Issue 7, October/November 2011

GMP Journal

The Journal for GMP and Regulatory Affairs

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Gemma Feenstra-Bielders
Abbott Healthcare Products B.V., The Netherlands

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Gempex, Germany

Holger Kavermann
Roche Diagnostics, Germany

Reiner Kirrstetter
Sanofi-Aventis Deutschland GmbH, Germany

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GmPlan, Germany

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Merck KGaA, Germany

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BIOIBERICA S.A., Spain

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Anthony Storey
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Francois Vandeweyer
Janssen Pharmaceutica, Belgium

Elmar Wenzel
Freelance Consultant, Germany

Frank Ziemke-Kägeler
Roche Diagnostics, Germany

Peter C. Zimmermann
Iskom, Germany

October/November 2011

Contents

GMP Journal

Publisher:	CONCEPT HEIDELBERG GmbH Rischerstraße 8 69123 Heidelberg, Germany HRB Mannheim Nr. 705125
General Manager:	Oliver Schmidt
Chief Editors:	Oliver Schmidt, Wolfgang Heimes
Editorial Staff:	Dr Gerhard Becker, Dr Günter Brendelberger, Dr Robert Eicher, Dr Andreas Mangel, Sven Pommeranz, Oliver Schmidt, Axel H Schroeder.
Editors on this Issue:	Dr Robert Eicher, Matej Janovjak, Dr Andreas Mangel, Sven Pommeranz, Yves Samson.
Graphic Concept & Realisation:	Wolfgang Heimes
Production:	KNOPF DRUCK MEDIA GmbH, Mannheimer Straße 62, 68535 Edingen-Neckarhausen, Germany
Contact:	info@concept-heidelberg.de

Editors' Note

Process Validation – Is there Harmonisation in Sight?

The subject process validation is omnipresent – for more reasons than only FDA's finalisation of their "Guidance for Industry Process Validation: General Principles and Practices" in January 2011.

This step had become necessary because the original version dated from 1987. New developments, as, for instance, with respect to ICH Q8, Q9 and Q10 had to be incorporated in the revision. The "traditional" approach, to prove a process' validity with three batches, is not mentioned any more.

Even if the principles of the new FDA Guidance are not questioned, it once again causes a problem due to deviating GMP requirements. In Europe the GMP Guide's Annex 15 continues to be state of the art. The Note for Guidance on Process Validation has not been revised either. But does this really mean that we can continue to do business as usual? What, for example, will international companies do that have to adhere to EU and US requirements?

In this issue of the GMP Journal we report about a very impressive survey on EMA's Process Validation Guidance revision. In this survey the European Compliance Academy (ECA) together with Concept Heidelberg asked professionals across the industry what they think about the changes. Only the fact that more than 500 professionals provided their input shows that this subject really bothers the industry.

In addition to the remarkable survey results you will also find interesting articles on other current GMP developments in this issue.

Enjoy your reading!

Oliver Schmidt

EUROPEAN PHARMACEUTICAL INDUSTRY DEFINES EXPECTATIONS WITH REGARD TO THE EU PROCESS VALIDATION GUIDANCE*

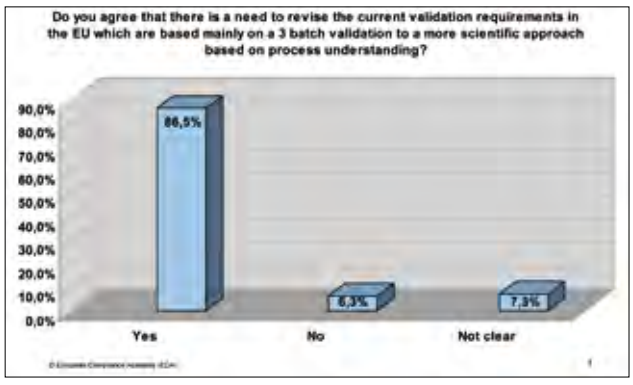
Sven Pommeranz, CONCEPT HEIDELBERG

In a "Concept Paper" from 2010 the European Medicines Agency (EMA) announced that they would revise their Note for Guidance on Process Validation from 2001. This revision's goal is to implement modern aspects ("enhanced approach") to move towards a "continuous process verification".

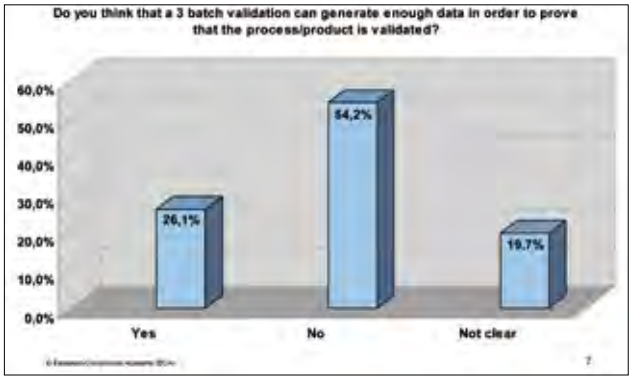
To find out what the industry thinks about this approach, the European Compliance Academy (ECA) together with Concept Heidelberg conducted a survey in September 2011. More than 500 professionals provided their input to the survey – single questions were skipped by some of the respondents, though.

The result relative to the first question asking for the respondents' background showed that the large majority came from medicinal products manufacturers (more than 50%), followed by respondents from API manufacturers and companies manufacturing both medicinal products and APIs (each 25%). Some additional respondents – not fitting into these categories – came from medical device manufacturers, consultants, vaccine manufacturers or food manufacturers. These "Others" only represent a single digit percentage, though. Three of those answering further came from the regulatory area.

