AMV Document Submission Guideline & Common Problems

Centre for Quality Control |
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1. Introduction
2. Analytical Method Validation (AMV)
3. Protocol of Analysis (POA)
4. Certificate of Analysis (COA)
5. The Requirement of AMV Document Submission
6. Common Problems
INTRODUCTION
National Pharmaceutical Control Bureau, was set up in October 1978.

This institution was established to implement quality control on pharmaceutical products.
Objectives of NPCB

- To ensure that therapeutic substances approved for the market are safe, efficacious and of quality.

- To ensure that the approved traditional medicines and the notified cosmetic products marketed are safe and of high quality.
Core activities of Centre for Quality Control (CQC)

1. **SAMPLE TESTING**
   a) Pre-registration of traditional products
   b) Post-registration for pharmaceutical, traditional and cosmetic products (surveillance program)
   c) Screening of adulteration products (Enforcement program)

2. **EVALUATION OF PROTOCOL OF ANALYSIS (POA) AND ANALYTICAL METHOD VALIDATION (AMV) DATA**
   - Registration of pharmaceutical products (1 January 2008)
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGĐ)


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Please visit the NPCB website for the latest updates
SECTION C: QUALITY CONTROL

The requirement for the submission of the protocol of analysis (POA), analytical method validation (AMV) and product samples for laboratory testing are presented in this section.

The submission of POA and AMV to the Centre for Quality Control shall be done via the online system (Quest system) and also using hardcopies, once payment for the registration has been confirmed. Documents to be submitted are listed below:

Documents to be submitted via online Quest system
1. E9 : Complete protocol of analysis for finished product including preservatives and diluents (if any).
2. E10 : Summary of AMV which includes all the relevant validation characteristics, its acceptance criteria and results.
3. E11 : Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches).

Documents to be submitted as hardcopy:
1. Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches)
2. Complete protocol of analysis for active drug substances and finished product (including preservatives and diluents, if any)
3. Complete testing method for the AMV.
4. Complete results for the AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)

Note:
1. A cover letter consisting of the following information should be enclosed with every hard copy document submission:
   i) Name of product;
   ii) Reference Number/ Protocol Number;
   iii) Contact person (name/ email address/ telephone no.);
   iv) Name and address of company.
2. Documents submitted should be well organized and indexed.
Analytical Method Validation (AMV)
OVERVIEW OF ANALYTICAL METHOD VALIDATION (AMV)

DEFINITION

Validation is the proof needed to ensure that an analytical method can produce results which are reliable and reproducible and which are fit for the purpose intended.

Results from method validation can be used to judge the quality, reliability and consistency of analytical results: it is an integral part of any good analytical practice.
Purpose of Analytical Method Validation (AMV)

- Identification of sources and quantitation of potential errors.
- Determination if method is acceptable for intended use
- Establish proof that a method can be used for decision making
When methods need to be validated or revalidated?

1. **Before** their introduction into **routine use**

2. Whenever the **conditions change** for which the method has been validated (e.g., samples with a different matrix)

3. Whenever the **method is changed** and the change is outside the original scope of the method
OVERVIEW OF ANALYTICAL METHOD VALIDATION (AMV)

Plan + Collection of data = Good AMV
Guidelines for AMV

ICH Topic Q2 (R1)
Validation of Analytical Procedures: Text and Methodology

Step 5

NOTE FOR GUIDANCE ON VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY
Q2(R1)

Current Step 4 version
Parent Guideline dated 27 October 1994
(Complementary Guideline on Methodology dated 6 November 1996 incorporated in November 2003)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
What are the type of analytical procedures to be validated?

Identification

Assay (content & dissolution measurement only)

Impurities (quantitative & limit test)
What are the parameters/validation characteristics to check for those analytical procedures?

- Specificity
- Accuracy
- Precision (repeatability, intermediate)
- Linearity & Range
- Detection Limit
- Quantitation Limit
- Robustness
System Suitability Testing (SST)

Test to verify the proper functioning of the operating system. i.e., the electronics, the equipment, the specimens and the analytical operations

The example of SST in HPLC system:

1. Minimum resolution of 3.0 between the analyte peak and internal standard peaks.
2. Relative Standard Deviation (RSD) of replicate standard injections of not more than 2.0 %
Validation vs Verification

Validation requirement = Non compendial methods (in-house)

Verification requirement = Compendial methods
# Validation Requirement – Non compendial / in house method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Identification</th>
<th>Testing for Impurities</th>
<th>Assay / Dissolution / Content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Quantitative</td>
<td>Limit</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Precision – Repeatability</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Precision – Intermediate Precision</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Detection Limit</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Quantitation Limit</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Linearity</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Robustness</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Validation vs Verification

Validation requirement = Non compendial methods (in-house)

Verification requirement = Compendial methods
Users of analytical methods described in USP are not required to validate accuracy and reliability of these methods, **BUT** merely verify their suitability under actual conditions of use.

