

APIC Position Paper

Need for GMP for API production

Quality of APIs is essential to ensure Drug Safety:

Historically, the need for GMP arose from serious quality defects of active pharmaceutical ingredients (APIs) and excipients, which resulted in the deaths of hundreds of patients. The 1937 sulfanilamide tragedy in the USA resulted e.g. in the deaths of 107 people. After 1938, manufacturers were obliged to prove the safety of their products. Yet, more accidents happened such as the thalidomide disaster in the late 1950s resulting in thousands of malformed babies. Such tragic accidents led for example to the creation of the 1968 Medicines Act in the UK.

Current experiences and tragedies:

Some of these accidents, like the sulfanilamide tragedy were not due to the quality of the active ingredient itself, but of an excipient (glycerin). In fact, since 1937, the number of deaths due to the use of substandard glycerol is in excess of 500 cases.

There can be several different causes for such tragedies, not all of these directly related to a lack of GMP. These include e.g. insufficient clinical evaluations, as was the case with thalidomide, but often GMP-related factors such as poor manufacturing practices and contamination or degradation throughout the distribution chain have also been causative factors.

Current situation on GMP for APIs:

GMP for APIs is regulated in the US since 1962. Until recently, there was no legal basis for GMP compliance for APIs in the European Union. The recent review of the European pharmaceutical legislation (Cf. Directive 2001/83 amended by Directive 2004/27/EC) has created such legal basis and implementation into the national legislations of the EU Member States is due by October 2005. This legislation does not directly impose European API producers to operate according to GMP, but the Marketing Authorisations Holders of the medicinal products, should only source “starting materials” (APIs) made according to the GMP requirements. The ICH Q7A standards for API’s are published in annex 18 to the EU Guide to Good Manufacturing Practice. Annex 18 will be enforced as soon as Directive 2001/83 amended by 2004/27 is implemented. Many European producers have been operating to appropriate GMP standards for many years. The final issuance of the ICH Q7A standard for GMP for APIs, which is a consensus document between authorities and industry, was a significant step towards a harmonised standard, which, if correctly implemented, should ensure that all APIs used in medicinal products are safe.

Harmonisation of GMP standards:

The ICH Q7A standards have been adopted by many countries such as the USA, Canada, Australia, Japan and all EU countries. Other countries such as China have established their own standards. The World Health Organisation (WHO) established GMP standards for active pharmaceutical ingredients

in 1992, and many countries aim to follow these standards. In 2001 the WHO has issued a proposal to adopt ICH Q7A as the WHO GMP standard for APIs (WHO Working Document QAS/00.004/Rev.1). APIC believes that, because the safety of APIs used in medicinal products should in no way be compromised, the same GMP standards - ICH Q7A - should be used throughout the world. Unfortunately, there is still a long way to go before this will become reality.

Controls and Inspection are key elements to enforce compliance:

To assist the marketing authorisation Holders in their obligation to source only API's made according to GMP, it is essential that reliable information is available on the compliance status of all API producers. Stringent standards are meaningful, provided that they are correctly implemented and enforced through world-wide inspections. The new EU legislation provides for the possibility of also inspecting API producers importing into the EU for GMP compliance, but this is not a mandatory process. APIC fears that these inspections will be fairly limited, considering the limited resources available for such inspections.

Avoiding counterfeit proactively:

Moreover, even companies found to comply at the time of the audit, may be tempted to adopt other practices thereafter, because of the high costs of GMP compliance and because the chance of re-inspections will be remote. APIC believes that GMP for APIs can only be enforced if inspection will be mandatory and if re-inspections will take place regularly.

Inspections should not be limited to the verification of GMP compliance in the facility itself. The distribution chain should also be verified. Traceability to the original manufacturer should be checked, because exchange of API products amongst manufacturers is a regular practice in some countries.

Conclusion

APIC believes that GMP for APIs can only be enforced if inspection will be mandatory and if re-inspections will take place regularly.