Surprisingly, many respondents (86,5%) agree with the statement that it would be necessary to modify the current validation requirements – which are mainly based on the 3 batch model – to a more scientific approach and process understanding. A clear "No" was expressed by only 6,3%.



The opinions with regard to „Data Quantity" provided by the 3 batch validation varied a bit more. Merely a little more than a quarter (26%) of those questioned believe that this approach generates enough data to show the process'/product's validity and therefore value it as efficient. However, more than half of the respondents (54,2%) do not agree with this estimation. Noticeable is the group of undecided respondents (20% "not clear").



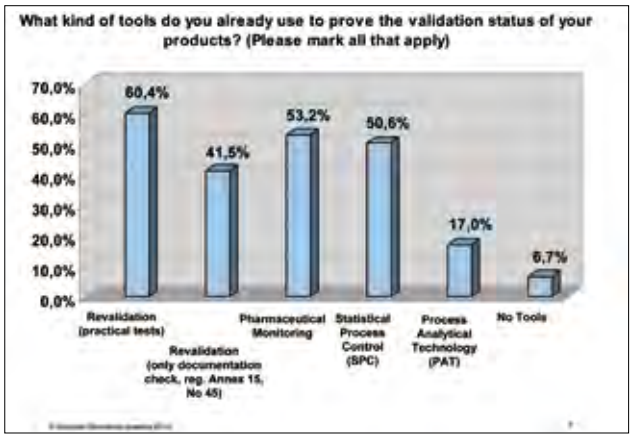
Asked for their estimation of the new FDA Guidance for Process Validation as a basis for a modern approach, almost 57% believe that the Guidance of the US authority would provide a good foundation. Close to 40% have not decided yet, and merely a small part of respondents – 3,4% – thinks that the FDA Guidance would rather not be a good basis. However, only a few from this group specified their opinion: "No clear / Too broad expectations" probably summarises the single comments the best. Only two participants mentioned "growing expenses" as main reasons for their criticism.

"Do you think that the approach for new products should be different to legacy/existing products?" Exactly 68% answered with "Yes" to this question, 19% negated it. Almost 13% have not decided yet. Among those considering a different approach as necessary, nearly three quarters think that legacy/existing products should be verified through statistical data (e.g. Cp, Cpk). For almost 27% legacy products should not be subject to new requirements. Further comments with regard to optional requirements for legacy products were quite heterogeneous. Five comments can be summarised with the intention to use the APR/PQR as a means for evaluation of legacy products, three respondents recommend the use of SPC for these products. Further, five persons providing input also plan (re-) validations for large process changes with regard to the manufacture of legacy products.

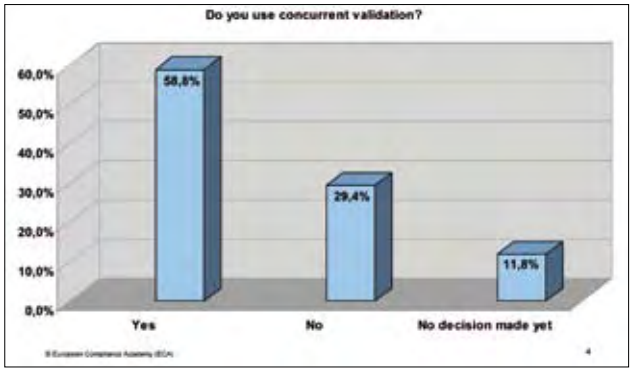
* The survey results were also forwarded to the EU Commission and the European Medicines Agency (EMA).

For the question "What kind of 'Tools' do you already use to prove the validation status of your products" respondents could choose between the answers Revalidation (practical tests), Revalidation (Documentation Check), Pharmaceutical Monitoring, SPC, PAT and No Tools with the option to mark all applying answers.

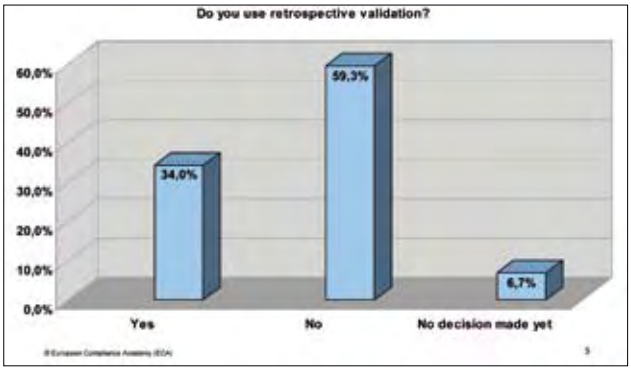
The feedback clearly showed that the pharmaceutical industry likes to take advantage of the width of possibilities. A little more than half of the respondents conduct SPC (50,6%) and pharmaceutical monitoring (53,2%). Some 41% use document check and 60,4% still perform practical revalidation tests. PAT is used by 17%, and 6,7% do not use any tools. These answers were substantiated by 33 additional comments. A large majority (20 comments) recommends APR/PQR. Three respondents mentioned trend analysis.



