Title: Labelling of APIs and API Intermediates					
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Introduction

Containers for APIs and API Intermediates should bear labels that give at least the following information:

- The name of the material,
- Site material identification code,
- Amount of material,
- The batch or lot number,
- The expiry date (if applicable),
- Any special storage or handling conditions, and
- The manufacturing site and contact information.

As appropriate, the grade or pharmacopoeia status, International Nonproprietary Name (INN) or country specific label information should be included. Certain APIs or intermediates for US import or export must be also bear label text consistent with FDA drug listing requirements.

Practice

The recommendations and requirements presented in this document are based upon Quality Standards and guidance documents published by the World Health Organization (WHO), the International Conference for Harmonization (ICH), the US Pharmacopoeia (USP), the European Pharmacopoeia (EP), the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicines (EMEA).

I. Recommendations and Requirements for Labels

- General Requirements for Labels
  - Labels should be clear, unambiguous, and permanently affixed to containers
  - Labels should follow an approved Site format, bear a label code number with revision code
  - The information on the label should be indelible

- Minimum Requirements for Label Content
  - Identification Name(s), including International Nonproprietary Name (INN) if Applicable
  - Grade (e.g. Sterile, Injectable, Veterinary) if applicable
  - Site article number
  - Manufacturer or re-packer lot number or batch number
  - Pharmacopoeia reference (e.g. USP, BP, EP, JP) if applicable
  - If a controlled substance appropriate codes must be included
  - Stability, Storage or Handling Information
  - Expiry date, if one exists; if a retest interval exists, a retest date may be included on the label or the certificate of analysis
  - Special storage or shipping conditions – based on formal stability studies and per requirements of EMEA/CVMP/422/99-Rev2 or CPMP/QWP/609/96/Rev 1
  - Handling precautions and safety information – may be presented on a separate label
  - Contact Information

> *repacker, if the material has been repacked or relabeled, e) the retest date or expiry date (where applicable), f) any special storage conditions, g) handling precautions, where necessary, h) identification number of the original manufacturing site, and i) name and contact details of the supplier."*

The WHO guidance encompasses and expands API GMP guidance for labelling recommendations presented in Q7A:

> *"Labels used on containers of intermediates or APIs should indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of intermediate or API."*
>
> *"If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, special transport conditions, and any special legal requirements should also be on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis."*

If an API or intermediate is claimed to meet the requirements of one or more pharmacopoeia, it is expected that this will be stated on the container label or on accompanying documentation. Most pharmacopoeias, including the USP, defer to the specific labelling requirements of the national or supranational health authorities. The USP also states that:

> *"A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labelled with a minimum of product identification (except for controlled articles), lot number, expiration date and conditions for storage and distribution."*

Occasionally, a pharmacopoeia monograph will include a labelling requirement. This will be described under the monograph subheading "Labelling" and is required to appear either on the container label or accompanying information, e.g. Certificate of Analysis.

Both FDA guidance (e.g. reference 5) and EMEA guidance (e.g. references 6 and 7) for label storage conditions indicate that any storage conditions or related information (i.e. expiry or retest date) be based on the results of formal stability studies. Storage conditions listed on the label (temperature, light, humidity) should be consistent with the language provided in these guidance documents. The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

The EMEA guidance also state *"for substances to be stored/transported refrigerated or frozen, the temperature range should be included in the labelling."* Material safety or hazard information is important to the handling of APIs and intermediates.

Often an abstract of this information has been included as text on the primary label. This is still acceptable practice but the API site should develop a separate labelling system for material safety and hazard information that at some point will supersede current practices. Hence, it is also considered acceptable to provide safety information on a label separate from the primary label used for GMP and/or regulatory purposes.

APIs or intermediates that are classified as controlled substances must bear labels indicating the appropriate designations or codes for such materials in the countries or regions in which they are produced and/or shipped.

The drug listing process requires the submission of FDA Forms 2656 (Drug Establishment Registration) and 2657(Drug Listing) to the FDA Drug Registration and Listing Office. The 2656 form is filed for a new establishment registration, or a revision to an existing registration. The information required to complete this form is: 1) site name/address/telephone number, 2) labeller code (for revisions only), 3) registration number (for revisions only), 4) reason for submission, 5) type of ownership, 6) labeler code/firm name of other firms doing business at this site.

The 2657 form is filed for new foreign-source bulk drug substances introduced for commercial distribution into the U.S. that have not been previously drug listed, for drug substances previously listed which have been discontinued, for previously discontinued drug substances which are being re-entered into commercial distribution, or for any change in the information previously submitted.

The information required to complete the 2657 form and the submission is: 1) site of manufacture of the API including site registration number and labeller code, 2) site labeller, product and package code, 3) label title, 4) package types (bag, drum, canister) and package quantities, 5) confirmation that the API meets the aforementioned criteria for drug listing, and 6) two original samples of the

API drum label that includes wording consistent with the requirements of 21CFR201.122. It should be noted that changes to the label for an API or intermediate that is drug listed requires updating the Form FDA 2657 drug listing information filed with FDA. Such changes should be communicated to Regulatory Affairs for human health products or animal health products.

References

1. Good trade and distribution practices for pharmaceutical starting materials, Annex 2, World Health Organization, WHO Technical Report Series, No. 917, 2003.
2. ICH Q7A Good Manufacturing Practice for Active Pharmaceutical Ingredients, CPMP/ICH/4106/00, November 16, 2000.
3. USP 27, General Notices, pg 10, Labelling.
4. European Pharmacopoeia 4.8, General Notices, pg 8, Labelling.
5. *Draft* Guidance for Industry, Drug Substance, Chemistry, Manufacturing, and Controls Information, US DHHS FDA January 2004
6. CPMP Note for Guidance on Declaration of Storage Conditions: A) In the product information of Medicinal Products, B) For Active Substances – Annex to guidance on stability testing of new drug substances and products; Annex to Note for guidance on stability testing of existing active substances and related finished products, CPMP/QWP/609/96/Rev 1, April 3, 2003.
7. CVMP Note for Guidance on Declaration of Storage Conditions: A) In the product information of Pharmaceutical Veterinary Medicinal Products, B) For Active Substances – Annex to guidance on stability testing of new veterinary drug substances and products; Annex to Note for guidance on stability testing of existing active substances and related finished products, EMEA/CVMP/422/99-Rev.2-FINAL, October 31 2003.
8. Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products, CPMP/QWP/122/02, rev 1, December 17, 2003.
9. Guidance to Industry and for FDA Employees on Import Alert #6666, Federal Register Vol. 65, No. 233, December 4, 2000.
10. Guidance for FDA Staff, Detention without physical examination of active pharmaceutical ingredients (APIs) that appear to be misbranded under 502(f)(1) because they do not meet the requirements for the labelling exemption in 21CFR201.122, US DHHS, FDA Office of Regulatory Affairs, October 3, 2000.
11. Import Alert #6809, New Bulk Animal Drug Substances, US DHHS, FDA Center for Veterinary Medicine, October 9, 2003.
12. Foreign Establishment Registration and Listing, 21 CFR Parts 207, 607, 807, DHHS,

