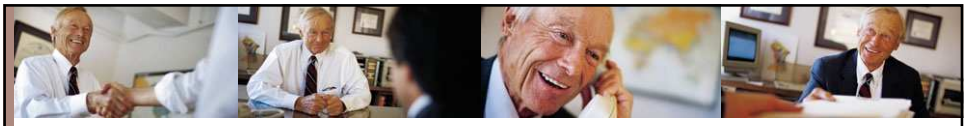
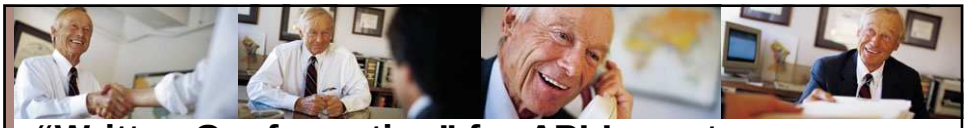


Recent Updates on European Requirements

and what QPs are expected to do

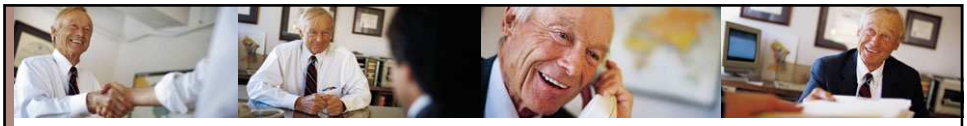
QP Forum
28/29 November 2013, Lisbon
Dr. Bernd Renger

Modified: Georg Goestl



"Written Conformation" for API-Import Actual Status of Implementation

- Progress report of the EU Commission lists 20 countries accounting for 97% (?) of all non-EU API manufacturing sites supplying the EU
  - Countries ***accepted*** for the waiver list
    - Australia, Japan, Switzerland, and US
  - Countries applying for the waiver list and ***under assessment***
    - Brazil, Israel, Singapore, and New Zealand
  - Countries that already have issued Written Confirmations or that have announced to issue Written Confirmations
    - Argentina, Brazil, Canada, **China, India**, Israel, Mexico, Malaysia, New Zealand, Russia, Singapore, South Africa, South Korea, Taiwan, Thailand, Turkey, and Ukraine

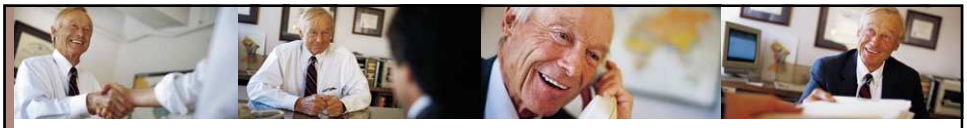


EU GDP Guideline, Revision 2013

- Good Distribution Practice of Medicinal ***Products for Human Use***
- Effective of September 2013
- Requirements
  - Critical steps to be validated
  - Quality System
  - Management Responsibility
  - Quality Risk Management
  - Management Review
  - Responsible Person
  - Dedicated transportation and equipment

Grey: new chapters
Blue: existing chapters

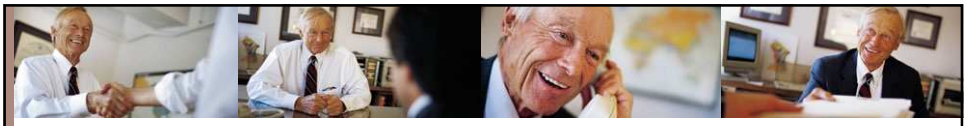
3



Draft EU GDP Guideline for APIs

- Draft Guideline outlining principles Issued for public consultation in February 2013, ended April 2013 (responses published on Nov.8)
- Addressed to distributors involved in procuring, importing, exporting, holding or supplying active substances
- Re-packaging, re-labelling or dividing up not in scope → considered manufacturing activities → GMP applies
- Registration required, Quality System required
- Requirements are very strict and very similar to :
  - GMP regulations
  - GDP for Medicinal ***Products for Human Use***
- … may pose problems to many of the actual distributors of APIs!