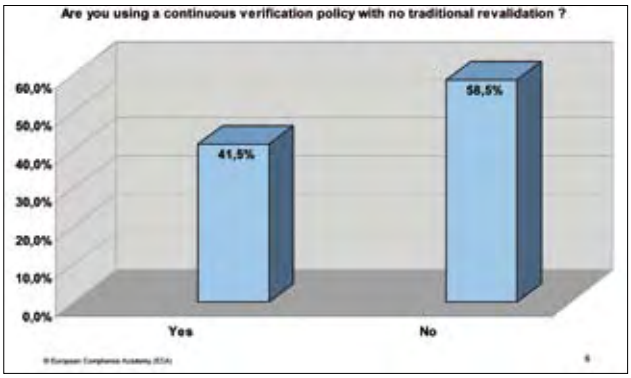
Quite surprising were the results with regard to the question "Do you use concurrent validation?" Nearly 60% answered with "Yes". Close to 30% (29,4) do not, and almost 12% remained undecided. The number of comments received to the additional question "Why do you use concurrent validation" for those affirming was also surprising (205 comments). This means that 40% of all survey respondents did also provide a comment to this question. A quarter of those (53) noted that they use concurrent validation for small batches or product volumes. Further, 17% (34) use it after slight changes, for 15% (39) "cost and time savings" are the reason for concurrent validation. Finally, seven respondents blame market pressure for this approach.



Another surprise provided the answers to the question "Do you use retrospective validation?" – which one third (34%) answered with "Yes". Almost 60% said "No", and 6,7% were undecided. As for the question before, the number of comments (116 comments) from those affirming the additional question "Why do you use retrospective validation" did surprise the survey designers. After all, that is close to 23% of all participating in the survey. Almost half of those (45%) use the retrospective validation for legacy products. Nearly one fifth (19,8%) mentioned to use it for verifying the process, and only four respondents do actually use it in the meaning of a revalidation.



Close to 84% noted that they do have a revalidation policy, a little more than 16% do not. Less than half of the respondents (41,4%) further use a "continuous verification policy" without traditional revalidation, the majority (58,5%) does not.



Conclusion

The survey yielded some surprises. Surprising was, for instance, the noticeable high number of participants (and also the number of comments). 509 persons providing input truly shows that validation is a topic that bothers the industry. Amazingly clear is also that the industry knows that the "3 batch model" should be modified towards a more scientific approach and process understanding, although a quarter of all respondents still believe that 3 batches can generate sufficient data to show the validity of a process. Vice versa, more than 50% do not believe this.

With regard to this specific question 20% were undecided – which also shows some uncertainty.

Whether the new FDA Process Validation Guidance provides a good basis for the new direction for a new validation approach in Europe is evaluated quite differently. 57% believe the new direction can be based on the US authority's Guidance, but nearly 40% have not made up their mind. Almost 70% would like to see different regulations with regard to new and legacy products – whereas nearly three fourths recommend statistical data as a tool for the validation of legacy products.

Interesting were the comments with regard to methods for showing the validation status of products. With some 50% SPC and pharmaceutical monitoring were represented equally often. A little more than 60% (60,4%) conduct practical revalidation tests and 40,5% perform document checks.

Statements with regard to the use of concurrent and retrospective validation were particularly interesting. Both are validation types that should rather be an exception. Still, almost 60% noted to validate concurrently, and 34% use the retrospective validation. However, the use is mostly regulation compliant. 25% apply concurrent validation for small batches and/or small product volumes, respectively 17% after (slight) changes. The retrospective validation is mainly used for legacy products (45% of the answers). Moreover, somewhat surprising are the statements by 15% of the respondents who either mentioned to use concurrent validation as a means for cost and time savings or due to market pressure. A revalidation policy seems to exist in most of the companies (> 80%), and more than 40% even have established a "continuous verification policy" – and thus already move towards a modern validation approach.

EUROPE'S LARGEST PHARMA CONGRESS WITH COMPREHENSIVE EXHIBITION BRINGS TOGETHER INDUSTRY

Dr Robert Eicher & Dr Andreas Mangel, CONCEPT HEIDELBERG

The Pharma Congress on Production & Technology will continue to be the meeting point for the industry in 2012. The well-proven concept of previous years has been adopted and advanced for the Congress which will open its doors again on 24 and 25 April in Düsseldorf. The ever-increasing demand for exhibition stands and the continually growing number of participants confirm this successful concept. Using daily tickets, participation is possible on one or both days. Participants can design their individual programme of lectures from all conferences. In the evening and during breaks, participants will have enough time to maintain their networks and make new contacts. Leading suppliers of the pharmaceutical sector will be taking part in the major special exhibition providing information on current technologies and services.

Delegate Voices from the Congress 2011

„I was pleasantly surprised about the density of information in the lectures and the high quality speakers – and this in a perfect combination with an exhibition. In total a very compact, very well organised and high-class event."
Dr. Hanns-Cord Walter, *General Manager Klosterfrau*

„I believe it was a very well attended event. As usual there were plenty of opportunities for networking with colleagues from industry and from suppliers and service providers."
Dr. Friedrich Haefele, *Vice President Biopharma Operations Boehringer Ingelheim*

Exhibitor Voices from the Congress 2011

„We were very satisfied with this year's congress. We already noticed the last time that the congress is quite popular with our customers, especially for those in the German speaking area. However, we also noticed that we had more foreign visitors due to the international orientation of the presentations."
Willem Berends, *groninger & co. gmbh*

„The participation was already quite good in the last year. And this year the positive trend continued. We had many good contacts with users as well as with technology representatives."
Jens Kubischik, *Pall Life Science*

As in 2011, the European Compliance Academy (ECA) will be conducting several conferences during the 2012 Congress. This time, delegates can choose between the five international conferences

- ECA Conference on Oral Solid Dosage Forms
- ECA Conference on Prefilled Syringes
- ECA Conference on Barrier Systems
- ECA Conference on Current Aseptic Technologies
- ECA Conference on Glass - Glass Breakage – (Micro-) Cracks

with more than 40 speakers, including speakers from Bayer, Boehringer Ingelheim, Cilag, CSL Behring, Roche, Fresenius, Holopack, Lilly, Lonza, Merz, Novartis, Nycomed, Pfizer and Vetter Pharma-Fertigung.

