GMP Ministerial Ordinance
the APIC view

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Introduction

- Marieke van Dalen
- Working for Aspen Oss B.V. in the Netherlands, an API producing site.
- Over 35 years of experience in the regulatory field
- Board member of APIC, a Technical European Industry Association, based in Brussels, with focus on APIs from a quality and regulatory perspective.
- APIC is the API observer in the ICH and is a recognized discussion partner for many authorities including Anvisa, EDQM, EMA and the FDA.
- Apologies for not being present in person.

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Global GMP

- ICH guidelines are intended to be used globally.
- ICH Q7 (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients) is one of the so-called “tier 1” guidelines, which means that a country that wants to become an ICH member needs to have implemented this guideline.
- Obviously, this ICH Q7 guideline is considered as one of the most important guidelines to ensure patient safety throughout the world.
- Yet, when you only look at the quality of a single batch of API, there is no way to tell if GMP was applied!

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Global GMP

- GMP requirements as laid down in e.g. ICH Q7 guidelines tells the Industry “what to do”. Industry always needs to know “how to do”.
- Often guidelines are “translated” from
  global (ICH)
  to regional (e.g. European)
  to national (e.g. the Netherlands)
  to company level (e.g. Aspen Oss B.V.).
- Each of these transformations/translations means that there can be a loss or addition of information (and maybe even of intent).

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Global GMP

- Because the Industry is very keen on learning “how to do”, APIC has published a document called the “Interpretation of ICH Q7”. The document is revised regularly to keep up with Industry practice.
- This document can be found on the APIC website (also open for non members)
  publications (cefic.org)
- APIC regularly gets positive feedback on this very useful document.

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Global GMP

- Example from the “Interpretation of ICH Q7” document

Chapter 2 Quality management

2.1 Principles

Among GMP other aspects, such as quality systems, environmental controls, and safety, are necessary to be taken into account in order to be in compliance with regulations. Business efficiency and continuous improvement are needed to be competitive. Therefore, GMP compliance should be incorporated into an overall Quality Management Systems (QMS) as it is recommended in the EU GMP philosophy and ICH Q10 ensuring benefit to the patient. Whether electronic or manual systems and records are used for all GMP requirements of ICH Q7, data integrity needs to be maintained. The importance of an effective QMS on customer relations, continuous improvement, regulatory compliance, inspection readiness and supports ensuring supply of drug products to the market.	
2.10	Company management should empower all appropriate organisational functions to apply the Quality policy and procedures. Assignment of clear Roles & Responsibilities for duties and decision making is the basic rule and can be achieved by e.g. process descriptions including principles of RACI (Responsible, Accountable, Consulted, and Informed) and decision trees. Delegated responsibilities should be documented, training given to relevant personnel and periodically re-training

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Global GMP

- A very important topic when it comes to GMP is the so-called “level playing field”. All companies should comply with the same set of rules (e.g. GMP) in order to protect patient safety.
- It is also important that companies know that their compliance with the rules can be checked, e.g. through on site inspections.

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Global GMP

- The level playing field:

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Global GMP

- GMP comes at a price: it takes time and effort to train personnel, it means that Quality Management Systems need to be fully in place and it means that the company needs to have a good Quality Culture.
  Doing things in a certain way “since the guideline says to do it in that way” should be replaced by a good understanding of the basis of the guidelines. GMP needs to become a way of thinking, not just doing.
- There is the expectation that companies are implementing programs to build/strengthen their quality culture

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The Japanese GMP Ministerial Ordinance

- APIC members have studied the ordinance and see only one point of concern.
- Obviously, we have studied the english translation, which means that there may be some misunderstandings as a result of that.
- The point of concern we found is article 15: control of deviations.

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The Japanese GMP Ministerial Ordinance

- It is stated in article 15 that marketing license holders are to be notified in case of *serious deviations*. There is however, no explanation of what the criteria to list a deviation as “serious” are.
- As a consequence, Japanese License holders are now requesting to be notified of <u>all</u> deviations.

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The Japanese GMP Ministerial Ordinance

- We do not disagree with the fact that License holders should be notified of critical deviations, e.g. deviations with a potential impact on API and/or Product quality, but the current wording is not transparent and leads to misunderstanding.
- We hope that there will be some further clarification on this point, to avoid unnecessary discussions with the Japanese License holders.

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International cooperation

- As stated, it is important for companies to realize that their compliance with the rules can be checked, e.g. through on site inspections. We all know that having requirements in place does not always mean that people will adhere to them.

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International cooperation

- Health Authorities worldwide acknowledge the need for inspections at API suppliers, however, resources are lacking.
- As a consequence only a small part of API sites world wide gets inspected on a regular basis.
- In some countries/regions there are provisions in the law that prevent inspections:
  * EU: no legal basis for API inspections: the responsibility for the GMP compliance of the API supplier lies with the Drug Product Manufacturer.
    Exception: EDQM in relation to the CEP system.
  * China: API company's only producing for export are not inspected.

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International cooperation

- There are many mutual recognition agreements, also with regards to inspections to better use the available resources.
- As an example EU has MRAs with:

✓ Australia
✓ Brazil
✓ Canada
✓ Israel
✓ Japan
✓ New Zealand
✓ Switzerland
✓ USA
✓ WHO

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International cooperation

- When authorities start to recognize each other's inspection outcomes, the total number of API sites inspected around the world will increase.
- Risk based approaches for inspection planning means that the risks related to non-compliance will decrease. This will have an immediate impact on drug shortages (as a result of non compliance) world wide.

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Conclusion

- Authorities need to work together with their local industry to provide a clear understanding of what is expected from them in terms of GMP.
- GMP is a way of thinking, it is more than merely “following the rules”.
- there is the expectation that companies are implementing programs to build/strengthen their quality culture.
- Worldwide inspections, preferrably with 100% coverage is needed to ensure a secure and non disrupted supply of good quality, reliable medicines for the patients.