since this limitation seems to be reversed. Missing a clear official statement from Microsoft about this limitation, it is really difficult for the industry to elaborate reliable support plans.
7 Non-standard conform implementation based on Chrome or Edge would jeopardize the long term compatibility of web-based user interfaces. A strict validity with W3C standard, based on HTML5, would secure the durability of the user interface. Firefox and Vivaldi could be meaningfully used for performing the functional testing (OQ) of the user interfaces.
8 According to a study made by Touche Ross.
9 Even up-to-date antivirus software is not able to detect reliably ransomware.
10 See http://www.zdnet.com/article/windows-as-a-service-means-big-painful-changes-for-it-pros/

Authors:

Axel H. Schroeder... *is Operations Director and plans and conducts courses and conferences for the ECA in the area biotechnology and microbiology.*

Dr Markus Fido... *is General Manager at Vela Labs in Vienna, Austria, and is in charge of the area Quality Operations and Regulatory Affairs.*

BACKGROUND

ANALYSIS OF BIOPHARMACEUTICALS – AUTHORITY EXPECTATIONS

The term "biopharmaceuticals" comprises a very heterogeneous group of products which range, among others, from monoclonal antibodies, hormones, enzymes, plasma products and ATMPs to biosimilars. This results in several new challenges for manufacturers as well as for authorities to ensure the required safety and quality of the products in accordance with Directive 2001/83/EC.

This means that the manufacturer must have excellent knowledge and complete control of the manufacturing process, as the product is defined there. During the manufacturing process, impurities have to be eliminated without any negative impact on the product's biological activity. Of course, various materials, media and reagents of constant quality from qualified suppliers play a key role here. To ensure this quality, the therapeutic agent must be thoroughly tested and characterized during the early stages of product and process development. Appropriate test methods must be evaluated and implemented accordingly to allow for sustainable product characterization. These analytical methods are performed throughout the complete development process – in its early stage during clone screening, in vitro and in vivo testing for example, during the pre-clinical phase and, finally, during clinical studies by selected trial centres. The samples to be analysed may have different matrices, which makes it very complex and tricky.

Regarding the product life cycle, this would require process validation, in-process control, release testing and, of course, the initial testing of reagents and excipients for the pre-marketing phase. In addition, for biosimilars, comparability with the reference product would have to be established in a stepwise approach (according to EMA/CHMP/437/04 Rev.1 and EMA/CHMP/BWP/247713/2012).

During the post-marketing phase, changes of the manufacturing process/the production site or the establishment of a new manufacturer may require further analysis and comparibility exercises.

Whereas inline, online or atline methods are commonly used with classical analysis, (matrix-specific) bioanalysis usually requires an offline methodology, since various methods, increase in time per method and specific measuring systems are frequently required. There, it is expected that the method used is sensitive, i.e. that it will detect the smallest structural differences or lowest amounts of impurities respectively that the smallest amount of an analyte can be quantified. Furthermore, high specification and robustness are expected to ensure the clear identification of the analyte.

The bioanalytical procedures used should also be validated according to ICH Q2(R1) as early as possible during development. Especially with high-quality analyses, e.g. during proof of similarity of biosimilars or characterization of critical molecules, it may be reasonable and necessary to use orthogonal methods, i.e. to analyse a parameter with different methods. The increasing focus of European authorities on the 3R strategy (reduction, replacement, refinement) with regards to animal testing should be observed when selecting the test methods.

As a consequence, authority expectations can be summarized as follows:

- The relevant guidelines are to be observed, e.g. ICH Q2(R1), the Pharm. EU Product Monographies or, for biosimilars, "CHMP/437/04/Rev.1 – Guideline on Similar Biological Medicinal Products".