The conference on solid dosage forms will be concentrating on two main topics: increasing efficiency in the manufacture of solid dosage forms and transition to continuous production. This transition is presented by Janssen Pharmaceutica, among others. Janssen Pharmaceutica is a company that has taken this step after conducting thorough analysis.

The topic of "Glass – Glass breakage – Glass particles and Delamination" and ensuring the integrity of pharmaceutical glass containers for parenterals came under the particular scrutiny of regulatory authorities in 2010/2011. The FDA in particular, was sensitised by several recalls by pharmaceutical companies owing to problems with glass as a packaging material. In the meantime, the FDA has defined its position in detail and formulated clear guidelines for industry at public events and on its homepage. This will have consequences especially for the glass suppliers' quality assurance. The aspect of Quality by Design will be stressed further. Another important point is the treatment of glass containers during the preparation and the filling process. One example represents stress-free transport of glass containers at pharmaceutical companies. The conference on "Glass – Glass breakage – (Micro-) Cracks" will look at the topic from the perspective of the three parties most involved – glass manufacturers, pharmaceutical companies and mechanical engineers.

Glass manufacturers of tubular and moulded glass explain the causes and show new approaches and developments for avoiding and reducing these problems. Several case studies by pharmaceutical companies sensitise for the problems of filling and show practiced approaches to avoiding glass breakages. Mechanical engineers show new developments concerning the stress-free transport of glass containers. But new possibilities for inline-detection of glass breakages will also be presented and the practical suitability thereof evaluated.

The event on "Current Aseptic Technologies" focuses on

the presentation of new trends and developments in aseptic production. The central theme of the conference will be to interpret and implement current regulatory requirements such as the revised version of the EU-GMP Guideline's Annex 1 but also new and further developments of existing technologies. A German inspector and two former inspectors of the French regulatory authority will present their point of view on the interpretation of Annex 1 as concerns technological feasibility. Pharmaceutical companies and engineering companies will describe new technological approaches and procedures for aseptic production in several case studies. These approaches and procedures will then be put up for discussion.

Another conference is dedicated to the special technology of prefilled syringes. It can still be observed that prefilled syringes are steadily increasing in importance. The market of prefilled syringes is dominated by syringes delivered by the manufacturers ready for use in tubs.

The conference on "Prefilled Syringes" will pick up on current topics such as the improvement of glass qualities, alternative plastic syringes with their advantages and disadvantages, the decontamination of tubs when infiltrating them in the filling process and the use of prefilled syringes in autoinjectors.

Today, barrier systems are roughly divided into two groups: RABS (Restricted Access Barrier Systems) and isolators. Both systems have points in common, but each also has specific advantages and disadvantages. In terms the operational method, the systems are already approaching one another considerably in some parts. They both separate products and operators by means of a "solid wall". Interventions during production are possible only via gloves. Another crucial difference, including from the inspector's point of view, is that isolators can be operated in clean room classes C or D whereas RABS always needs class B as a background of the aseptic core area in Europe.

In the context of the "Barrier Systems Conference" the advantages and disadvantages of both technologies are dealt with in detail and discussed intensively. New developments at the plant construction firms, case studies taken from pharmaceutical practice and future trends are presented in detail. The focus will be on aseptic barrier systems. But in this context, aspects of the handling of highly-potent active ingredients and drugs will also be addressed.

All further information on the individual conferences, lectures, speakers and exhibitors are available at www.pharma-kongress.com. Only the social event for the evening of 24 April remains a well-kept secret.

Conference Tip

- **Pharma Congress 2012**
  Düsseldorf/Neuss, Germany, 24-25 April 2012

  www.pharma-kongress.com

EUROPE'S ANSWER TO COUNTERFEITING OF MEDICINAL PRODUCTS: DIRECTIVE 2011/62/EU

Dr Robert Eicher, CONCEPT HEIDELBERG

In the form of Directive 2011/62/EU published on 1 July 2011, which will widely be applicable from 2 January 2013, the EU has issued a document that extends Directive 2001/83/EC with further requirements in four areas in order to contain the counterfeiting of medical products:

1. Introduction of obligatory safety features
2. Further requirements in the area of Good Distribution Practice (GDP) / Supply Chain
3. Requirements concerning active substances
4. Distribution of medicinal products via the Internet

Strictly speaking, very little is known regarding the introduction of safety features on the packaging of medicinal products subject to prescription. According to Article 54 of the new Directive, these features should enable the relevant entities of the supply chain to verify the authenticity and integrity of packaging. In order to verify the authenticity of a medicinal product, serialisation systems with 2D-datamatrix codes – as proposed by EFPIA or "securPharm"– could be used. But the EU Commission first has to specify this in delegated acts. For the implementation of the requirement concerning integrity, tear-open wrappers, seals or labels on the flaps might be possible. Working groups within the EU Commission are currently working on detailed specifications for these requirements. According to Dr Katrin Nodop, European Medicines Agency (EMA), implementing these requirements in practice will still take another three to five years. Nevertheless, most new packaging lines are already sold with an online 2D-code printer and reading unit today. This

may also be due to the fact that in some countries such as France, Turkey, China and Brazil 2D-datamatrix codes are already applied or will be shortly. They are/will be used, for example, for registration and reimbursement of the costs for medicinal products. Dr Martin Friedrich of Bayer Technology Services also advises dealing with the new requirements at this stage. It is also possible that member states such as France will start even earlier with implementation.