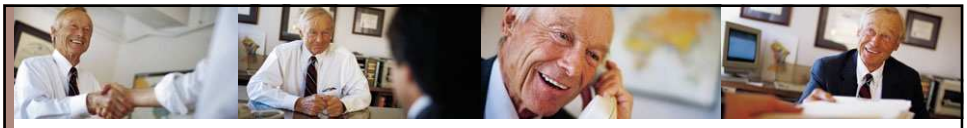
4



GMPs for Excipients

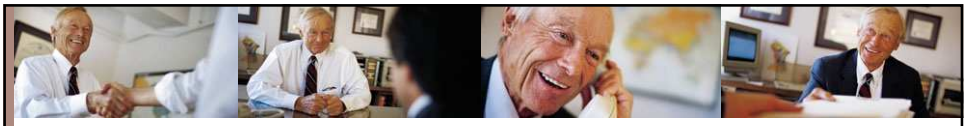
Required by Directive 2011/62/EU

- The holder of the manufacturing authorisation shall ensure that the ***excipients*** are suitable for use in medicinal products by verifying the ***appropriate good manufacturing practice*** on the basis of a ***formalised risk assessment*** …
- May accept ***other suitable quality system requirements***
- … risk assessment … shall take into account the ***source and intended use of the excipients*** and previous incidents
- ***Draft Guideline on the formalised risk assessment issued by the European Commission, public consultation ended April 2013*** (responses published on Nov.8)



Guideline on the Formalised Risk Assessment

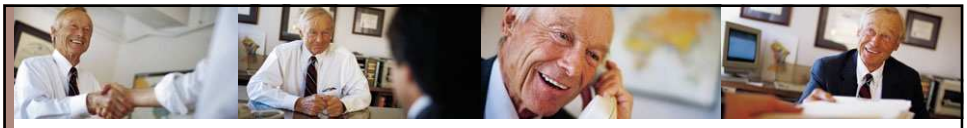
- *Guidelines on the Formalised Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use* (responses published on Nov.8)
  - ...provides guidance on how to assess and rank the risk presented by the excipient itself
  - ...describes identification of appropriate GMP and assessment, ranking and control of the risk profile of the excipient manufacturer
    - Other quality system may be accepted - ISO 9001, ISO 13 485
  - ...presents guidance on how to manage the risks of use of the excipient on an on-going basis
  - Monitoring



EU GMP Guide Part I, Revision

Chapter	Title	Status
1	Pharmaceutical Quality System	Effective 31 Jan. 2013
2	Personnel	Effective 16 Feb. 2014
3	Premises and Equipment	Draft, public consultation*)
4	Documentation	Effective 30 June 2011
5	Production	Draft, public consultation*)
6	Quality Control	Draft, public consultation*)
7	Outsourced Activities	Effective 31 Jan. 2013
8	Complaints, Quality Defects and Product Recalls	Draft, public consultation*)
9	Self Inspection	*Not under revision yet*

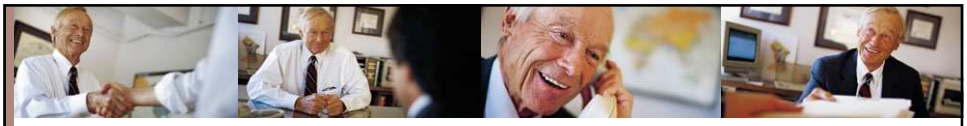
*) Public consultation of all 4 drafts ended 18 July, 2013 , responses published on 8 Nov. 2013



EU GMP Guide, Annexes, Revision

Annex	Title	Status
1	Manufacture of Sterile Medicinal Products	*Under discussion (EMA)*
2	Manufacture of Biological Active Substances and Medicinal Products for Human Use	Effective 31 Jan. 2013
11	Computerised Systems	Effective 30 June 2011
15	Qualification and Validation	Public consultation of Concept Paper (closed)
16	Certification by a Qualified Person and Batch Release	Draft, public consultation *)
17	Parametric Release	Public consultation of Concept Paper (closed)

*) Public consultation ended 5 November 2013



Revision EU GMP Guide, Part I, Chapter 2

- "***Personnel***"
- Basic principles of the chapter have been unchanged; however a few new topics have been introduced
  - ➢ More important role of Senior Management
    - o Has the ultimate responsibility to ensure an effective quality management system is in place
    - o Must maintain the quality management system and continually improve its effectiveness
    - o Has to establish a Quality policy
    - o Should participate in the Management Review
    - o Must provide adequate resources

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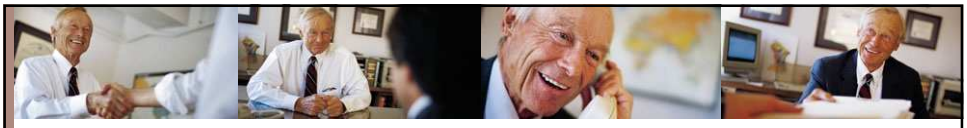

Revision EU GMP Guide, Part I, Chapter 2

- The current version assigned quality related responsibilities to
  - ➢ the Head of Quality Control
  - ➢ the Head of Production
- The heads of Production and Quality Control must be independent from each other
- Key positions should be occupied by full-time personnel
- If neither of these two is also responsible for the duties and responsibilities of a Qualified Person (QP), an adequate number, but at least one QP has to be designated.