- Validated methods should be used as early as possible during development – at the latest, during clinical phase III.
- Action mechanisms should be described in detail and clearly demonstrated, e.g. the binding capacity of specific receptors or antigens (possibly through different assays).
- If certain functional structures are not analysed, a scientific justification is required.
- In case of impurities, those reflecting activity or potency that influences the biological activity of the active ingredient and those with immunogenic properties should be determined (product-specific side effects).
- Furthermore, the reduction of contamination within the production process should be examined and limits should be determined according to the relevant industry guidelines if necessary.
- For raw and auxiliary materials, especially for those of biological origin, a content determination in the end product should be available and their possible influence on the active ingredient should be evaluated.
- Concerning the detection of so-called adventitious agents (e.g. mycoplasma or viruses), testing of the starting material and of the unprocessed bulk and/or evidence of the effective elimination of viral contaminants by the manufacturing process is expected. A potential contamination with prions must also be examined for some products.

Heterogeneous product groups such as biopharmaceuticals and biosimilars require the development of new test methods or the adjustment of existing ones. In that case, a corresponding justification of the chosen method, a short description, a list of differences to the previous method and relevant comparative data should be presented to the authorities. A good method transfer proving that other test laboratories/devices/etc. deliver comparable results is key here.

Author:

Dr Afshin Hosseiny... *has more than 20 years of experience in the pharmaceutical industry – at first in analytical services, later in quality assurance. Today he is General Manager of Tabriz Consulting and Chairman of the European GDP Association.*

SERIALISATION: WHAT IS THE QUALIFIED PERSON'S (QP) ROLE?

The falsified Medicine Directive was developed in response to growing concern in the market place after discovery of unauthorized sale and supply of counterfeit medicines with potential risks to the patients. The Falsified Medicine Directive (FMD) (Directive 2011/62/EU) published on 1 July 2011, introduced tougher rules with intention to improve the protection of public health with new harmonized measures ensuring that medicines supplied within the EU territory are safe and the trade in medicines is rigorously controlled. This directive introduced several control measures including obligatory safety features on the outer packaging of the medicines, to be detailed via a delegated act.

The delegated act (Commission Delegated Regulation (EU) 2016/161) detailing the characteristics of the safety features, how medicines authenticity should be verified, and by whom, was published by the European Parliament and the Council, on 9 February 2016.

The delegated Regulation, will apply as of 9 February 2019, in other words pharmaceutical industry is legally obliged to ensure implementation of these regulations on or before 9 February 2019.

Whilst the directive and the delegated act introduced several measures to improve safety of medicines, the current regulatory focus is on the implementation of two key features; tamper evident and the provision of a 2D barcode for verification of authenticity of each unit in the supply chain. These features are expected to ensure legitimate medicines are traded and supplied across the European Union.

With short time remaining for implementation and full compliance with the regulations, very little attention is being paid to inclusion of the tamper evident feature on the packs. This is partly because the tamper evident feature is an old technology and very well known to the pharmaceutical industry. However, all the focus is on the verification and traceability of each single unit to the original manufacturer. In early 2009, various options were evaluated by a group of major pharmaceutical companies supported by EFPIA which resulted in recommendation for use of 2D barcode on individual packs to deliver the regulatory expectations as outlined in the FMD Directive.

Whilst the technology for creation, application, reading and verifying the 2D barcodes has been around for many years; used widely in the food industry for example; it is a new challenge for the pharmaceutical industry. Fur-

thermore, the security measures required to ensure data integrity on the single unit throughout the supply chain are very complex, requiring extensive and complicated control systems. Therefore, implementation of the serialisation system for the companies is very challenging which requires design, selection, validation/ qualification of the equipment, software and the process before going live.

So, at a manufacturing site, what activities and systems need to be developed and implemented to enable full compliance?

- Development, design, implementation of the 2D barcodes on all product labels and cartons (as appropriate).
- Changes to the packaging of the products to introduce a 'tamper evident' feature for each pack.
- These changes will require submission of variations and approval of the new labels and packs.
- Application of a temper evident feature on packs and printing a unique barcode on each pack will also require physical changes to the packaging machinery and very possibly addition of new equipment.
- Selection of a suitable vendor, to supply, install and validate the software package to generate unique barcodes, manage rejects, reworks, returns, QA sampling and of course product recall.
- Develop specification, select, purchase, install and validate on-line printing systems, and verification devices to ensure each barcode is printed correctly and is legible at the running speed of the packing machinery.
- Incorporation of the software into the existing site inventory management system, to ensure delivery of the products to the approved customers.
- Introduction of the capability to trace materials in the site warehouse, and the company's supply chain.
- Provision of access to the central database using trained staff to ensure each batch is correctly allocated to the desired market, and make the changes to the database when required. For example, reallocating a batch already in one-member state to another can only take place by the MAH.

