

## 21.A.11 Laboratory controls

### Here you will find answers to the following questions:

- Which requirements are API specifications expected to meet?
- What content is required for certificates of analysis?
- What are the requirements in terms of stability testing, establishing retest periods and retention samples?

### 21.A.11.1 General control

The laboratory facilities at disposal of the Quality Unit can be internal or external:

- In the Quality Control Department
- In the Production Department
- At other sites of the same organisation
- As contract laboratories, provided they comply with chapter 21.A.16 *Contract manufacturers, including laboratories*.

Whatever the laboratory selected, the *responsibilities* remain within the Quality Unit of the producer. The characteristics of the facilities (internal or external) have to be in accordance with the type of tests performed (i.e. microbiological tests require sample protection from particulate contamination when handled, the weighing room should not have vibration, ...). Separate rooms for different kind of tests (microbiology, chemistry, powder handling, etc.) can be needed.

The **laboratory** should have *SOPs* describing:

- **Sampling** Different approaches are possible: a general method, different methods grouping products (liquids, solids, dangerous, hygroscopic, ...), one sampling SOP for each product, or a combination of them. Clearly defined and documented procedures have to be available. Sampling plans for raw materials, intermediates and APIs have to be available.
- **Testing** Analytical methods and test procedures should be described in such detail that analysts with the usual knowledge and expertise are able to understand how to proceed. It is recommended to include the necessary formulas (such as one including all the factors with explanation of each one, and another simplified) to carry out any calculation needed, and to make easy the review by the supervisor.
- **Approval or rejection of results**
  - Before approving and rejection of materials the criteria to be used, the results to be averaged should be specified in SOP(s).
  - The SOP(s) should describe the criteria for averaging and/or rounding results, comparing results against specifications and approving or rejecting results.
  - Control charts can be used in detecting trends and atypical results

- Rounding results should be performed according to pharmacopoeia or other recognised system (see also revised ICH Guideline Q3A - chapter E.3.A).
- Care should be taken when averaging results involving atypical values (e.g. outliers) or when single values are out of the specification limit.
- **Recording and storage of laboratory data**

The content of the SOP(s) has to be in accordance with requirements of ICH Q7A, section 6.6 Laboratory Control Records in chapter E.7, and should describe what data should be recorded and reported, and where and how long this data should be retained. The responsibility for the integrity of retained records and relevant raw data should be assigned. When managing electronic data, systems should be appropriately validated.

In order to check the specifications, sampling plans and test procedures for raw materials and intermediates, only *selected parameters* need to be tested. Sometimes one test method can provide enough information (e.g. an HPLC method may be at the same time an identification, purity and impurity method). The detection and quantification limits and precision of the methods used should be in accordance with the specification levels.

The Quality Unit is responsible for reviewing and approving *sampling procedures*, but sampling may be carried out by people from other departments provided they have been appropriately trained. When appropriate there can be "in-house" specifications in addition to those in the registration/filing.

When establishing **API specifications** the following guidelines should be taken into account:

- ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (chapter E.6.A).
- ICH Q3A(R2): Impurities in New Drug Substances (see chapter E.3.A).
- ICH Q3C(R3): Guideline for Residual Solvents (see chapter E.3.C)
- Ph. Eur. Technical Guide for the Elaboration of Monographs – Dec. 1999

Once historical data have been collected, the established specification limits may be based on process capability, wider ranges should be justified (even complying with ICH guideline). Never tighten specifications unless there is a therapeutic or safety justification.

The QC laboratory should use *laboratory notebooks* (bound notebook pre-numbered) or an equivalent system (one option is the use of loose sheets pre-numbered, the printing have to be controlled and also the storage as control records) to record the raw data at the time they are produced. A deviation report procedure is advisable.

Any **out-of-specification (OOS) result** obtained should be investigated and documented according to a procedure. For product manufactured for the US

market specific legal requirements (e.g. Barr Judgement, FDA "Guide to Inspection of Pharmaceutical Quality Control Laboratories") are to be followed.