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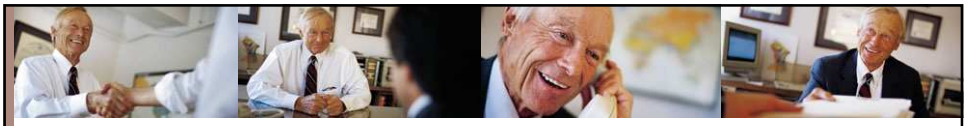
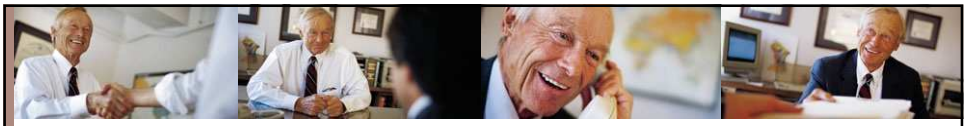


Revision EU GMP Guide, Part I, Chapter 2

- Following actual industry trends, additionally and depending on the size and organisational structure of a company …
  - …a "*separate Head of Quality Assurance or Head of the Quality Unit **may** be appointe*d"
  - In this case, some of the responsibilities ***can be*** shared with the Head of Quality Control and Head of Production.
  - Roles, responsibilities, and authorities must be clearly defined
- Does not support the wide spread concept that QC is subordinated to and must be monitored by QA ("QC as manufacturing department production analytical results")
- Section „Consultants" has been added (similar to 21CFR & WHO-GMP)



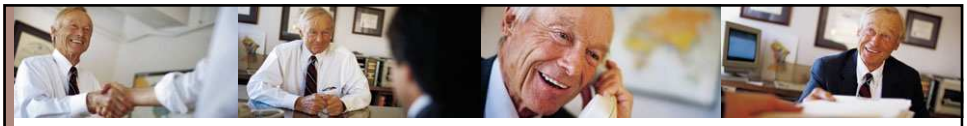
Draft Revision EU GMP Guide, Part I, Chapter 3

- ***"Premises and Equipment "***
- Sections 6 on prevention of cross contamination has been expanded
  - The unclear and controversial wording "particular medicinal products" for which dedicated facilities had been required has been deleted completely and been replaced by
    - *Dedicated facilities are required for manufacturing when a medicinal product presents a risk:*

      a) Which cannot be adequately controlled by operational and/ or technical measures or

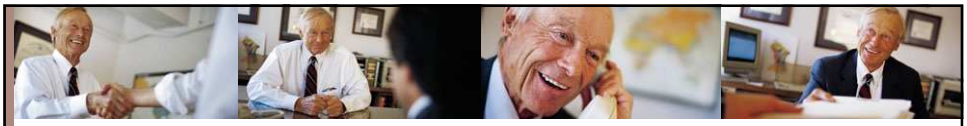
      b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

      c) Threshold values derived from the toxicological evaluation are below the levels of detection



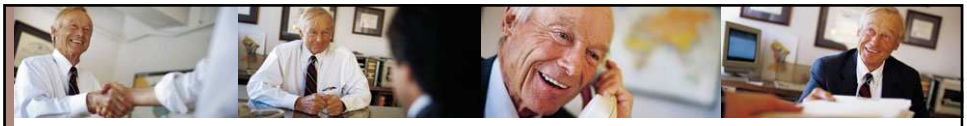
Draft Revision EU GMP Guide, Part I, Chapter 3

- Section 6 refers to revised chapter 5 and use of the new toxicological guidance
  - EMA: **Draft guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities**
  - Developed by Safety Working Party (not only inspectors)
  - Released for public consultation in January 2013; deadline for comments 30 June 2013
  - Chapters 3 and 5 should be read in conjunction with this Guideline → more scientific approach to cleaning validation!
    - 1/1000 dosage or 10 ppm criterion abandoned!