The Qualified Person (QP) responsible for batch certification for release needs to play a key role in all the tasks listed above. This will include being involved in developing the specifications, defining the validation criteria, and the test protocols to ensure ongoing compliance with the requirements. Management of the changes, management of the deviations and complaints occurring post implementation of the verification codes will be an additional challenge for the QPs. There is no doubt that this is a step change in our operations, where QPs need to be very pro-active and focus on both technical and operational challenges, and where possible apply risk management principles to make decisions and proceed. The QP should also play a key role in preparing the site team and more specifically the QA personnel to handle the issues developing detailed operating procedures and training all involved. There is no doubt there will be few teething problems in early days of implementation, however, with good planning and ongoing monitoring of issues, the benefits of the new process will be realized across the supply chain and for the benefit of the patients as well as the Pharma industry.

Authors:

Dr Robert Eicher... *is Operations Director and organises and conducts courses and conferences on behalf of the ECA Academy around pharma technology.*

As Operations Director **Dr Andreas Mangel** *organises and conducts courses and conferences for the ECA Academy in the areas sterile production and computer validation.*

CONFERENCE REPORT

TECHNICAL AND REGULATORY DEVELOPMENTS IN THE PHARMACEUTICAL INDUSTRY

Photo: iStock # 648413674; NicoElNino

Sterile dosage forms and their GMP-compliant manufacture were once more key topic at the 19th Pharma Congress which took place in Düsseldorf/Neuss at the end of March. In the light of the revision of Annex 1 EU Guidelines to Good Manufacturing Practice whose first draft is still expected, the contributions dealt with the current regulatory developments and with their possible consequences for the pharmaceutical production.

Jörg Zimmermann, Vetter Pharma-Fertigung, addressed the current trends concerning sterile dosage forms already in his keynote lecture. Ultimately, the global demographic developments, the increasing individualization of treatments as well as changes (cutbacks) in the national health systems have a significant impact on the treatment of patients with medicinal products. Jörg Zimmermann pointed out the resulting requirements for parenteral medicinal products. He supported keywords such as a more precise dosage patient safety or patient compliance with current technological developments concerning application systems.

True to the motto "Users report for Users" the current trends were again conveyed through a lot of case studies – among others by Ferring, GSK Vaccines, MSD, Octapharma, Vetter Pharma-Fertigung, Pfizer, Roche and Janssen.

State of the Revision of Annex 1

Again the main focus of the conference "Regulatory Trends – Revision of EU GMP Annex 1" was on the actual state of the development of Annex 1 of the EU Guidelines to Good Manufacturing Practice. Authority representatives put up first information on the imminent changes for discussion. The representatives of industry, in contrast, articulated their expectations, also against the background of the deficiencies of the current EU GMP Annex 1.

The Pharmaceutical and Healthcare Sciences Society (PHSS) primarily wants to take into consideration new technologies and remove ambiguities and uncertainties. PHSS-Chairman James Drinkwater reminded the audience that there had been several small revisions of the document since its first publication in 1972, but never a comprehensive new wording. His comparison of the current EU GMP Annex 1 with WHO Annex 6 (GMP for sterile pharmaceutical products) highlighted that the much more recently published WHO document addresses a variety of issues that are missing in Annex 1 GMP Guidelines. By means of two case studies he explained PHSSs expectations especially with regard to environmental monitoring.

