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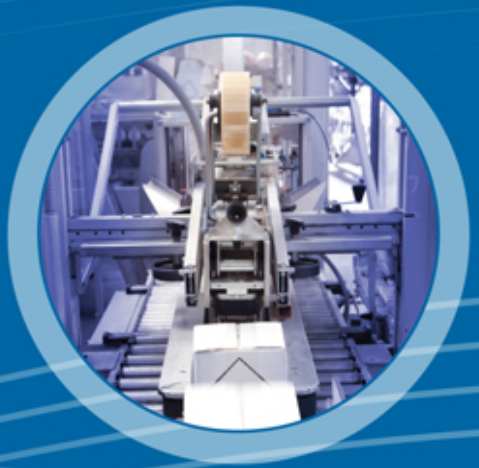
GMP challenges to the API manufacturing sites



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APIC presentation/perception

- This presentation reflect the views of the Active Pharmaceutical Ingredients Committee (APIC),

  a non profit association of European API manufacturers
  - research based and generic companies
  - focused on GMP and regulatory topics of APIs

Agenda

- Is ICH Q7 still relevant ?
- What has changed / impacting the industry
- How can the industry take advantage of current GMP requirements for APIs or what can industry “do better “
- What is challenging and what is right with current Inspection practices?
- Conclusions

ICH Q7

- Finalised November 2000
  - Transcribed to an EU Directive (‘delegated act’ 2014)
- “Globally accepted”
- Why?
- It tells you “what to do” but not “how to do”
  - Based on good scientific understanding
  - Flexible
    - You can do things your way
  - Pragmatic
    - Applying increase in GMP from RSM to final API
  - Was developed visionary
    - Include already GDP elements and support principles of ICH Q-11

ICH Q7 – still applicable ?

- ICH Q7 was ahead of its time
  - *In this Guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.*
  - *Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.*

  - Risk Management principles
  - Allows industry to use its knowledge of manufacturing site, facilities and process(es) to determine criticality

ICH Q7 – still applicable ?

- ICH Q7 has imbedded into itself current GMP and GDP concepts
- Consider ICH Q9, 10 and 11/8 and the previous statements
- Overall ICH Q7 is current, however:
  - Industry has not embraced Q11 principles retrospectively as expected
  - ICH Q7 is not always followed as intended
  - ICH Q9 principles is sometimes miss understood
    - Risk Management and Assessment is not Risk allowance
- **Other factors affecting the Industry to be discussed later**

What has changed since Nov 2000?

- Globalisation of API manufacture
- Serious quality defects with API and the API supply chain being open to fraud/counterfeit activities which drives additional requirements
- Economic pressure on the Industry – is it still a level playing field?
  - QP API declarations
  - Written Confirmation
    - But still we have issues with API supply chain
  - Mandatory API Inspections – why not ?
  - More fraudulent acts/poor GMP standards being exposed. Why is this ?
    - Better detection/focus
    - More issues
- Audit and inspection requirements/frequency – some sites struggle to support demand

Experience with Shared Audits – preventing audit overload

APIC Third Audit Party Program – A success story since 2005

- **Benefit**
  - Companies can focus audit activities on there ‘critical’ APIs and other commodity items
  - No conflict of interest and confidentiality is maintained
  - Audit reports / companies responses are made available after the audit
  - Re-audits are possible under the scheme

Other considerations

- Regulatory Requirements – are they harmonised globally ?
- ICH Q9, ICH 10 and ICH 11 (8)
- Lack of regulatory relief
  although better than it was stifles innovation/cost saving
- Definition of a Registered Starting Material (RSM)
  - Where does GMP begin?
  - RSM is where GMP according to ICHQ7 beings
- Control of more highly hazardous APIs
  - e.g. EMA view on cleaning of dedicated facilities, Will probably not include APIs as the wording in Q& covers current philosophy and concepts

What does this mean to Industry ?

- Current risk based approach and application of good science/ process knowledge imbedded into current GMP requirements aids the Industry and Authorities/Inspectors

- For example “all critical deviations….” “evaluate critical raw materials…..”
  - Companies can use knowledge of *their* process to demonstrate what is and what is not critical:
    - Defines what needs to be covered by ICH Q7
    - Leads to less rejections, reprocessing…..

What does this mean to Industry ?

- The flexibility of ICH Q7 allows for innovative thinking and practices
  - Remember ICH Q7 is a what to do not a how to do guideline
- Industry should use existing knowledge and expertise on current GMPs to aid continuous improvement from a GMP and business perspective
- Remember ICH Q7 needs to be read and understood in its entirety not focus on one specific statement
  - The ICH Q7 Implementation Working Group (ICH Q7-IWG) is working on a Q&A document

What does this mean to Industry ?

- Economics and globalisation has made the control of the supply chain more difficult
  - Industry and Authorities were slow to react to the consequences
- Some might consider ICH Q7 does not cover globalisation adequately
  - Anyhow these aspects related to manufacturing and distribution of APIs goes beyond the GMP/GDP scope
  - There is limited enforcement and control outside the GMP/GDP area
- Frequency of Inspections/audits are not always risk based

Inspections by Authorities

- Inspections play a vital role in ensuring patient safety
- People may sometimes forget they are a snap shot in time (same as audits) nor do they cover every aspect of a facility, process, documentation etc. during a site visit
- Inspectors/authorities are encouraged to share more information to make Inspections:
  - More effective
  - More risk based
  - Reduce the burden on Industry
- Consider quality culture as part of risk assessment of companies for Inspection agenda and frequency

Inspectors

- Be more open to fraudulent acts and data integrity issues
- Remember there are many ways of operating within the API Industry and do not bring unconscious bias to Inspections
- Separate successful application of the principles according to ICH Q7 from imposing more stringent *'requirements'* based on 'best practices' they might have seen in one company
  - API companies/ facilities know their site and processes to enable appropriate definition of what is and what is not critical
- Remove inconsistent approaches to Inspections by facilitating harmonised training (e.g. with PIC/S)
- Authorities – promote the globalisation of ICH Q7 principles and not individual country requirements
  - Do we need a "how to do" for inspections ?

Inspectors – some examples

- A company was cited for not doing an audit of a Registered Starting Material (RSM) and reference was made to ICH Q7 section 7.11

  "Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials"

- RSM was an API from a facility frequently Inspected by authorities. This data formed part of their evaluation of the RSM supplier

Inspectors – some examples

- An Inspector wanted testing for process related impurities if certificate of cleaning was not part of the QC release documentation for a solvent delivered in road tankers. Certificates were removed from the QC documentation requirements based on a satisfactory audit of the solvent supplier

- ICH Q7 section 7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:
  - certificate of cleaning
  - testing for trace impurities
  - audit of the supplier

Conclusion

- Industry has a good GMP guideline(s), which includes todays expectations on ‘GDP for API’ aspects, to use for regulatory compliance
- ICH Q7 is appropriate and will be better supported with the ongoing ICH Q7 Q and A activity by ICH, which is developed jointly with EMA/EC, US-FDA, MHLW/PMDA, PIC/S, EDQM-CEP, WHO and authority representatives from Brazil, South Korea and Singapore
- Industry needs to develop based on the principles of ICH Q7 to improve compliance and business requirements
- Inspections should be risk based for frequency and focus on the appropriate areas of concern
- Globalisation of ICH Q7 as the standard to be used to be advocated wherever possible

APIC fully supports this

PIC/S-PDA ICH Q7 training curse

for industry and regulators

to facilitate harmonised interpretation of

ICH Q7