EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2011
EMA/CHMP/600958/2010
Committee of Medicines for Human Use (CHMP)

Appendix IV of the Guideline on the Investigation on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1): Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1

Draft

Draft Agreed by Pharmacokinetics Working Party	January 2011
Adoption by CHMP for release for consultation	17 February 2011
End of consultation (deadline for comments)	31 May 2011

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

Keywords	*Generic applications, bioequivalence data, BCS biowaiver documentation, Standardised presentation, CHMP, EMA, Guideline*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Appendix IV of the Guideline on the Investigation on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1): Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1

Table of contents

1. Introduction

The objective of CTD Module 2.7.1 is to summarize all relevant information in the MAA dossier with regard to biopharmaceutic studies and associated analytical methods

This Appendix contains a set of template forms to assist applicants in the preparation of Module 2.7.1 providing guidance with regard to data to be presented. Furthermore, it is anticipated that a standardized presentation will facilitate the evaluation process. Applicants are therefore encouraged to use these template tables when preparing Module 2.7.1.

This Appendix is intended for generic applications according to Directive 2001/83/EC, Article 10(1), but might be used in other applications including variations, fixed combinations, extensions and hybrid applications.

2. Instructions for completion and submission of the tables

The tables should be completed only for the pivotal studies, as identified in the application dossier in accordance with section 4.1 of the Bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1). If there is more than one pivotal bioequivalence study, then individual tables should be prepared for each study. In addition, the following instructions for the tables should be observed:

- Details of non-EU reference products are not needed.
- Tables in Section 3 should be completed separately for each analyte per study. If there is more than one test product then the table structure could be adjusted.
- Tables in Section 4 should only be completed for the method used in confirmatory (pivotal) bioequivalence studies. If more than one analyte was measured then Table 4.1 and potentially Table 4.3 should be completed for each analyte.

In general, applicants are encouraged using cross-references and footnotes for adding additional information. Fields that do not apply should be completed as "Not applicable" together with an explanatory footnote.

In addition, each section of the template should be cross-referenced to the location of supporting documentation or raw data in the application dossier.

It is recommended that the content of the tables is searchable and that the tables are not scanned. Applicants are encouraged to provide Module 2.7.1 also in Word (.doc) or RTF format.

3. A note about BCS-based biowaiver documentation

Relevant data for justification of BCS-based biowaiver requests should be included in Module 5.3.1.2 "Comparative BA and Bioequivalence (BE) Study Reports". A summary of the data should be provided in Module 2.7.1 with a justification for this biowaiver and a list of relevant references.

1. BIOWAIVER REQUEST

Table 1.1 Qualitative and quantitative composition of the Test product

Ingredient	Function	Strength (label claim)					
		XX mg (Production Batch Size)		XX mg (Production Batch Size)		XX mg (Production Batch Size)	
CORE		Quantity per unit	%*	Quantity per unit	%*	Quantity per unit	%*
TOTAL			100%		100%		100%
COATING							
TOTAL			100%		100%		100%

**each ingredient expressed as a percentage of the total core or coating weight*

Instructions
Include the composition of all strengths. Add additional columns if it is necessary.

Table 1.2 In vitro dissolution data for biowaiver request

Dissolution testing Site		Study Report Location (vol, page,link)
Dissolution Conditions	Apparatus	
	RPM	
	Volume	

Dissolution Medium			Collection Times (minutes or hours)						f2
			5	10	15	20			
Strength 1	pH=								
# of units	pH=								
# Batch no	pH=								
Strength 2	pH =								
# of units	pH=								
# Batch no	pH=								
Strength 3	pH=								
# of units	pH=								
# Batch no	pH=								

Instructions

Fill this table only if biowaiver is requested for additional strengths besides the strength tested in the bioequivalence study. Only the mean dissolution values should be reported. f2 values should be computed relative to the strength tested in the bioequivalence study. Expand the table with additional rows if more than 3 strengths are requested. Fill a similar table for the reference product if sink condition could not be achieved.