The Pharma Congress Production & Technology
24/25 April 2018 – Düsseldorf

Main Subject Areas are:
- Current Aseptic Technologies
- Continuous Manufacturing
- OSD Manufacturing and Packaging
- Barrier Systems
- Operational Excellence
- Revision of EU GMP Annex 1

The conferences will be supplemented by the exhibition PharmaTechnica, where nearly 90 internationally oriented exhibitors will present their latest products and services. There you can also touch and experience technology – in Live Demos. The social event on the evening of the first Congress day – including an entertaining programme, will provide plenty opportunities for networking and relaxation.

www.pharma-congress.com

Dr. Friedrich Haefele, Boehringer Ingelheim in Biberach, talked about current and future requirements concerning clean rooms and barrier systems. In his opinion essentially the following five requirements should be adopted in the revision of Annex 1:

- Maintain ISO 14644 as the basis for the international alignment of clean room qualification;
- Deletion of the 5µm particles criterion for the clean room classification;
- Encourage isolator technology for aseptic processing and in general foster continuous improvement of facilities and processes;
- Strive for global harmonisation and related with this the need for revision of other major guidelines;
- Pave the road for Mutual Recognition Agreements (MRAs).

Arjan Langen, MSD, formulated current deficiencies and in relation with these deficiencies his expectations on the imminent revision as regards media fills:

- "The process simulation should simulate the routine aseptical manufacturing process as comprehensively as possible and contain all critical consecutive stages of manufacture. It should also take into consideration all interventions known to take place during normal production as well as worst case situations." Concerning this detailed information on the worst case situations should be given in relation to process, personnel, interventions, hold times and process simulations lasting several days.
- So far the requirements put the focus especially on the aseptic filling process, but references to process simulations in earlier process steps are missing.
- Requirements concerning the 4-eyes-principle, video recordings and aspects of QA oversight should be included.
- Rules should be indicated when a process simulation can be aborted and
- Indications on the process simulation in closed systems should be included.

Continuous Manufacturing

Wendy Zwolenski Lambert from Novartis, representing the efpia at the conference „Continuous Manufacturing“, explained her view on the future of "continuous manufacturing". The efpia, which is the European federation of national associations of researching pharmaceutical companies and brings together industry and authorities, has formed an expert group in order to prepare an ICH document. In their opinion the topic is not addressed sufficiently in the current guidelines. They say that continuous manufacturing is pushed forward by the FDA and that there are also positive signals coming from EU countries. But the industry fears that there will be other countries which will not support this development. A result of this could be that two marketing authorisations would be required (continuous and batchwise) which would be extremely impracticable and very expensive. It would also make necessary two product developments, two different equipment parks and two different product life cycles. As a first step efpia has questioned 26 of its member companies to be able to define the most important topics as concerns continuous manufacture. The result showed that the following topics are the most important: General definitions, batch definition, process validation and the content of the marketing authorisations (CTD). But data management also made it onto the list because continuous processes which usually are continually monitored by means of PAT systems create huge amounts of data. This is easily understandable, especially in times in which the topic data integrity is at the focus of the authorities and industry.

Especially in the initial phase when experiences still are made and the technologies are changing rapidly the organisation wants to react flexibly or to extend the document more easily and has therefore created a questions and answers document. It will possibly be transferred into a guidance in a later step. The paper is supposed to address continuous processes in the manufacture of active pharmaceutical ingredients and finished medicinal products as well as marketing authorisation and GMP aspects. This development shows clearly that the topic continuous manufacturing has reached the (European) pharmaceutical industry and that the interest is increasing steadily.

As Daniel O. Blackwood, Leader of Pfizer's PCM&M Programm in the USA, reported in his lecture, Pfizer also has gained some experience in the area of continuous manufacturing. He showed what a risk-based approach might look like and illustrated by means of concrete numerical examples how Pfizer has carried out such analyses. This included the results from 19 runs under different process conditions which had been defined in a DoE. Particularly impressive was the fact that all these experiments could be carried out in only two days thanks to the continuous operation. Daniel Blackwood stated "the bottleneck now is analytics" – a statement which was confirmed by other speakers.

Global Player Janssen Pharmaceutica has three platforms for continuous manufacturing at sites in Puerto Rico, Italy and Belgium. Lawrence de Belder, Senior Principal Engineer Continuous Manufacturing, explained in his case study that a HIV medicinal product is already manufactured at the facility in Puerto Rico. So far, this medicinal

product had been manufactured batchwise and had been approved for this kind of production. Upon request he explained that no bioequivalence studies had to be carried out for this change in registration. He also pointed out that this will surely not be transferable to other medicinal products but that each case would have to be considered separately. According to his opinion the marketing authorisation for a product manufactured continuously might even be carried out faster than for the conventional batch production.