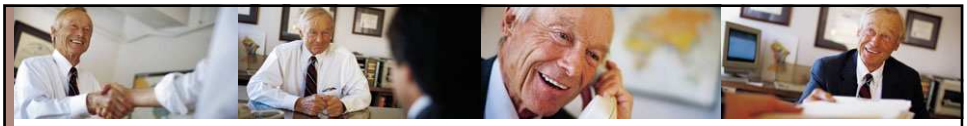
Draft Revision EU GMP Guide, Part I, Chapter 5

- ***"Production"***
- Includes new requirements for
  - Prevention of cross contamination → Use of the new toxicological guidance
  - Qualification and auditing of suppliers
  - Supply chain traceability
  - Appropriate procedures or measures to assure ***the identity of the contents of each container of starting material***
  - Acceptance of supplier CoAs
    - Only to be accepted if a formal agreement is in place, and audits and full analysis are performed at appropriate intervals
  - Guidance on notifying EMA in case of restrictions of supply



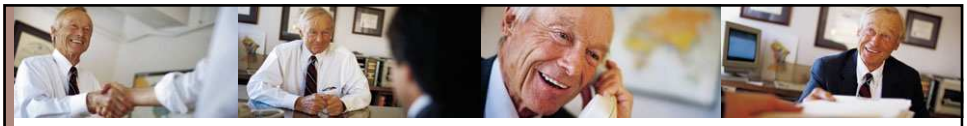
Draft Revision EU GMP Guide, Part I, Chapter 5

- Prevention of cross contamination
  - Follows Quality Risk Management approach
  - New list of technical measures & organisational measures that may be taken to minimise the risk of cross contamination
    - Use of barrier systems (RABS or isolator)
    - Localised extraction of dust
    - Use of dedicated equipment including maintenance tools
    - Use of disposable equipment
    - Use of validated CIP processes
    - Air and surface sampling outside the working area to demonstrate the efficiency of the measures chosen
    - Campaign basis (dedicated by separation in time)
  - Proposal of cleaning verification after each product campaign instead of a cleaning validation (already existing but more or less neglected yet)



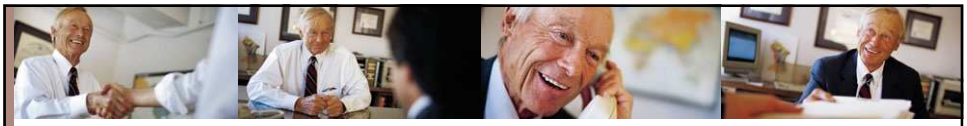
Draft Revision EU GMP Guide, Part I, Chapter 6

- "***Quality Control***"
- Revision focus on current practice in analytical method transfer
  - Method transfer considered root cause for OOS results at contract laboratories (?)
- Other new requirements
  - Procedure for the investigation of Out Of Specification and anomalous results and Out Of Trend results
  - In-use shelf life of chemicals and reagents should be established / documented and scientifically justified
  - Some specific requirements related to microbiological testing



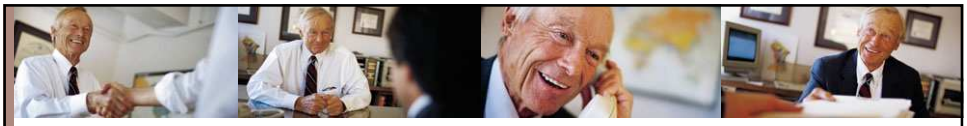
Draft Revision EU GMP Guide, Part I, Chapter 8

- Name changed to "***Complaints, Quality Defects and Product Recalls***" including Quality Defects
- Major revision to reflect ***Quality Risk Management*** principles and clarify expectations for defect reporting.
- New chapters on
  - Investigation and Decision Making
  - Root Cause Analysis and Corrective and Preventative Actions
- Clarifies reporting responsibilities in case of quality defects or suspected defects or falsifications



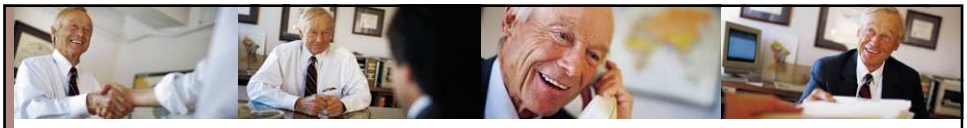
Draft Revision EU GMP Guide, Annex 15

- "***Qualification and Validation***"
- Concept paper, public consultation ended February 2013
- Revisions needed include elements of ICH Q8 -10 and advancing technologies, such as PAT and the new chapters 3 & 5
- To be harmonised with ***revised EMA Guideline on Process Validation*** (to replace the 2001 version)
  - Draft for public consultation, deadline for comments ended October 2012
- Introduces several new elements & concepts
  - Process Analytical Technology (PAT), Quality by Design (QbD), Real-Time Release Testing (RTRT), Continual Verification



