Current regulatory requirements for APIs

The adoption of a global regulatory framework for active pharmaceutical ingredients (APIs) can only be of benefit to the licensing authorities, the industry and - last but not least - the patient.

Dr Chris Oldenhof, DSM/Gist-brocades

Active pharmaceutical ingredients (APIs) are the constituents which give medicinal products their pharmacological activity. For this reason, the quality (and the consistency thereof) and the stability of APIs are crucial factors in the overall quality, safety and efficacy of medicinal products. This article highlights the very rapid developments which have recently taken place and are still taking place in the area of regulatory requirements for active pharmaceutical ingredients (APIs) in various parts of the world. These developments are translated into their current and expected future impact on the marketplace. Suggestions are given for regulatory API frameworks which will result in optimal benefits for the licensing authorities, for industry and, last but not least, for patients.

The US Food and Drug Administration (FDA) already for several decades has had an extensive and complex set of API requirements in place covering the areas of Drug Registration (1) and current Good Manufacturing Practice (cGMP) (2) - and new FDA regulations and guidelines are still continually being issued. Since about 1990, the authorities within Europe especially have also acknowledged the importance of APIs, as illustrated by a steep increase in the amount of information on the manufacture and control of APIs to be included in Marketing Authorisation applications within the EU (3). In addition, legal provisions are being developed by the European Commission for the mandatory application of cGMP principles in API manufacture (4).

Obviously, a basis is thus being laid for full harmonisation and/or mutual recognition of API requirements for the US and EU markets in the future. This is also illustrated by, for example, the current ICH (International Conference on Harmonisation) initiatives in which the US, EU and Japan participate, and by the start of the implementation of the Mutual Recognition Agreement (MRA), which was signed by the US and the EU at the end of 1998 (5). Both harmonisation and mutual recognition may well be the leading principles with regard to regulatory developments worldwide in the years to come.

Authorisation of medicinal products

In many countries of the world, information relating to the API must be included in the registration document for the medicinal product itself. However, for registrations in the US, the EU Member States and several other countries, such as Australia, Canada and New Zealand, the possibility exists for bulk manufacturers to file separate dossiers for APIs (and in the US, also for API intermediates) with the authorities as “supporting information” to the registrations of medicinal products. Such dossiers, which usually contain detailed – and therefore confidential – information on the manufacturing process, in most cases are called “Drug Master Files” (DMFs). For the older, off-patent APIs, a specifically designed alternative system has been made available through the European Pharmacopoeia. This system, called “Certification of Suitability”, provides for the centralised assessment of API-related information; the resulting Certificate (“CEP”) may be used in Medicinal Product registrations in countries that are signatories to the European Pharmacopoeia Convention.

The US FDA system includes worldwide inspections of API manufacturers... in contrast to the current European system, which today can still be characterised as a “paper tiger”
Authorisation of changes in API manufacture

The US FDA procedures for the authorisation of changes in API manufacture, and to some extent also those which have recently been implemented in the EU, require that authority approval for such changes should be obtained by the holder of the registration of the medicinal product. This regulatory principle has been found to result in extreme hardship for, especially, the dedicated API and intermediates manufacturing industry and, in particular, for the industry sector involved in the manufacture and supply of the older, mainstay APIs. Their numerous customers for each API product will normally not be willing to go through often complex, tedious and expensive approval processes. As a result, the implementation of - for many reasons, often very necessary - changes has frequently been blocked.

The FDA is in the process of revising its regulations and guidelines on bulk post-approval change authorisation procedures through its “BACPAC” (Bulk Actives Post Approval Changes) initiative (6). It is the industry's hope that this new Guidance will lead to a resolution of this serious flaw in the authorisation process. For countries accepting CEPs, authorisation problems of a similar nature occur less frequently.

Current good manufacturing practice

The US FDA requires by law that APIs are manufactured under pharmaceutical cGMP. Its worldwide inspection system enables it to verify whether companies comply with these cGMP requirements. When serious cGMP deficiencies are identified during such inspections, this may result in the US borders being closed for APIs from that specific manufacturer. The EU is still in the process of implementing legal requirements for cGMP to be applied to API manufacture. The European Commission expects these requirements, plus a worldwide API inspection system, to be fully in place within three to four years from now, but many hurdles still need to be overcome to accomplish this.
The API market under the current regulatory framework

The enormous differences which exist between the regulatory requirements in the various areas/countries of the world imply that the standards to be met by API manufacturers will differ widely, depending on the countries where the derived medicinal products will be marketed. APIs used in the manufacture of medicinal products marketed in the US will have to meet all of the FDA's regulatory and cGMP requirements, as enforced through the FDA's inspection system. This constitutes a significant cost factor for the manufacturer. Producers of such APIs are in addition still experiencing severe limitations to improve their operations, due to the FDA's as yet often insurmountably complex bulk post-approval procedures. Full FDA regulatory compliance, therefore, intrinsically will imply seriously higher API manufacturing costs.