Changes regarding the supply chain will have particular affects on brokers and distributors in particular. In this context, a broker is a natural person or a company that never actually possesses the product but brings together two trading partners. In future, both will need to have a quality assurance system. Requirements on documentation will increase significantly. It is also new that the European authorities are going to inspect distributors in future. High priority is given to the creation of a European database, containing distributors and their GDP status. Dr Nodop states that this database will be ready for use at the beginning of 2013.

The measures regarding active ingredients and excipients shall render more secure products manufactured in third countries. These measures aim at assuring that the active ingredients have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the Union. A falsified ingredient is an ingredient for which wrong statements are made concerning identity, composition, manufacturer, country of manufacture or concerning its history, including the relevant documents and the channel of distribution.

In future, authorisation holders must confirm in writing that their API suppliers have been audited and that the EU GMP requirements (Part 2) on manufacturing are complied with. Manufacturers who wish to import an ingredient to the EU must have written confirmation from the competent authority of the exporting country confirming that the standards of good manufacturing practice during production are at least equivalent to those laid down by the Union. This also includes the necessity for a repeated and unannounced inspection of the manufacturer by the relevant authorities of that country. Exceptions to this rule are those countries appearing on the equivalence list maintained by the EU. The EU is going to evaluate the supervision of medicinal products in non-EU countries by means of an assessment procedure. This supervision includes the existing GMP rules, the system of inspections by the authorities and the question as to whether the Union is reliably informed on *cases of non-compliance*. The assessment has to be repeated every three years and authorises importing API without the written confirmations referred to above. This assessment shall take place in the relevant country by document review and a visit. If necessary, manufacturers will also be controlled by inspectors from EU authorities. According to Dr Jürgen Hoose, GMP Inspector, Hamburg, implementation will pose a great deal of problems. He states that accompanying an inspection in China would only be possible with the extensive help of interpreters.

The new Directive also deals with sales via the Internet. EU citizens shall be sensitised for the dangers of buying medicinal products via the Internet. Member states are furthermore invited to list authorised Internet pharmacies. These will have a logo on their Website showing their authorised status. EMA is going to provide for a Website referring to the relevant pages of the member states.

In addition to implementation of the new Directive 2011/62/EU an amendment to Chapter 5 (Production) of Part 1, EU GMP Guideline is also planned. This change comprises an extension regarding the qualification of suppliers of APIs and excipients posing an aggravated risk. Apart from securing compliance with GMP rules during production, integrity of the complete supply chain of starting materials will need to be ensured. That means auditing distributors and brokers in turn. These additional requirements will necessitate an increased involvement by the Purchasing Department of pharmaceutical manufacturers in the quality assurance system of the manufacturer of medicinal products.

BIO PRODUCTION FORUM MOVES R&D CLOSER TO INDUSTRIAL MANUFACTURING

Matej Janovjak, InSysteA*

The 7th Bio Production Forum which took place in Ulm this year, has once again succeeded in merging topics from the sectors of Product Development and Process Development to Production in one conference. Participants from ten European countries and the USA met for three days in June to exchange experience during the Conference. Further, various specialist exhibitors offered the opportunity to obtain information on the sectors of Production Technology, Analytics and Laboratory Services.

The declared aim of the Forum is to bring together the areas of early development and industrial manufacture even more closely. For this reason, this year's Forum also comprised an academic poster session for the first time. This poster session was supported by Boehringer Ingelheim and Cilag and attracted young scientists from Zurich, Vienna, Munich and Debrecen. The conference also reserved some time to provide the scientists with the chance to present their research in short lectures. The contributions – which were one of the Forum's highlights – ranged from lyophilisation of monoclonal antibodies and the influence of cyclodextrins on the stability of highly-concentrated antibody formulations to the examination of mechanical stress factors in disposable pumps used in biotechnology. The European Compliance Academy (ECA) awarded a prize to the three best posters (chosen by a jury).

The Conference was opened with a lecture by Prof R. Werner, Corporate Senior Vice President, Boehringer Ingelheim. He showed the methods for and trends towards long-term viable biopharmaceutical production. He explained the product and market connections in a clear context and described the practical aspects of technology platforms and integrated concepts from process development to large-scale manufacturing in a holistic manner.

The following lectures on product and process development focussed on protein stability and immunogenicity of protein aggregations in various formulations and the influence of factors such as pressure. Furthermore, insight was also provided to the control and characterisation of biopharmaceutical products using analytical methods such as capillary electrophoresis and analytical ultracentrifugation.

Using concrete data the speakers showed how misinterpretations of known data or prior knowledge influence the formulation or characterisation of proteins and can lead to incorrect formulations or characterisations.

The topic of "Quality by Design" was examined by Victor Vinci, Eli Lilly, through a highly-topical "A Mab Study" (PQLI Initiatives) from the industry's point of view. A special focus was attributed to CMC development processes, risk-based process development and the use of multidimensional data models.

The following contribution by Michele Dougherty, FDA, provided the participants with an overview of the authority's perspective of Quality by Design.

Two lectures on disposables in development and manufacturing processes and on GMP and the regulatory aspects of development of biopharmaceuticals constituted the transition to the last section of the Bio Production Forum. Topics such as requirements on classical rooms and ventilation shafts were explained and comparisons made between modern barrier systems such as isolator and RABS. This section was concluded with a lecture on visual control of the manufactured products.

A further highlight was, of course, the guided tour of the biopharmaceutical production at Boehringer Ingelheim in Biberach which was supported professionally in an excellent manner. The tour was intensively attended by Dr Friedrich Haefele and his colleagues and provided Conference participants with an insight into the production of active ingredients and isolator production. Details on planning and implementation of room concepts, production processes and material flow were also presented.

