National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

World Health Organization
WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

PIC/S
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

QUALITY SYSTEM
SIRIM
Certified to ISO 9001:2000
Cert. No: AR 2293

STANDARDS MALAYSIA
ACCREDITED LABORATORY
MS ISO/IEC 17025:2005
[illegible]

AMV Document Submission Guideline & Common Problems

Centre for Quality Control|

National Pharmaceutical Control Bureau
Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor

DL: +6.03.78835400 | F: +6.03.79567075 |

WS : www.bpfk.gov.my |

PRESENTATION OUTLINE

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

Background

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)

NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH, MALAYSIA

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)

First Edition – Revised July 2014

Address:

Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor Darul Ehsan, Malaysia

+603-7883 5400

+ 603-7956 2924, 7956 7075

http://www.bpfk.gov.my

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

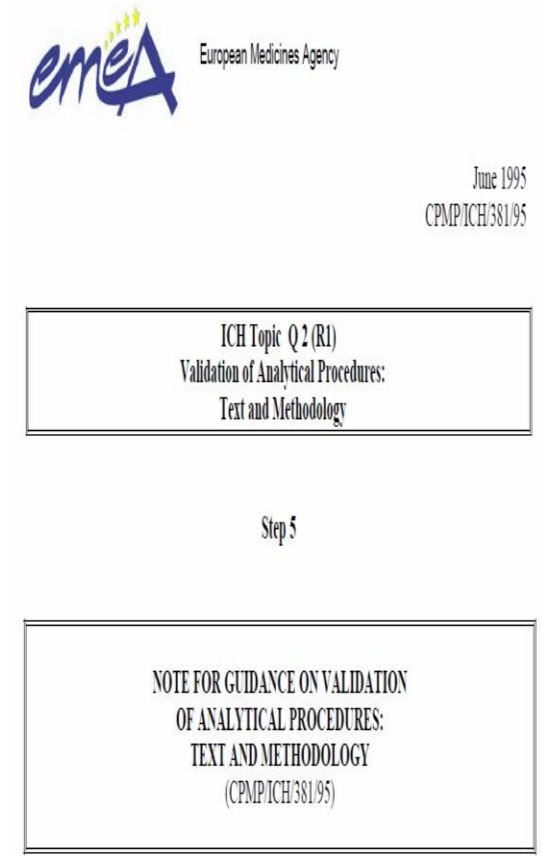
2. Whenever the conditions change for which the method has been validated (e.g., samples with a different matrix)

3. Whenever the method is changed and the change is outside the original scope of the method

OVERVIEW OF ANALYTICAL METHOD VALIDATION (AMV)

NPCB
MOH

Guidelines for AMV



European Medicines Agency

June 1995
CPMP/ICH/381/95

ICH Topic Q 2 (R1)
Validation of Analytical Procedures:
Text and Methodology

Step 5

NOTE FOR GUIDANCE ON VALIDATION
OF ANALYTICAL PROCEDURES:
TEXT AND METHODOLOGY
(CPMP/ICH/381/95)

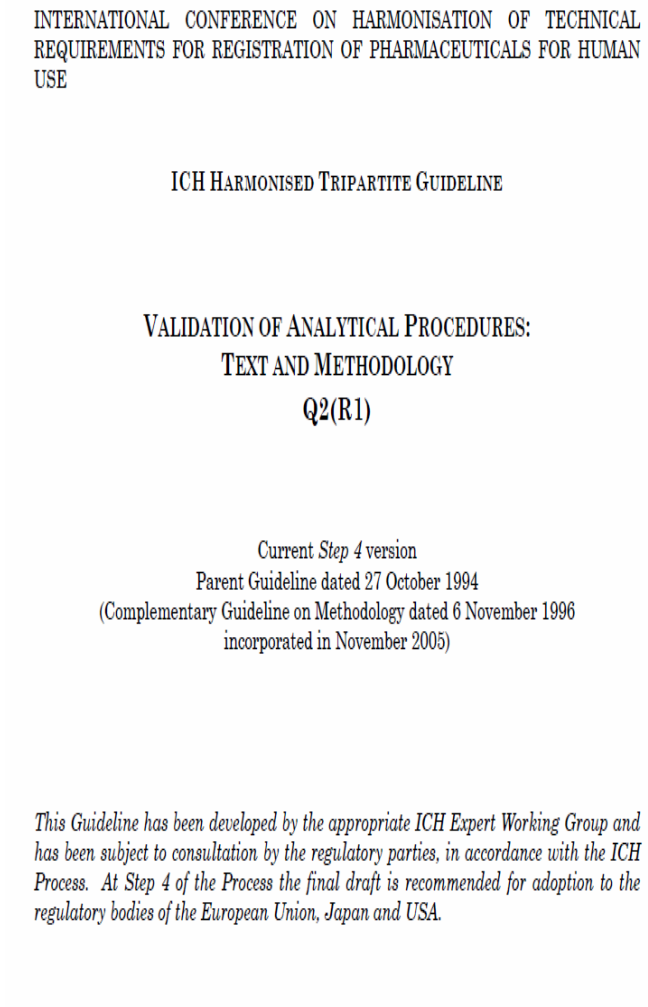
The Fitness for Purpose of Analytical Methods