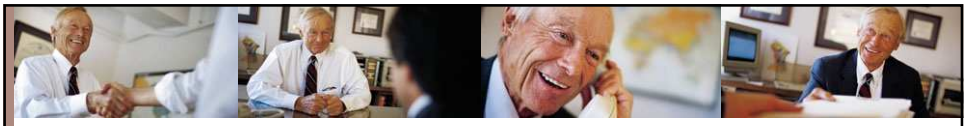
Draft Revision EU GMP Guide, Annex 16

- "***Certification by a Qualified Person and Batch Release***"
- Draft issue 5 July 2013, deadline for comments 5 November 2013
- Intention of the revision:
  - Clarify ***certification*** versus ***batch release***
  - Specify QP Discretion (replace "Discretion Paper") in case of unplanned deviations during manufacture and testing
  - Address supply chain knowledge
  - Address QP delegation
- Emphasises applicability in the EEA region



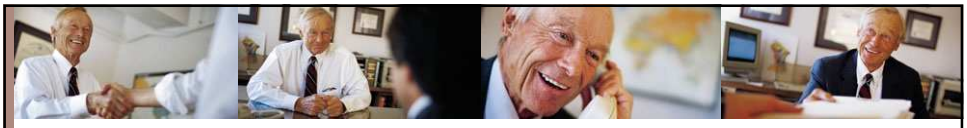
Draft Revision EU GMP Guide, Annex 16

- 2.1. The ***ultimate responsibility*** for the performance of an authorised medicinal product over its lifetime; its safety, quality and efficacy ***lies with the marketing authorisation holder*** .
- 2.2. However, the ***responsibility for ensuring that a particular batch*** has been manufactured in accordance with its marketing authorisation, with EU Good Manufacturing Practice (GMP), or equivalent, and that it is in compliance with the laws in force in the Member State where certification takes place and of the destination country of the medicinal product, ***lies with the QP certifying that batch as being suitable for release***.



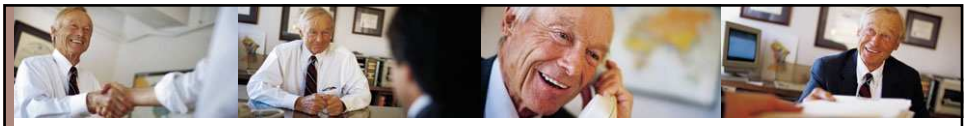
Draft Revision EU GMP Guide, Annex 16

- The process of batch release comprises of:
  - The checking of the manufacture and testing of the batch in accordance with defined release procedures.
  - The ***certification of the finished product batch performed by a Qualified Person*** signifying that the batch is in compliance with EU GMP and the requirements of its marketing authorisation
  - Assigning of ***release status*** to the finished batch of product which ***takes into account the certification performed by the QP***. This is the final step in the process which effectively releases the batch for sale or export. This could be done by the QP as an integral part of certification or it could be done afterwards by another person. In this case, this arrangement should be delegated by the QP in a SOP or contract.



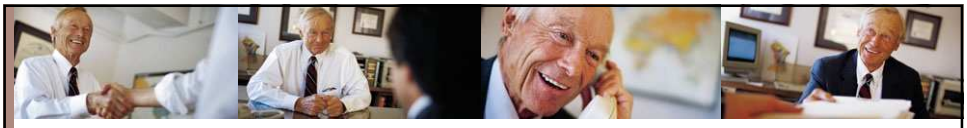
Draft Revision EU GMP Guide, Annex 16

- 3.5. ***Operational responsibilities*** of the QP prior to certification of a batch for release to market or for export, the QP must ***personally*** ensure that:
  - 3.5.1 Certification is permitted under the terms of the manufacturing / importation authorisation (MIA).
  - 3.5.2 Any additional duties and requirements of national legislation are complied with.
  - 3.5.3 Certification is recorded in a register or equivalent document.