The regulatory standards with respect to the EU are today of a level similar to those of the FDA. The same may be expected for cGMP requirements within several years. However, at this moment, the lack of a means for the EU to verify compliance with the numerous EU regulations and guidelines pertaining to submitted API information raises serious doubts as to whether all API material used for medicinal products manufactured in the US will have to meet all of the FDA's regulatory and cGMP requirements, as enforced through the FDA's inspection system. 

The API market under the future regulatory framework

The global developments which have been set in motion in the regulatory and cGMP areas have now gained a momentum which allows us to visualise the standards we may expect to become a reality in the near and further future.

The ICH initiative “Q7a”, aimed at defining a harmonised cGMP Guideline for API manufacture, has reached a stage which indicates that a successful result will most probably be reached (7). So we may expect a common, accepted cGMP standard for the US, the EU and Japan to become effective by the year 2001. Thus, all API manufacturers wishing to (continue to) supply their products for use in medicinal products manufacture for these markets will have to comply with these high cGMP standards (8). It may be expected that, in the longer term, the Q7a Guidance will become the world standard.

Based on this harmonised Guideline, and on the soon to be amended EU Directive on APIs (“Starting Materials”), the EU will probably have fully implemented its worldwide API inspection system by the year 2002/2003. The implementation process will be under continual time pressure from the US/EU MRA process, which makes it improbable that serious delays will occur. The inspection system will force all API manufacturers supplying the EU market to comply, not only with the high ICH cGMP standards, but also with the submitted regulatory information on API manufacture. Post-approval change procedures will have to be carefully adhered to.

Massive differences still exist between the three ICH partners with respect to their requirements on the extensiveness of information on API manufacture to be included in regulatory submissions. This makes harmonisation - as currently pursued within the ICH initiative “The Common Technical Document” (CTD) - an extremely challenging objective. Agreement on the API part of the CTD, and subsequent implementation, may probably not be expected before the year 2005. When a world standard for this will become a reality - if ever - is anybody's guess.
Conclusion

Roughly speaking, we may characterise the period that lies behind us as one of a "double standard" of regulatory requirements for the manufacture of APIs: the level demanded by the US FDA and that required by the rest of the world. There can be no doubt that we are on the verge of entering a new era.

The market for APIs has become global. Differences in regulatory requirements for different markets have made this global market an extremely complex one to operate in. Fierce competition within the market, on the one hand, and the very strict limitations imposed by regulatory requirements in only some parts of the market, on the other hand, have been the source of numerous dilemmas for the API industry. Especially, the fact that "FDA compliance" and high manufacturing costs go hand-in-hand has made it extremely difficult for manufacturers to supply the entire global market and at the same time maintain competitiveness.

Now that the EU, and in due time increasingly more countries, are adopting regulatory requirements and - very importantly - enforcing API inspection systems which will be of a level similar to those of the FDA, the time is rapidly approaching when there will only be a business future for companies that can meet the new high, and ultimately global, regulatory standards. This will be an enormous step forward in terms of securing the safety of medicines.

Finally, in order to make feasible procedures available to the industry for the authorisation of bulk post-approval changes, a system for the authorisation of APIs themselves would offer a much required degree of relief. A "DMF approval system" has already been under consideration at the FDA for many years. The author expresses his hope that the creation of such a system will represent a valuable spin-off of the FDA BACPAC initiative.

References


Dr Chris Oldenhof is Head of International Regulatory Affairs in the Safety, Health and Compliance Department of the Anti-Infectives Business Group of DSM/Gist-brocades in Delft, The Netherlands. He has a PhD in organic chemistry from the University of Leyden, The Netherlands. In his 20 years with Gist-brocades, he has held positions in Research, Marketing & Sales and Regulatory Affairs for APIs and intermediates. Dr Oldenhof is a member of the Board of Management of the CEFIC-API Committee, chairman of its Working Group on Biotechnology and a member of its Working Group on Regulatory Affairs.