Whereas Pfizer wants a global standardization of the facilities as concerns development and manufacture Janssen takes a different path and tries each time to develop the ideal configuration for the different applications. Janssen has decided at the hightest level that new OSD products will only be developed in the continuous production method, says de Belder. This statement first had to be digested by the audience.

New Technologies and Trends

At the second conference day the case studies on continuous manufacturing were followed by further technological innovations and trends with respect to medicinal products. Apart from the 3D printing of medicinal products presented by Prof. Stephen Hilton of the University of London, Dr Stefan Henke, Managing Director of Lohmann Innovative Injektionssysteme (IIS) talked in his lecture about two new approaches to transport medicinal products needlefree through the human skin into the body.

On the one hand these works are pushed by the fact that only 30 out of the ca. 7.000 known drug substances can be transported passively through the skin (as used in transdermal systems). On the other hand a significant part of people is afraid of injection needles. About 50% of all children is afraid of needles. Another disadvantage of injection needles is the danger of needle-prick injuries, especially as concerns medical staff.

The first system presented is a syringe injecting a liquid jet with high pressure through the skin. Here, a reduced perception of pain can be observed because the amount of liquid can be reduced considerably as compared to conventional syringes. Currently, there are systems for 100 and 500 µl. By adapting the system it is possible to choose beforehand for each medicinal product how deep it will be injected into the skin. This can easily be simulated by means of a simulator with a skin model. In the meantime there are practical results from animal testings as well as first results from human trials with a monoclonal antibody.

The second system he presented uses micro-needles which dissolve completely in less than 10 minutes in the skin. These needles are each 600 µm long and are applied on flexible carriers to form areas of 600 per cm². The application is completely free of pain. This system seems to be ideal for the application of vaccines. Firstly, only small amounts of active ingredients are required (this constitutes a limitation of the system) and secondly, the vaccine is only injected in the outermost skin layers where the highest density of immune cells can be found.

New construction or conversion projects

Topics at the 19th Pharma Congress were also current construction, conversion and technology projects. Dr Alexander Herrmann (Director USP Clinical Supply Center at Roche Diagnostics in Penzberg) explained the successful conversion of the Clinical Supply Center where biopharmaceutical active ingredients are manufactured, harvested and purified for clinical studies using fermenters with the sizes 1000l and 250l. In order to comply with the current state-of-the-art the USP and DSP areas (upstream and downstream) were separated. Furthermore, the capacity of fermentation was increased from 1000 l to 2000 l. This classical reconstruction project of an existing building dating back to 1986 with four floors plus basement was complicated by the fact that it was a multipurpose plant in which eucaryotic cells as well as bacteria in fermentation have to be handled. And naturally, the facility plans were not up to date, says Dr Herrmann. He explained the project phases of the extension: in order to be able to house the new USP equipment the fronts had to be opened. The nasty surprise when carrying out the FAT of the vessel was unexpected – the outer double casing did not comply with the specification. With regard to the static they also had expected something different. In the basement pillars were needed for support. But the enclosure of the high purity media worked well. It was carried out during the two shutdowns for maintenance. Important point: new loops in the distribution system were connected only after the successful qualification, prior to that the material had been rejected. The costs were slightly lower than the budget of 19,4 million. In total 38.000 working hours were registered for the project, half of them for intern work and the other half for extern work. The planning company W&M supported the works. As conclusion of his lecture Dr Hermann recommended never to take over a project too early, even if the project management says it is „almost completed". There were several changes in the management of the project which weren't very helpful should always be avoided.

Manufacture of WFI

Concerning pharmaceutical water

Klaus Feuerhelm, GMP inspector from the Leitstelle Arzneimittelüberwachung (control centre of surveillance of medicinal products) in Baden-Wuerttemberg, presented the new possibilities to produce WFI with other procedures than distillation. Main parts of his lecture were references and information in the European Pharmacopeia (Ph. Eur.) and in EMA's questions and answers document (draft version).