Participants and speakers were very satisfied with the topics and the overall organisation of the Conference. For many of the international participants the visit to Ulm, until then unknown, and the tour to the Cathedral and through the historical Fischerviertel (Fisherman's Quarters) represented further highlights of their trip.

***On the Author:**

Matej Janovjak, InSysteA GmbH, has more than 30 years experience in development, development strategies as well as in engineering and production of biopharmaceuticals. He worked for several years for Cilag AG in Schaffhausen. His last position was Director of Cross-Platform Process Management & Methods, GPSG EMEA. In 2010 he founded his own company with focus on the life cycle management of biopharmaceutical products.

EVOLUTION: NEW ANNEX 11 SUPPORTS A RISK BASED APPROACH

Yves Samson, Kereon*

After a three year long waiting time, the new Annex 11 to the European GMP has been released on 12th January 2011. This document comes within the continuity of the first version by covering more exhaustively the system life cycle. As a major evolution, based on ICH Q9 principles, this document takes into account and focuses on a risk-based approach.

A 20 years experience background

The genesis of this revision of Annex 11 should probably be found in the elaboration work for the PIC/S Guide PI 011. Indeed, the purpose of this Guide, released in 2003 – i.e. around 10 years after the first version of Annex 11 – is to provide recommendations to the inspectors – and consequently to the regulated user[1] and its suppliers – for reviewing the implementation of Annex 11. Between 1992 and 2003, the use of computerised systems experiences a dramatic increase. At the same time, the industry developed various approaches for fulfilling regulatory expectations as good as possible.

Main evolutions

The draft released in 2008 had to face numerous comments provided by the pharmaceutical industry and its suppliers. Finally, the 2011 version of Annex 11 gets back to and develops the topics addressed in the previous version.

- The necessity of mastering the life cycle – from the requirement until the retirement phase – is now an explicit requirement. This principle has been extended to the control of processes.
- One of the major evolutions is that IT infrastructures supporting regulated systems have to be "qualified", i.e. such IT infrastructures have to be kept under control trough the life cycle of the supported systems. As such, this requirement is not really new since it was widely implicit in the previous version of Annex 11 but mainly explicit in PIC/S Guide PI 011, §17.3.
  - It is also stipulated that internal IT organisations as well as external service providers have to be considered in the same way. This concerns in particular the needs for formal service respective operation level agreements defining the operational conditions of supported applications and systems.
- The key-principles of a science-based risk management derive directly from ICH Q9[2] focused on data integrity, patient safety, and product quality. Supplier management and service provider management rely on such consistent risk management as well. Although such requirements were not mentioned in the previous version of Annex 11, they were already part of PI 011.
- Different roles such as system owner and process owner are now clearly identified as major compliance actors. Even if the definition of these roles is less detailed than described in GAMP® 5**, the stipulated responsibilities are essential.
- Within the framework of a risk-based compliance approach, supplier effort could be significantly leveraged as long as the supplier has been consistently assessed.
  - For this reason, it is expected that "*quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request*". [A11:3.4]
- The section about the validation phase has been significantly improved.
  - The need to maintain an up-to-date system inventory – already mentioned in Annex 15 and promoted in PI 011 – is now emphasised in Annex 11.
  - The necessity to ensure a systematic requirement traceability throughout the life cycle is now clearly required. Additionally it is expected that this traceability is based on a documented risk assessment and GxP impact.
  - For critical systems, it is expected that a system description showing the system configuration, data flows, and security measures is available.
  - It is expected that the regulated user is able to provide evidence of the pertinence of test methods and that test scenarios could be demonstrated. Additionally, automated testing becomes acceptable as long as the adequacy of testing tools and test environments is documented.
    - Since automated testing tools could fit into the GAMP® Software Category 1, one of the ways for keeping such tools under control could be to apply recommendation and approach promoted by the GAMP® Good Practice Guide on "*IT Infrastructure Control and Compliance*".
  - Then data have to be converted in another format or transferred between two systems, it is necessary to validate such conversion or transfer and to include data verification in terms of value and meaning.
- The electronic signature is now officially recognised without becoming mandatory.
- The requirements regarding the operational phase are

[1] see PI 011, note 1

[2] Within the European GMP, ICH Q9 has been initially established as Annex 20. Since February 2011, this document – as well as ICH Q10 – has been released as part of European GMP Part III.

mostly based on good business and operation practices. Such requirements have been already widely mentioned in the previous version of Annex 11, however some of them have been established with more details in the new version.

- The operational requirements cover:
  - Data and accuracy checks
  - Data Storage
  - Printouts
  - Audit trails
  - Change and configuration management
  - Security
  - Incident management
  - Business continuity
  - Archiving
- Additionally to Annex 15 clauses 23 and 45 – establishing since 2001 the need for a formal periodic evaluation – the new Annex 11 repeats explicitly this requirement applying it to computerised systems.

Consequences

Without representing a revolution, this new version of Annex 11 has some implications, e.g.:

1. Compliance decisions based on results of risk management activities have to be justified. This expectation – already mentioned in PI 011 – is now becoming a mandatory regulatory expectation. This implies that risk management activities must be conducted consistently and rigorously.
2. The condition for leveraging supplier involvement is to put in place rigorous processes regarding supplier evaluation and selection as well as supplier management. At the same time, some transparency to inspector is expected (and necessary), see clause 3.4.
   For critical systems, the need for a stand-alone detailed description – not only embedded in the Validation Plan or in the URS – as described in the previous version of Annex 11 is confirmed. It is to notice that such document can be easily prepared based on the recommendations provided in GAMP® 5, Annex D6.
3. The yearly revision of Validation Master Plans (VMP) offers an excellent opportunity for reviewing and maintaining the system inventory up-to-date.
4. The supporting processes to the operational phase – already mentioned in the previous version of Annex 11 – are clearly stated. Additionally the requirement to evaluate periodically the compliance state of the systems enforces the importance of the operational supporting processes.