**system suitability testing**
Verification Requirement for Compendial method: (Ideally)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Identification</th>
<th>Testing for Impurities</th>
<th>Assay / Dissolution / Content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Quantitative</td>
<td>Limit</td>
</tr>
<tr>
<td>Precision – Intermediate Precision</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Specificity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>System suitability testing</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Good validation data should have:

- Validation protocols / methods
- Acceptance criteria
- Results
- Raw data
1. Validation protocol / method

Example 1

Specificity
Preparation of Standard Solution
0.01 mg/mL of USP atenolol RS in Mobile phase

Preparation of Sample Solution
Centrifuge a portion of the Sample stock solution, and dilute a volume of the supernatant with Mobile phase to obtain a solution nominally containing 0.01 mg/mL of atenolol

Blank
Mobile phase

Stress study
A minimal list of stress factors suggested for forced degradation studies must include acid and base hydrolysis, thermal degradation, photolysis, and...
1. Validation protocol / method

**Example 2**

**Standard Operating Procedure**

- Procedure for validation of Assay of Atenolol 50 mg tablet

<table>
<thead>
<tr>
<th>%</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>0.005 mg/ml</td>
</tr>
<tr>
<td>80%</td>
<td>0.008 mg/ml</td>
</tr>
<tr>
<td>100%</td>
<td>0.010 mg/ml</td>
</tr>
<tr>
<td>120%</td>
<td>0.012 mg/ml</td>
</tr>
<tr>
<td>150%</td>
<td>0.015 mg/ml</td>
</tr>
</tbody>
</table>

**Linearity**

Prepare the standard with the concentration of 50 – 150% of working concentration (0.01 mg/ml):

**Intermediate Precision**

Analyst A will prepare standard at 100% of working concentration and inject the standard by using HPLC 1.

Analyst B will prepare standard at 100% of working concentration and inject the standard by using HPLC 2.
## 2. Acceptance Criteria

### Example 1

<table>
<thead>
<tr>
<th>Analytical method</th>
<th>Parameter</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay of atenolol 50 mg tab USP</td>
<td>Specificity</td>
<td>No interference from diluent, placebo</td>
</tr>
<tr>
<td></td>
<td>Linearity</td>
<td>$R^2 &gt; 0.995$</td>
</tr>
<tr>
<td></td>
<td>Intermediate precision</td>
<td>RSD &lt; 2%</td>
</tr>
</tbody>
</table>
### Example 1

**Summary of AMV results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acceptance Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>No interference from diluent, placebo</td>
<td>The excipient, diluent, placebo do not interfere with the main peak</td>
</tr>
<tr>
<td>Linearity</td>
<td>$R^2 &gt; 0.995$</td>
<td>$R^2 = 0.999$</td>
</tr>
<tr>
<td>Intermediate precision</td>
<td>RSD &lt; 2%</td>
<td>RSD = 0.5%</td>
</tr>
</tbody>
</table>
4. Raw data

Example 1

Specificity

Chromatogram of standard solution

Chromatogram of sample solution

Chromatogram of mobile phase
PROTOCOL OF ANALYSIS (POA)
The way of performing the analysis

Describe in detail the steps necessary to perform each test
General requirement of POA for finished product

Product name
Name & address of manufacturer
Name, signature & designation of authorized person
Effective date
General requirement of POA: Example

- **Product name**: Atenolol 50 mg tablet
  - **Name & address of the manufacturer**: XX S/B
    - Lot 36 Jalan Universiti, Selangor
  - **Name, signature & designation**:
    - QC Manager: Raihan
    - QA Manager: Zainab
    - Date: 12/12/12

**Assay**

**Mobile phase**: 1.1 g of sodium 1-heptanesulfonate and 0.71 g of anhydrous dibasic sodium phosphate in 700 mL of water. Add 2 mL of dibutylamine, and adjust with 0.8 M phosphoric acid to a pH of 3.0. Add 300 mL of methanol, and pass through a filter having a 0.5-μm or finer porosity. Degas this solution before use.