A Laboratory Guide to Method Validation and Related Topics

Eurachem — A FOCUS FOR ANALYTICAL CHEMISTRY IN EUROPE

This document has been developed by a EURACHEM Working Group from a draft originally produced by LGC. The membership of the EURACHEM group is

Prof P de Bievre	IRMM, Belgium
Dr D Böttger	Hoechst AG, Germany
Dr C Eastwood	Zeneca Specialties, UK
Prof J Hlavay	University of Veszprem, Hungary
Mr M Holmgren	SP, Sweden (Eurolab Secretariat)
Dr W Horwitz	Food and Drug Administration, USA
Dr M Lauwaars	AOAC International, The Netherlands
Dr B Lundgren	SP, Sweden
Prof L Massart	Vrije Universiteit Brussel, Belgium
Prof J Miller	University of Loughborough, UK
Dr J Morkowski	EMPA, Switzerland
Dr B te Nijenhuis	Working Party on Analytical Chemistry (Secretary), The Netherlands
Ms B Nyeland	National Environment Research Institute, Denmark
Dr R Philipp	BAM, Germany
Dr P Radvila	EMPA St Gallen, Switzerland
Prof J Smeyers-Verbeke	Vrije Universiteit Brussel, Belgium
Dr R Stephany	RIVM, The Netherlands
Dr M Suchanek	Prague Institute of Chemical Technology, Czech Republic
Ms C Vandervoorst	Dr L Willems Instituut vzw, Belgium
Dr H Verplaetse	Ministry of Economic Affairs - Central Laboratory, Belgium
Ms H Wallien	VTT, Finland
Dr M Walsh	The State Laboratory, Ireland
Prof W Wegscheider	Leoben University of Mining & Metallurgy, Austria
Dr D Westwood	Environment Agency, UK
Mr H J van de Wiel	RIVM, The Netherlands



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 2005)

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

Parameter	Identification	Testing for Impurities		Assay / Dissolution / Content
		Quantitative	Limit	
Accuracy	-	+	-	+
Precision – Repeatability	-	+	-	+
Precision – Intermediate Precision	-	+	-	+
Specificity	+	+	+	+
Detection Limit	-	-	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+
Robustness	-	+	-	+

Validation vs Verification

Validation requirement = Non compendial methods (in-house)

Verification requirement = Compendial methods

Compendial method

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)

Parameter	Identification	Testing for Impurities		Assay / Dissolution / Content
		Quantitative	Limit	
Precision – Intermediate Precision	-	+	-	+
Specificity	+	+	+	+
System suitability testing				

Good validation data should have ;

- ✓ Validation protocols / methods
- ✓ Acceptance criteria
- ✓ Results
- ✓ Raw data

1. Validation protocol / method

Example 1

XXX	Procedure for validation of Assay of Atenolol 50 mg tablet	Mukasurat : 1 / 1

SEJARAH SEMAKAN					
Terbitan	Semakan	Ditulis oleh	Disemak oleh	Dilulus oleh	Tarikh Kuatkuasa
	0	Ameena	Raihan	Zainab	12/12/12

RUJUKAN	
No.	Tajuk
1.	USP

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

1. Validation protocol / method

XXX	Standard Operating Procedure	No. Dokumen: 12/2014
	Procedure for validation of Assay of Atenolol 50 mg tablet	Mukasurat : 3 / 1