Annex 11 vs. 21 CFR 11: Differences and Similarities

Annex 11 and 21 CFR 11 have different positions within their respective regulatory contexts. Indeed, while 21 CFR 11 discusses only the implementation of electronic records and electronic signatures within the GxP scope as defined in the predicate rules, Annex 11 is focused on the use of computerised systems in GMP environments.

Therefore the main requirements related to system life cycle (until system retirement), supplier management, as well as to qualification and validation activities as defined in Annex 11 could be summarised in 21 CFR 11 by the paragraph 11.10(a) which stipulates that the validation of computerised systems is the necessary and unavoidable requirement for establishing electronic compliance. Additionally the revised Chapter 4 about documentation is much more detailed and prescriptive than 21 CFR 11.

The electronic signature manifestation is not explicitly identical in both texts. 21 CFR 11 requires the signature meaning as part of the signature. Annex 11 does require it implicitly since signature meaning is in all cases a requirement for GxP documentation as stated in Chapters 1 and 4. However, excepted for batch release – which is specifically discussed in Annex 11 – the impact of electronic signatures as equivalent to hand-written signatures is limited to the boundary of the company[3]. Within a different legal context as in the European Union (see 1999/93/EC and 2000/31/EC), 21 CFR 11 establishes electronic signatures as "*legally binding equivalent*" to hand-written signatures.

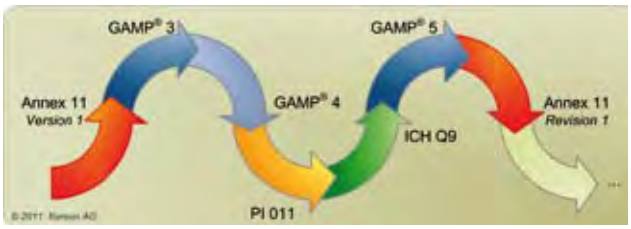
Nevertheless both texts lay down the principle of an immutable link between the signature and the signed record as an essential and unavoidable compliance requirement.

Annex 11 does not require that organisations submit to the Agency a declaration regarding the use of electronic signature for GxP activities. Likewise Annex 11 does not require that persons using electronic signature have to provide a specific certification regarding the use of such signature.

Convergence and future developments

This revision of Annex 11 – including Chapter 4 of European GMP – results from an iterative process along two decades, see Figure 1.

Based on a continuous and valuable experience sharing between regulators and industry, this process allows to



define a demanding but consistent approach to electronic compliance commensurate to the criticality of the concerned processes. The convergence between regulatory requirements and industry recommendations such as provided by GAMP® establishes a stable regulatory basement allowing the pharmaceutical industry and its suppliers to define a cost-effective and efficient approach to compliance.

[3] The wording of this requirement is particularly important since it gives a more limited and more pragmatic definition of the electronic signature than settled in the European Directives 1999/93/EC and 2000/31/EC.

The next version of the PIC/S Guide PI 011 should give the opportunity to the regulators to precise and to clarify the impact and the extent of some requirements as well as the expected level of implementation detail. Regarding the draft for comment published in 2008, the new revision of Annex 11 as released in January 2011 represents both a return to the roots as well as a significant evolution in terms of compliance maturity.

*On the Author:

Yves Samson is founder and Director of the consulting firm Kereon AG located in Basle, Switzerland. He has been in computerized system validation since 1992. He is the editor of the French Version of GAMP® 4 and GAMP® 5 and he translated the PIC/S Guide PI 011 into French. He is the co-founder and chair of GAMP Francophone. He is an active member of the ISPE IT infrastructure SIG and member of the French affiliate board.

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cGMP COMPLIANCE QUESTIONS TO AUTHORITY REPRESENTATIVES AND INDUSTRY EXPERTS

Authority representatives and industry experts regularly answer questions frequently asked during courses and conferences. This time the series covers questions with respect to Annex 11 that were asked during the German Computer Validation Conference and answered by various speakers.

Q&As ON ANNEX 11*

Compiled by Dr Andreas Mangel, CONCEPT HEIDELBERG

Since 30 June 2011 the industry has to implement all requirements of Annex 11 "Computerised Systems" of the EU GMP Guideline. Within the context of the Conference on Computer Validation in Mannheim, Germany, in June 2011, authority representatives and industry experts have answered questions concerning the 17 chapters of Annex 11. Here you will find the questions and answers on some of these chapters.

Chapter 1 – Risk Management

Speakers:

- Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
- Dr Jörg Schwamberger, Merck KGaA

Annex 11: "Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system."

What can elements of risk management contribute towards defining the extent of testing of specific elements (such as validation, data integrity)? What does it mean "to determine the extent of validation through risk management"? Does it mean the number of test cases or the depth of the test?

Using elements of risk management, validation measures such as design specifications, extent and depth of testing as well as type and frequency of tests/reviews after putting into operation (periodic evaluation) etc. can be determined precisely.

Chapter 2 – Personnel

Speakers:

- Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
- Dr Jörg Schwamberger, Merck KGaA

Annex 11: "There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT. All personnel should

have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties."