**Standard solution**: 0.01 mg/mL of USP atenolol RS in Mobile phase
POA for finished product

1. It must be in Bahasa Malaysia / English
2. It contain all the updated test methods & the shelf life specifications
3. Methods must be described in detailed procedures
   1. - equipment/ reagent/ standards required
   2. - detailed dilution for standard / sample solution
   3. - detailed preparation of mobile phase/ diluent/ medium
   4. - system suitability test (resolution, %RSD, tailing factor, theoretical plate)
   5. - complete formula for calculation and interpretation of the results
   6. - chromatogram
POA for finished product

4. The latest BP / USP shall be used as the main references.
5. Photocopies or methods directly copied from pharmacopoeias will not be accepted.
6. All test specifications set by the manufacturer shall be in line or more stringent than BP / USP.
The manufacturer can set the specification in line (90.0 – 110.0%) or more stringent (95.0 – 105.0%).
Certificate of Analysis (COA)
Certificate of analysis

Finished product
3 batches

Active Pharmaceutical Ingredient(s)
1 batch

Note:
The test specifications must be listed in the certificate as well as actual results obtained
<table>
<thead>
<tr>
<th>Bil</th>
<th>Kod</th>
<th>Ujian</th>
<th>Spesifikasi</th>
<th>Keputusan</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>A00001</td>
<td>RUPABENTUK FIZIKAL</td>
<td>RUPABENTUK FIZIKAL</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>B01103</td>
<td>ID PARACETAMOL [TAKAT LEBUR]</td>
<td>HAD PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>4</td>
<td>B01105</td>
<td>IDENTIFIKASI PARACETAMOL [COLOUR TEST]</td>
<td>169 DEG CELCIUS PROTOKOL PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>5</td>
<td>B01107</td>
<td>IDENTIFIKASI PARACETAMOL [IR]</td>
<td>PROTOKOL PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>6</td>
<td>B02205</td>
<td>HEAVY METALS</td>
<td>&lt; 20 PPM</td>
<td>0.3 PPM</td>
</tr>
<tr>
<td>7</td>
<td>B02211</td>
<td>RELATED SUBSTANCE</td>
<td>NMT 0.1</td>
<td>0.001%</td>
</tr>
<tr>
<td>8</td>
<td>B03311</td>
<td>4-AMINOPHENOL</td>
<td>HAD PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>9</td>
<td>B04109</td>
<td>KANDUNGAN PARACETAMOL [UV/VIS]</td>
<td>TIDAK &gt; 0%</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>10</td>
<td>B07201</td>
<td>MELTING POINT</td>
<td>103 - 107 DEG</td>
<td>104 DEG</td>
</tr>
</tbody>
</table>

**Example of Active Ingredient:**

- **COA OF ACTIVE INGREDIENT**

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**Printed Date:** 08/09/2008

**T.T. KETUA MAHKAM:** Amerah

**T.T. TIM PENGARAH BAHU:** Raihan
<table>
<thead>
<tr>
<th>No.</th>
<th>KOD</th>
<th>UJIAN</th>
<th>SPEKIFIKASI</th>
<th>KEPUTUSAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A0000</td>
<td>PEMBUNGKUSAN</td>
<td>BLISTER PACK OF 10 TABLETS</td>
<td>LULUS</td>
</tr>
<tr>
<td>2</td>
<td>A00001</td>
<td>RUPABENTUK FIZIKAL</td>
<td>WHITE, ROUND SHAPED, UNCOATED TABLETS</td>
<td>LULUS</td>
</tr>
<tr>
<td>3</td>
<td>B01103</td>
<td>TIDAK LEBUR</td>
<td>169 DEG CELCIUS</td>
<td>LULUS</td>
</tr>
<tr>
<td>4</td>
<td>B01105</td>
<td>IDENTIFIKASI PARACETAMOL [COLOUR TEST]</td>
<td>169 DEG CELCIUS</td>
<td>LULUS</td>
</tr>
<tr>
<td>5</td>
<td>B01107</td>
<td>IDENTIFIKASI PARACETAMOL [IR]</td>
<td>PROTOKOL PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>6</td>
<td>B02205</td>
<td>PENGECARAN TAB TAK BERSALUT</td>
<td>HAD PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>7</td>
<td>B02211</td>
<td>KESERAGAMAN BERAT TABLET</td>
<td>(TIDAK &gt; 15 %)</td>
<td>22 MINIT</td>
</tr>
<tr>
<td>8</td>
<td>B02311</td>
<td>4-AMINOPHENOL</td>
<td>TIDAK &gt; 0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>9</td>
<td>B04109</td>
<td>KANDUNGAN PARACETAMOL [UVVIS]</td>
<td>TIDAK &gt; 0.1%</td>
<td>LULUS</td>
</tr>
<tr>
<td>10</td>
<td>B07201</td>
<td>PELARUTAN PARACETAMOL (UV)</td>
<td>95.0 ± 10.0 % AKT</td>
<td>99.4 % AKT</td>
</tr>
</tbody>
</table>