Example 2

Linearity

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

%	Concentration
50 %	0.005 mg/ml
80%	0.008 mg/ml
100 %	0.01 mg/ml
120 %	0.012 mg/ml
150 %	0.015 %

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

XXX	Standard Operating Procedure	No. Dokumen: 12/2014
	Procedure for validation of Assay of Atenolol 50 mg tablet USP	Mukasurat : 4 / 1

Example 1

Analytical method	Parameter	Acceptance Criteria
Assay of atenolol 50 mg tab USP	Specificity	No interference from diluent, placebo
	Linearity	$R^2 > 0.995$
	Intermediate precision	RSD < 2%

3. Results

Example 1

Summary of AMV results

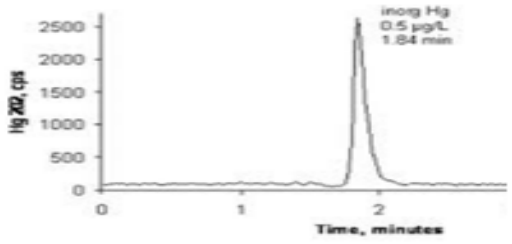
Parameter	Acceptance Criteria	Results
Specificity	No interference from diluent, placebo	The excipient, diluent, placebo do not interfere with the main peak
Linearity	$R^2 > 0.995$	$R^2 = 0.999$
Intermediate precision	RSD < 2%	RSD = 0.5%

4. Raw data

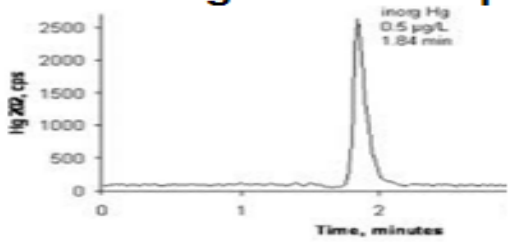
Example 1

Specificity

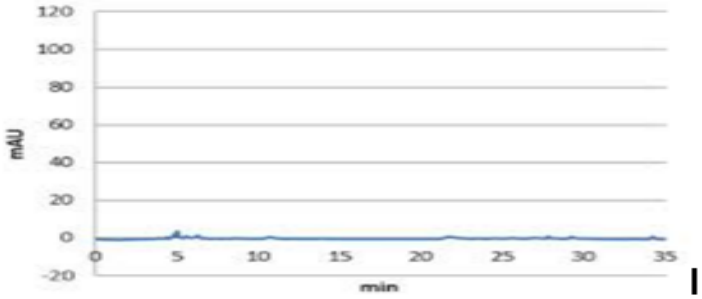
Chromatogram of standard solution



Chromatogram of sample solution



Chromatogram of mobile phase



PROTOCOL OF ANALYSIS (POA)

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

Xxx S/B Lot 36 Jalan Universiti, Selangor	Standard Operating Procedure	No. Dokumen: 12/2014
	Atenolol 50 mg tablet	Mukasurat : 1 / 1

Product name

Name & address of the manufacturer

SEJARAH SEMAKAN

Terbitan	Semakan	Ditulis oleh	QC Manager	QA manager	Tarikh Kuatkuasa
1	0	Ameena Ameena	Raihan Raihan	Zainab Zainab	12/12/12