The written **procedure** describing clearly what to do when an OOS is obtained should follow good scientific practice:

- Checklist of potential defects in laboratory (e.g. calculations, methods, visual appearance, test procedure modified, experience of analyst during test, calibration of equipment ...)
- Similar checklist for potential deviations in production units
- Check sampling and sampling devices
- Guidance on re-sampling and re-testing including justification
- Testing of a known control sample
- A valid OOS result should result in production investigations; a checklist can be useful

"Use by" dates of reagents and standard solutions are appropriate for those where its purity or standardised value can potentially change with the time. When appropriate, standard solutions can be re-standardised again and assigned a new "use by" date.

An SOP describing the policy of the company related to **standards** (both primary and secondary) use, records, obtaining, identification and storage should be in operation. When methods described in an official pharmacopoeia ask for reference standards, those have to be acquired from this pharmacopoeia. The routine use of a secondary standard tested against the primary standard is recommended.

For *non compendial APIs*, in house standards or those obtained from other sources may be used. In any case the identity has to be proven, the identity and purity by direct purity testing and/or impurity testing assigned. Accepting a standard may require different tests than those applied to the regular product in order to confirm its suitability (purity determination by absolute methods, not applied currently in process testing), however some routine tests may be omitted. When a standard is used as a reference point for assays the mean and standard deviation of the assigned assay value should be known.

The method for obtaining and testing an *in house primary standard* should be described in writing. The purity may be assigned through a specific test for purity or by assigning a purity of 100% taking away all the impurities (including water) determined by validated methods. Records of the tests carried out to identify and determine the purity should be maintained. A retest/expiration date should be assigned to the standard. It may need to be re-qualified. A formal certification of standards is needed when those are sent outside the control of the manufacturer.

The method of obtaining and testing *secondary standards* should be described in writing. The purity of those should be known. If used in assay determination the purity should be assigned testing it against the primary standard. A retest/expiration date should be assigned. It may need to be re-qualified.

### 21.A.11.2 Testing of intermediates and APIs

ICH Q7A mentions “appropriate laboratory tests”. Determine these accurately as it does not mean “a lot of laboratory tests”. Guidance for defining **impurity profile(s)** is provided in ICH Q3A (see chapter E.3.A) and Q3C (see chapter E.3.C). The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or against historical data. A practical approach of “appropriate interval” may be in the product regular quality review. The impurity profile could be useful for evaluating the impact on the product of critical deviations or major process changes. See and follow ICH Q6A to determine if a defined **microbial quality** is necessary (chapter E.6.A). Not every API needs to have specific microbiological specifications.

### 21.A.11.3 Validation of analytical procedures

See section 12 Validation in chapter E.7.

### 21.A.11.4 Certificates of analysis

Authentic certificate means: true, accurate record of results obtained, signed (also electronically) by authorised person (from Quality Unit) and dated.

Request for Certificate of Analysis may require the date of manufacture (final purification leading to API). Retest dates on Certificates of Analysis are normally calculated from date of release, should the date of release be well beyond the date of manufacture appropriate allowances in retest date should be made.

The acceptance limits should be included in the certificate of analysis. When introducing numerical results, have in mind that limit tests allow only to state “less than” value of the standard. Also consider non-numerical results. Certificates of Analysis for blended batches should be based on the results of sampling and testing the blend and not just taken from one of the components.

The certificate of analysis should allow **traceability** to the manufacturer and the way to contact the organisation that issues it. It is not allowed for repackers/reprocessors, agents and brokers to copy the data reported by the original manufacturer and eliminating the reference to it (see figure 21.A-23).

#### Certificate of analysis

- Name of the API/intermediate, with quality grade, if applicable
- Batch number and release date
- Expiration date, if applicable, or retest period
- All test results obtained in accordance with the pharmacopoeia or customer requirements, with details of the acceptance criteria and numerical results
- If a new certificate is issued, e.g. after re-packaging, and attached, this should include the address of the original manufacturer.