What should be understood by "close cooperation between all relevant personnel …"? What formal requirements should be observed?
No defined formal requirements exist for close co-operation between all relevant personnel during validation. But efforts must be made to ensure that a corresponding division of roles and tasks between the relevant personnel is clearly defined and implemented, including IT.

What training is expected of the relevant personnel?
Requirements concerning training result from the relevant operational provisions on validation. This means that the relevant personnel should know the main regulations concerning their tasks and be able to demonstrate the internally required qualifications to perform the tasks in question. This already arises from the general GMP requirements over and above Annex 11.

Is a formal qualification required (such as ITIL training or something similar)?
Annex 11 contains no further formal requirements concerning personnel qualification other than that resulting from the operational context (see answer above).

What role has a QP to play in validation?
The QP does not have to play a formal role in validation. But inclusion of a QP is recommended as it is the task of the QP to finally release the manufactured product. This release can only be authorised knowing the quality systems used for the proper validation.

Does the QP substitute QA in validation?
The exact responsibilities need to be laid down in the operation procedures. Annex 11 proposes a division into roles that may, however, be independent of a QP and/or QA. Thus the role of the QA has to be defined internally and independently of the function of a QP.

Chapter 3 – Suppliers and Service Providers
Speakers:
- Klaus Eichmüller, Local Administration of Upper Bavaria (Regierung von Oberbayern)
- Dr Jörg Schwamberger, Merck KGaA

Annex 11:
"3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.

3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.
3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.
3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request."

Why do inspectors want to see the supplier's audit reports? Doesn't this contradict the confidentiality agreements with the suppliers?
Without the opportunity to inspect the activities concerning qualification of suppliers, inspectors may not be able to fully evaluate whether due care was applied. In principle, confidentiality agreements are legally subordinated to the relevant legislative provision. Nevertheless, it is recommended that the confidentiality agreements are adjusted accordingly. Apart from that, inspectors are bound by an obligation of secrecy ex officio.

Which points should be taken into account from the inspectors' point of view when evaluating suppliers?
When evaluating suppliers it has to be ensured in general that the supplier's suitability for the task to which he is to be entrusted, is evaluated as well as his ability to accept responsibility for this task.

Are there requirements concerning the auditing of sub-suppliers?
Sub-suppliers (= external suppliers, sub-contractors) must not be audited separately by the contractor if it can be ensured that the principle supplier has laid down regulations ensuring the quality of his suppliers and that these regulations are demonstrably used. The relevant revisions must be documented. The contractor's evaluation should include the ability of the supplier to evaluate the suppliers on his part.

What demands on user requirements are put on COTS (commercial off the shelf) products?
Insofar as COTS products are used for GMP-regulated tasks, their suitability must be demonstrated accordingly within the context of validation. In doing so, the user requirement should define the intended purpose in the company.

What formal requirements exist concerning the choice of a supplier? Must the choice be documented and justified?
The choice of a supplier must be documented and his suitability demonstrated by means of compliance with the pre-requisites in the user requirements.

Does the external supplier/internal IT have to have his/its own QMS? If so, what requirements does this QMS need to fulfil?

If it is ensured that the external supplier/internal IT works according to the customer's regulations, the external supplier does not need his own QMS. It is recommended that this is possibly laid out in a contract and supported among other things by way of respective training. Otherwise the supplier is obliged to maintain a QMS that is demonstrably suitable for his activities.

Chapter 4 – Validation

Speakers:

- Dr Arno Terhechte, Regional Government of Münster (Bezirksregierung von Münster)
- Eberhard Kwiatkowski, Bayer HealthCare

Annex 11:
"4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.
4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.
4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.
For critical systems an up to date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.
4.4 User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.
4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.
4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.
4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.
4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process."

What is the definition of "relevant systems"?
Inventory: Relevant / Substantial systems are systems used in order to implement or assist GMP requirements. These systems can be identified within the context of a risk analysis (also supported by a questionnaire).

Is there a definition for "critical"?
No, but Annex 11, chapter 1 gives an indication. Critical systems are systems that directly or indirectly influence patient safety, product quality and data integrity.

How exact must GMP functionalities be described in the inventory?
Only relevant to GMP – yes/no. In the inventory, a description of the general functions is sufficient, i.e. archiving of data, parts list management etc. Detailed information can be found in the system description.

In what way can the URS be created on the basis of a risk analysis if the risk analysis requires an URS as a pre- requisite?
URS and risk analysis are two elements within the context of validation of computerised systems which are closely linked with each other. Requirements can result from a risk analysis but on the other hand it is possible to reach functional solutions on the basis of user requirements on the assessment of risks.

Data flows – does this also mean intersystem interfaces (for example, the interfaces between different modules in ERP- systems)?
Every intersystem interface should be described, including any relevant changes of data format.

Must all user requirements be traceable or only the ones classified as being GMP-relevant?
User requirements, especially those classified as being GxP-critical should be traceable in order to evaluate whether the computerised system is fit for the respective purpose.

What levels of control are expected when using automated test tools?
The level of control results from the criticality of the systems tested and the type of test tools used. A complete validation is not generally expected.

What should test scripts and test results look like in order to be accepted by the inspectors?
Test scripts should contain a specification (expected result) and a description (test performance). The test result should indicate whether the specifications are fulfilled. Failed tests must be evaluated.

Conference Tip

- **ECA European Computer Validation Conference – The new Annex 11**
  Copenhagen, Denmark, 15/16 May 2012

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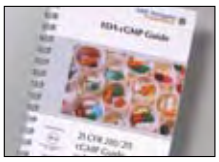

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ISSN 1867-7975