The new monograph of the European Pharmacopeia doesn't contain concrete specifications as concerns the facility design. GMP aspects are not addressed. For this reason he takes the view that they should be regulated in other documents. Reference is made repeatedly to the revision of Annex 1 of the EU GMP Guidelines in this regard. But the draft of the new Annex 1 which is not official yet gives only little hope.

The first important information referred to the change carried out in the monograph as compared to the draft version. The monograph states in respect to the method of manufacture: *„by a purification process that is equivalent to destillation*." This means that the method of manufacture is no longer focused on reverse osmosis. Reverse osmosis is described as possible alternative. But finally it remains the decision of the operator to introduce also other methods. This does not hinder the state of the art in science and technology. But the GMP inspector also stated that this more liberal phrasing also entails some risks. He then discussed EMA's questions and answers document for which the deadline for comments expired in November 2016 and which has now been published in its final version. It is structured into two parts:

- Part I Production of WFI by non-distillation methods – reverse osmosis
- Part II Biofilms and control strategies

Klaus Feuerhelm stated in his presentation of some questions and their comments that the document tries to explain GMP aspects. According to him there are some statements which aren't easily comprehensible such as:
"*Systems should be in place to test membranes routinely for any potential integrity breaches that could lead to a significant contamination event.*"

Integrity testing for RO membranes is not possible yet. In this respect the requirement doesn't make sense. Mr Feuerhelm emphasized again and again that the main content of the document is about the formation and removal of biofilms. The reference to biofilms is a central topic in the complete EMA document. Sanitization of the systems will play a central role during inspections in addition to the monitoring. The questions and answers paper also contains several references and requirements concerning sanitization. If the sanitization concept is insufficient this will have consequences for the operation of the system. The following reference in the Q&A document was highlighted:
"*The distribution and storage systems should be designed as to permit routine steam sanitisation along with routine chemical sanitization and in accordance with other good design practice to minimize areas of reduced flow.*"

Accordingly, the material of the distribution and storage systems should allow for a steam sanitization as well as for a chemical sanitization. This means that a steam sanitization will usually be expected for distribution and storage systems. But elsewhere reference is made to ozone. Apparently ozone is to be used also in routine operation. This can only mean that the storage tank is continuously treated with ozone. In several parts of the document rapid microbiological testing is mentioned as control strategy in respect to the formation of biofilms. But the document does not explain in detail which rapid tests are meant and at which position they should be carried out using which frequencies. There remain a lot of unanswered or insufficiently answered questions for the GMP inspector. They include the following ones:

- How are AP and HPW systems handled which will be used for the manufacture on WFI in future?
- How many TOC measuring points and measuring points for the conductivity are required?
- Clear and detailed requirements for the routine monitoring are missing.
- Can we count on a uniform way of working of the GMP inspections within Germany or in the EU?

In the last part of his lecture Mr Feuerhelm addressed the main points with regard to inspections during the period 2016/2017. These included especially sanitization concepts, the prevention of biofilms, calibration and the handling of data and data integrity.

Especially the topic data integrity will play an important role in future GMP inspections concerning water systems. Mr. Feuerhelm mentioned the following examples:

- Which data or raw data with GMP relevance will be generated?
- How is data documented?
- Has it been defined which reports must be documented?
- Can the acknowledgement of a report be assigned unambiguously to persons or groups of users?
- Is the history of reports stored?
- Which data is stored or archived for how long?

lot of relevant topics from a design of storage facility to transport route profiling qualification etc. However these guidelines and supplements are not easy to find on WHO's websites. The European GDP Association has now put together all these documents to provide a better overview and easier access.

www.good-distribution-practice-group.org

Additional Activities

- In addition ECA replied to the FDA Docket on Conti Manufacturing (comments are available at https://www.regulations.gov/docketBrowser?rpp=50&so=DESC&sb=postedDate&po=0&dct=PS&D=FDA-2017-N-2697.
- A Task Force has sent a comment to USP regarding USP Chapters relating to Packaging and Process materials.
- Dr Afshin Hosseiny prepared a review on the WHO Draft Guidance on testing of suspect falsified medicines (which was sent to WHO).

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