Figure 21.A-23 Contents of a certificate of analysis in accordance with ICH Q7A

### 21.A.11.5 Stability monitoring of APIs

Results of *on-going stability programs* have to be evaluated at least in the product quality reviews. The following documents may be used as guidance:

- ICH Q1A(R2): Stability Testing of New Drug Substances and Products (see chapter E.1.A).
- ICH Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products (see chapter E.1.B).
- ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (see chapter E.1.D)
- CPMP/QWP/122/02: Guideline on Stability Testing: Stability of Existing Active Substances and Related Finished Products.

Regarding the requirements of validation of test methods used in stability testing see 12.8 Validation of Analytical Methods in chapter E.7 *ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*.

Demonstrate that a method is **stability indicating** by stressing the API (temperature, humidity, ...) to achieve a significant degradation and determination of the purity and impurities: when purity decreases, new impurities should appear and/or existing impurities should grow.

For products known to be stable from scientific point of view no stability testing required (e.g. inorganic salts).

If appropriate, store different bags of different batches of the same API into the same small-scale drums.

Representative qualities and packaging configurations may be used to confirm expiry and retest dates for a range of equivalent products (see chapter E.1.D).

First commercial production batches should normally be placed on the stability program. However, an example where 3 additional batches are not necessary is when the commercial batches are produced in the same equipment using the same process as that previously used in development.

Fewer batches may also be taken if previous data (it may be data from pilot scale batches or from other site batches obtained by the same process) show that the API is stable for at least 2 years. This offers a reduction in current practice.

It is very important to remark that the guideline allows testing "at least annually" for batches introduced in the stability program after the first commercial production batches. When stability of API is beyond two years the annual batch needs only be tested at 0, 12, 24, 36 ... months. Based on scientific judgement, major changes or critical deviations may require additional batches to be placed on stability. Be careful with APIs with short shelf lives: section 11.54 of ICH Q7a is not applicable, and as a consequence the testing frequency will increase.

### 21.A.11.6 Expiry and retest dating

The supporting stability information on **intermediates** is not necessary to be obtained through stability studies complying with the ICH requirements for APIs. It may be obtained from published data or from a simple study based on test results of materials stored for some time.

The use of a **retest date** is recommended, this will allow using the API after this date, provided it complies with specifications.

It is recommended to carry out stability tests following ICH guidelines on pilot scale batches. The data obtained (provided that commercial manufacturing scale employs the same manufacturing method and procedures and the quality of the API is equivalent) may be used to establish a preliminary retest period. When stability data from first commercial manufacturing batches are being obtained, this preliminary retest period can be extended if they allow it.

When performing a retest, the sample should be taken again from the containers where the API is, and should be representative of all the remainder of the batch. Retention samples should not be used.

### 21.A.11.7 Reserve/retention samples

Reserve/retention samples should be different from stability samples. It is not necessary that conditions of packaging and storing of reserve samples are equivalent to those of the stability samples.

Storage containers and conditions should attempt as far as possible to preserve the original quality and should be no worse than claimed storage conditions.

To avoid having different *retention times* for reserve samples for each product and each batch manufactured, it may be workable for companies to define a unique retention time for all batches and products of 3 years after the expiry or retest date (provided that there will not be distributed any batch or portion of a batch after its retest date).

The retention times are minimum time frames and provided these are met, reserve samples may be disposed after that time.

#### Summary

The requirements for laboratory controls of APIs correspond to those for drug (medicinal) products. For API specifications, an impurity profile and limits for residual solvents should be established.

As well as the test results, certificates of analysis should always enable traceability to the original manufacturer and have to be released by the quality unit.

At least one batch per year is to be included in the stability program. Retest dates are established on the basis of stability results. Retention samples have to be taken from each batch of API. The packaging system should be the same as or better than the packaging used for market products.