2. BIOEQUIVALENCE TRIAL INFORMATION

Table 2.1 Test and reference product information

Product Characteristics	**Test product**	**Reference Product**
Name		
Strength		
Dosage form		
Manufacturer[1]		
Batch #		
Batch size (Biobatch)		
Assay %		
Commercial Batch Size		
Expiry date (Retest date)		
Location of product certificate	Vol/page, link	Vol/page, link
Member State where the reference product is purchased from:		

Table 2.2 Study site

Study ID (vol/page,link)	Study title			Has this site been inspected by an EU Authority?
Clinical Study Site	Name	Address	Study period:	Authority: Year:
Bioanalytical Facility	Name	Address	Study period:	Authority: Year:
Data analysis	Name	Address		Authority: Year:
Sponsor of the study	Name	Address		

Table 2.3 Study design

Study ID: Report Location (vol/page, link): Design: Dose: Single/Multiple dose: Number of periods: Two-stage design: (yes/no) Fasting, Fed: # Volunteers (dosed): # Volunteers (evaluated):

3. RESULTS

Table 3.1 Pharmacokinetic data for <analyte>

Pharmacokinetic parameter	**Arithmetic Means (±SD)	
	Test product	**Reference product**
$AUC_{(0-t)}$ [1]		
$AUC_{(0-\infty)}$ [2]		
Cmax		
Tmax		
Others		

[1] $AUC_{(0-72h)}$ can be reported instead of $AUC_{(0-t)}$, in studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable
[2] $AUC_{(0-\infty)}$ does not need to be reported when $AUC_{(0-72h)}$ is reported instead of $AUC_{(0-t)}$.

Table 3.2 Additional pharmacokinetic data for <analyte>

Records[1] where $AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$[2]	List patient IDs and period numbers
Records where Cmax is the first point	List patient IDs and period numbers
Records with significant carry-over (pre-dose sample > 5% Cmax)	List patient IDs, period numbers, treatment, pre-dose concentration

[1] A subject record is a list of concentrations after one administration
[2] Only if the last sampling point of $AUC_{(0-t)}$ is less than 72h

Table 3.3 Bioequivalence evaluation of <analyte>

Pharmacokinetic parameter	**Ratio Test/Ref**	**Confidence Intervals**	**CV%[1]**
$AUC_{(0-t)}$			
Cmax			
Others			

[1]Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

4. BIOANALYTICS

Table 4.1 Bioanalytical method validation

Analytical Validation Report	<Study report number Locations (vol/page, link)>
This analytical method was used in the following studies:	<Study IDs>
Short description of the method	<e.g. HPLC/MS/MS, GC/MS, Ligand binding>
Analyte	<Name, location of product certificate (vol/page, link)>
Internal standard (IS)	<Name, location of product certificate (vol/page, link)>
Calibration range	
Linearity	<r>
Lower limit of quantification (LOQ)	<Accuracy, Precision>
Standard curve concentrations (units/mL)	
QC concentrations (units/mL, vol/page link)	
Between-run accuracy	<Range or by QC>
Between-run precision	<Range or by QC>
Within-run accuracy	<Range or by QC>
Within-run precision	<Range or by QC>
Matrix Factor % (Analyte and IS) CV% of IS normalized matrix factor	
Short term stability of the stock solution and working solutions	<Confirmed up to (Time). Observed change % at Temperature °C>
Long term stability of the stock solution and working solutions	<Confirmed up to (Time). Observed change % at Temperature °C>
Short-term stability in plasma at room temperature (QC)	<Confirmed up to (Time). Observed change %>
Post-preparative stability (dry extract stability)	<Confirmed up to (Time). Observed change %>
Long term stability in plasma (vol/page,link)	<Confirmed up to (Time). Observed change % at Temperature °C>
Autosampler storage stability	<Confirmed up to (Time). Observed change %>
Freeze and thaw stability (-Temperature °C)	<# cycles, Observed change %>
Dilution integrity	<Concentration diluted X-fold, Accuracy % Precision %>
Partial validations 1 Location (vol/page, link)	<Describe shortly the reason of revalidation>
Partial validations 2 Location (vol/page, link)	<Describe shortly the reason of revalidation>
Cross validation	<Describe shortly the reason of crossvalidation>

[1]Might not be applicable for the given analytical method

Table 4.2 Storage period of study samples

Study ID	Longest storage period

Table 4.3 Study sample analysis

Study ID	
Total numbers of collected samples	# collected samples
Total number of samples with valid results	# samples
Total number of reassayed samples[1,2]	# reassayed samples
Total number of analytical runs[1]	# runs
Total number of valid analytical runs[1]	# valid runs
Incurred sample reanalysis	
Number of samples	# samples
Percentage of samples where the difference between the two values was less than 20% of the mean"	% samples

[1] Without incurred samples
[2] Due to other reasons than not valid run

Instructions
Fill Table 4.3 for each pivotal trial.