Printed Date: 08/09/2008

T.T. KETUA MAK MAL

T.T. TIM PENGARAH BANU
The Requirement of AMV Document Submission
1. Protocol of analysis for finished product (POA)

2. Certificate of analysis for finished product and active pharmaceutical ingredient(s) (COA)

3. Analytical method validation documents
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E9</strong></td>
<td><strong>Complete protocol of Analysis for finished product including preservatives (if any)</strong></td>
</tr>
<tr>
<td><strong>E10</strong></td>
<td><strong>Summary of AMV which include all the relevant validation characteristics, its acceptance criteria and results</strong></td>
</tr>
<tr>
<td><strong>E11</strong></td>
<td><strong>Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches)</strong></td>
</tr>
</tbody>
</table>
Requirements

- submit through the Quest System
- hardcopy version sent to Laboratory Services Section

Note:

If the file is too big, then a summary of the validation data may be uploaded but the hardcopy version has to be a complete set of documents.
Documents to be submitted as hardcopy

1. Certificate of analysis (COA) for active drug substance (1 batch) and recent batches of finished product (3 different batches)

2. Complete protocol of analysis (POA) for finished product (including preservatives, if any)

3. Complete testing method for the AMV

4. Complete results for the AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatogram, spectrums etc)
1. A cover letter consisting of the following information should be enclosed with every hard copy documents submission;
   i) Name of product
   ii) Reference Number / Protocol Number
   iii) Contact person (name/email address/ telephone no.)
   iv) Name and address of company

2. Documents submitted should be well organized and indexed
Common Problems in Submitting the Documents
Common problems in submitting the document: COA

1. COA of active ingredient not available
2. Incomplete number of COA of finished product
3. Incomplete information on COA
   - no specification
   - the results was written as “complies” or “conform” (esp. for the results for Related Substance / Particulate matter)
4. The specifications are too lenient
Common problems in submitting the document: COA

The manufacturer can set the specification in line (90.0 – 110.0%) or more stringent (95.0 – 105.0%).

DO NOT set the specification too lenient than this!! e.g. 85.0 – 115.0%
<table>
<thead>
<tr>
<th>No.</th>
<th>Bil.</th>
<th>Kod</th>
<th>Ujian</th>
<th>Spesifikasi</th>
<th>Keputusan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<td>2</td>
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<td>RUPABENTUK FIZIKAL</td>
<td></td>
<td>WHITE POWDER</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>B01103</td>
<td>ID PARACETAMOL [TAKAT LEBUR]</td>
<td>HAD PEMBUAT</td>
<td>LULUS</td>
</tr>
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<td></td>
<td>B01105</td>
<td>IDENTIFIKASI PARACETAMOL [COLOUR TEST]</td>
<td>169 DEG CELCIUS PROTOKOL PEMBUAT</td>
<td>LULUS</td>
</tr>
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<td></td>
<td>B01107</td>
<td>IDENTIFIKASI PARACETAMOL [IR]</td>
<td>PROTOKOL PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>B02205</td>
<td>HEAVY METALS</td>
<td>&lt;20 PPM</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>B02211</td>
<td>RELATED SUBSTANCE</td>
<td>NMT 0.1</td>
<td>0.001%</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>B03311</td>
<td>4-AMINOPHENOL</td>
<td>HAD PEMBUAT</td>
<td>LULUS</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>B04109</td>
<td>KANDUNGAN PARACETAMOL [UV/VIS]</td>
<td>TIDAK &gt; 0.1%</td>
<td>LULUS</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>B07201</td>
<td>MELTING POINT</td>
<td>95.0 - 105.0% AKT</td>
<td>99.4% AKT</td>
</tr>
</tbody>
</table>

Should write the actual value e.g 0.01 ppm
Common problems in submitting the document: POA

Protocol of analysis

- Methods are directly copied from pharmacopeias
- Methods are not updated to current pharmacopeias
- Critical test are not performed (dissolution, related substance/impurities)
- Test parameters are listed in COA but not found in POA
Common problems in submitting the document: AMV

**Validation Data**

- Methods are not validated as per ICH guidelines
- Validation protocol is not provided. Only provide validation report
- Different test methods in POA and protocol validation
Common problems in submitting the document: AMV

Validation Data

- Test method for validation was not mentioned
- No acceptance criteria
- Raw data not given / manufacturer refuse to give the raw data
THANK YOU