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APIs regulation for Pharmaceutical application

1/ What is an API?

Active Pharmaceutical Ingredient (API) = any substance or mixture of substances intended to be used in the manufacture of a medicine and that, when used in the production of a drug product, becomes an active ingredient of the drug product.
Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the body's structure or function.

Linked to their uses, APIs should be manufactured according to the current regulation in order to reach a high level of safety, efficiency and quality.

2/ How to manufacture an API?

Any kind of API has to be manufactured under cGMP (Current Good Manufacturing practices) and distributed under GDP (good distribution practices) for pharmaceuticals.

For the manufacture of medicines, GMPs were implemented and regulated a long time ago (around 1970).

A few years ago (1990), ICH (International Committee of Harmonization) was created to provide guidelines applicable in several regions of the world as US, EU…..
The ICHQ7A guideline is the one related to the Good Manufacturing Practices, it is dedicated to the manufacture of pharmaceuticals.

In Parallel, the compliance with local regulation must be taken into consideration.
The Inspection of National Health Authorities generally ensures compliance of the product with the guidelines and with the regulatory dossier registered by the manufacturer to the Health Authorities.

3/ How to register an API?

To obtain a marketing authorization, the drug product manufacturer submits a registration dossier to the Health Authorities. The format of this dossier follows the ICH M4 - Common Technical Document (CTD) which is composed of 5 Modules.
The Module 3 concerns the quality part of the dossier and is dedicated to the Drug substance (Section 3.2.S) and to the drug product (Section 3.2.P).
To sum up, the Module 3.2.S contains all the information related to the quality of the active substance (manufacture, characterization and control of drug substances, container closure system and stability data) and is based on the API information.
The name and the composition of the quality part of the registration dossier can differ following the countries.

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The quality information related to API manufacturer may be considered as confidential. Hence, the API manufacturer builds and submits a registration dossier to the Heath Authorities in the different countries of interest. This registration dossier follows the CTD format for the 3.2.S section.
The regulatory dossier is mandatory, in some foreign countries to be able to sell the API as such (China for example).

Once the registration is obtained, the approved dossiers need to be renewed on a periodic time and revised as soon as a change in the API manufacturing process is introduced. The implementation of the changes and the content of the revision dossier follow the local approved guidelines dedicated to classification of changes.
(minor, major, etc..).

Generally when a product has a monograph recorded in a National Pharmacopeias, the manufacturer must sell the API in compliance with it.

Europe

Two type of regulatory dossiers exist which allow confidential information "know-how" of the API manufacturers to be protected :

The CEP:
A Certificate of Suitability (CEP) certifies the compliance of a material with the requirements laid down in the relevant monograph of the European Pharmacopoeia.

After submission by the API manufacturer, the European Directorate for the Quality of Medicines (EDQM) assesses the CEP dossier and grants a certificate.

A declaration of access to the CEP is signed by the API manufacturer and is added to the Marketing authorization application of the Drug product manufacturer.

The ASMF:
The Active substance Master File is composed of two parts: the open part and the closed part. The open part is included in the Marketing authorization of the drug product manufacturer while the closed part (confidential information) is submitted by the API manufacturer to the Health Authorities.

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USA

DMF (Drug Master File) type II:

The manufacturer could submit a DMF (Drug Master File) type II - this one is dedicated to API; it is divided in two parts (open and closed).
In the same way, the API'S manufacturer provides to his customer an LOA (letter of access) to his DMF to protect confidential information, this dossier and GMP will be also the basis in case of FDA inspection.

Japan

To API, the manufacturer needs to obtain an authorization through a "DMF like" dossier. If the evaluation is positive, the Health Authorities, to approve the GMP and dossier compliance, will do a paper inspection on a second dossier. As soon as a new customer wants to set up a new NDA, the API dossier is reviewed and re- evaluated

In other countries around the world

As a minimum, the APIs need to comply with the local monograph when existing or with EP or USP one and need to be manufactured under GMP.
More and more, the regulation changes and you must file DMF dossier (instead of IDL – Import Drug License) following local requirements and/or guidelines, it is the case today for example in Russia, South Korea, China, etc.… In addition to the DMF dossier, if the evaluation is positive, some National health authorities as Russia, South Korea, require a physical inspection before allowing the product to enter their national market.

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