Name, signature & designation

Effective date

RUJUKAN

No.	Tajuk
1.	USP

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*

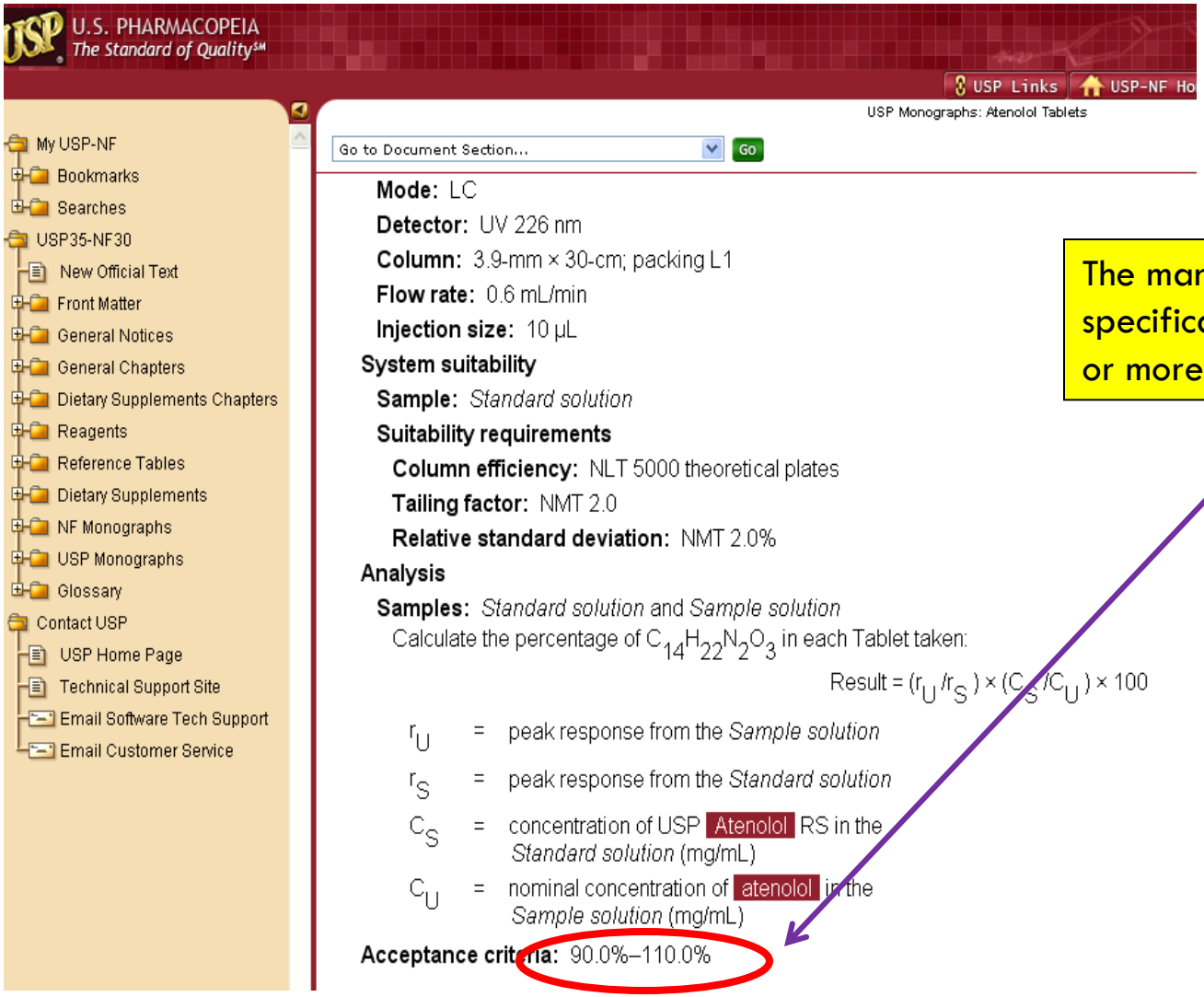
POA for finished product

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

POA for finished product



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

SYARIKAT MAJU SDN BHD

LOT 36 JALAN UNIVERSITI

PETALING JAYA

NAMA KELUARAN PARACETAMOL

NO KUMPULAN 2014XXX

DATE MANUFACTURE : 31 DISEMBER 2013

EXP DATE 31 DISEMBER 2016

BIL	KOD	UJIAN	SPESIFIKASI	KEPUTUSAN
2	A00001	RUPABENTUK FIZIKAL		WHITE POWDER
3	B01103	ID PARACETAMOL [TAKAT LEBUR]	HAD PEMBUAT	LULUS
4	B01105	IDENTIFIKASI PARACETAMOL [COLOUR TEST]	169 DEG CELCIUS PROTOKOL PEMBUAT	169 DEG CELCIUS LULUS
5	B01107	IDENTIFIKASI PARACETAMOL [IR]	PROTOKOL PEMBUAT	LULUS
6	B02205	HEAVY METALS	< 20 PPM	0.9 PPM
7	B02211	RELATED SUBSTANCE	NMT 0.1	0.001%
8	B03311	4-AMINOPHENOL	HAD PEMBUAT TIDAK > 0.1%	LULUS <0.1%
9	B04109	KANDUNGAN PARACETAMOL [UV/VIS]	HAD PEMBUAT 95.0-105.0% AKT	LULUS 99.4% AKT
10	B07201	MELTING POINT	103 – 107 °C	104°C