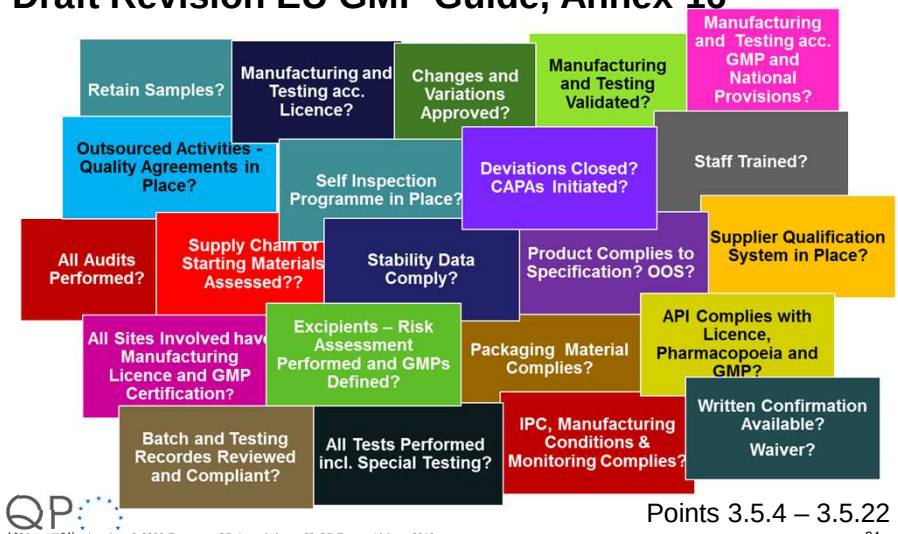


Draft Revision EU GMP Guide, Annex 16

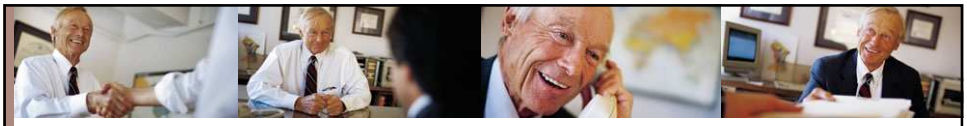
- In addition the QP has responsibility for ensuring the following ***points 3.5.4 – 3.5.22***. These may be ***delegated to appropriately trained personnel*** or ***third parties***. It is recognised that ***the QP will need to rely on a quality management system.***
- The QP should ***have on-going assurance that this reliance is well founded.***



Draft Revision EU GMP Guide, Annex 16

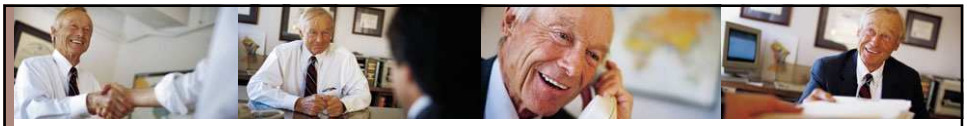


Points 3.5.4 – 3.5.22



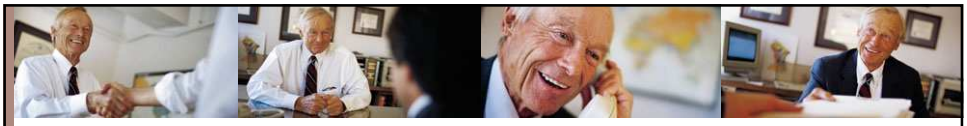
Draft Revision EU GMP Guide, Annex 16

- Includes main features of the EMA Position Paper as Chapter 5 "***Handling of Unplanned Deviations***"
  - Registered specifications for active substances, excipients and finished products must be met
  - A batch with an unplanned/unexpected deviation from details contained within the Marketing Authorisation **and/or GMP** may be certified if…
  - … a risk assessment clearly indicates deviation has no "material effect on product quality, safety or efficacy" and
  - … the need for inclusion of the affected batch in the on-going stability programme has been evaluated



Draft Revision EU GMP Guide, Annex 16

- QP performing certification must be aware and take into consideration any deviations which have potential impact for compliance with GMP or the Marketing Authorisation
- The ***entire supply chain*** of the medicinal product must be documented and available for the QP
  - Manufacturing sites of the starting materials and components
  - All parties involved in any manufacturing and importation activities of the medicinal product
- Preferably in the format of a ***comprehensive diagram***
  - including subcontractors of critical steps such as e.g. the sterilisation of components and equipment for aseptic processing



Draft Revision EU GMP Guide, Annex 17

- ***"Parametric Releas***e"
- Concept paper, public consultation ended February 2013
- Intention of the revision:
  - Align the annex with technology advances and changes to other chapters and annexes since it was first published in 2002
  - Extend underlying concepts to areas other than sterility tests