EXAMPLE
COA OF ACTIVE INGREDIENT

Printed Date 08/09/2008

T.T. KETUA MAKMAL Ameenaa

T.T. TIM. PENGARAH BAU Raihan

SYARIKAT ABC SDN BHD

LOT 36 JALAN UNIVERSITI

PETALING JAYA

NAMA KELUARAN: UBAT DEMAM ABC

NO KUMPULAN: 2014XXX

NO PENDAFTARAN: MAL20140000X

DATE MANUFACTURE: 31 DISEMBER 2013

EXP DATE: 31 DISEMBER 2016

BIL	KOD	UJIAN	SPESIFIKASI	KEPUTUSAN
1	A0000	PEMBUNGKUSAN		LULUS
2	A00001	RUPABENTUK FIZIKAL		BLISTER PACK OF 10 TABLETS LULUS WHITE, ROUND SHAPED, UNCOATED TABLETS
3	B01103	ID PARACETAMOL [TAKAT LEBUR]	HAD PEMBUAT 169 DEG CELCIUS	LULUS 169 DEG CELCIUS
4	B01105	IDENTIFIKASI PARACETAMOL [COLOUR TEST]	PROTOKOL PEMBUAT	LULUS
5	B01107	IDENTIFIKASI PARACETAMOL [IR]	PROTOKOL PEMBUAT	LULUS
6	B02205	PENGECAIAN TAB TAK BERSALUT BERSALUT	HAD PEMBUAT (TIDAK > 15 MINIT)	LULUS 22 MINIT
7	B02211	KESERAGAMAN BERAT TABLET	HAD BP 200[illegible]	LULUS
8	B03311	4-AMINOPHENOL	HAD PEMBUAT TIDAK > 0.1%	LULUS <0.1%
9	B04109	KANDUNGAN PARACETAMOL [UV/VIS]	HAD PEMBUAT 95.0-105.0% AKT	LULUS 99.4% AKT
10	B07201	PELARUTAN PARACETAMOL (UV)	BP (TIDAK < 75% LARUT DALAM 45 MINIT)	LULUS MAX: 93.0% MIN: 75.8%

Printed Date: 08/09/2008

T.T. KETUA MAKMAL: sukaili

T.T. TIM. PENGARAH BAU: azman

The Requirement of AMV Document Submission

Requirements

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

Documents to be submitted via online Quest system

E9	**Complete protocol of Analysis for finished product including preservatives (if any)**
E10	**Summary of AMV which include all the relevant validation characteristics, its acceptance criteria and results**
E11	**Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches)**

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)

Additional

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

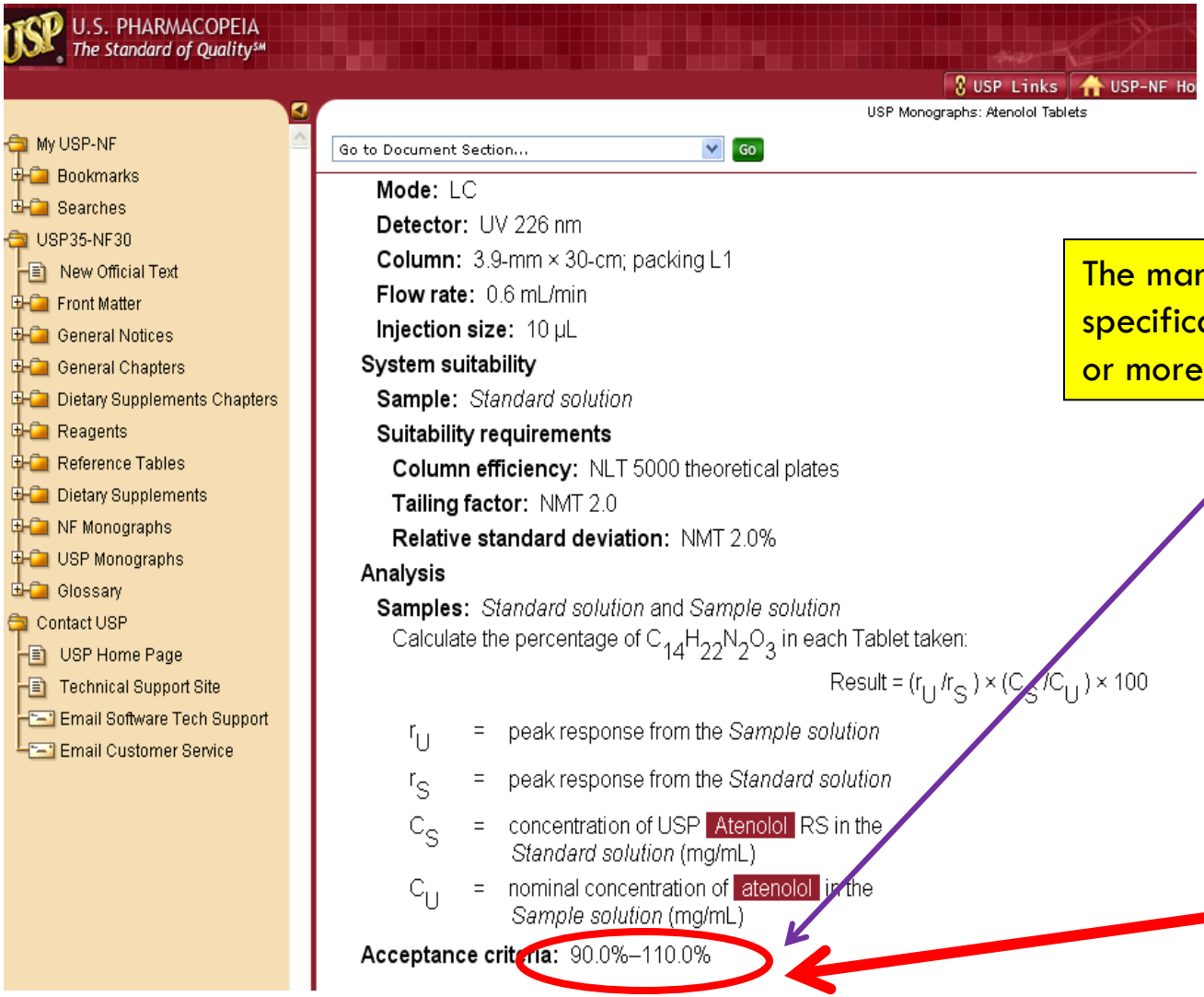
1. COA of active ingredient not available
2. Incomplete number of COA of finished product
3. Incomplete information on COA

   - no specification

   - the results was written as “complies” or “conform” (esp. for the results for Related Substance / Particulate matter)

1. 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 %

SYARIKAT MAJU SDN BHD

LOT 36 JALAN UNIVERSITI

PETALING JAYA

NAMA KELUARAN PARACETAMOL TABLET

NO KUMPULAN 2014XXX

DATE MANUFACTURE: 31 DISEMBER 2013

EXP DATE 31 DISEMBER 2016

BIL	KOD	UJIAN	SPESIFIKASI	KEPUTUSAN
2	A00001	RUPABENTUK FIZIKAL		WHITE POWDER
3	B01103	ID PARACETAMOL [TAKAT LEBUR]	HAD PEMBUAT 169 DEG CELCIUS	LULUS 169 DEG CELCIUS
4	B01105	IDENTIFIKASI PARACETAMOL [COLOUR TEST]	PROTOKOL PEMBUAT	LULUS
5	B01107	IDENTIFIKASI PARACETAMOL [IR]	PROTOKOL PEMBUAT	LULUS
6	B02205	HEAVY METALS	< 20 PPM	COMPLIES
7	B02211	RELATED SUBSTANCE	NMT 0.1	0.001%
8	B03311	4-AMINOPHENOL	HAD PEMBUAT TIDAK > 0.1%	LULUS <0.1%
9	B04109	KANDUNGAN PARACETAMOL [UV/VIS]	HAD PEMBUAT 95.0-105.0% AKT	LULUS 99.4% AKT
10	B07201	MELTING POINT	103 – 107 °C	104°C

Printed Date 08/09/2008

T.T. KETUA MAKMAL Ameenaa

T.T. TIM. PENGARAH BAU Raihan

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