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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

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*The correction concerns clarifications/corrections in Tables 3.2 and 4.1.

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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 tables 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. The use of these template tables is therefore recommended to applicants when preparing Module 2.7.1. This Appendix is intended for generic applications according to Directive 2001/83/EC, Article 10(1). Furthermore, if appropriate then it is also recommended to use these template tables in other applications such as 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 should 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 to use cross-references and footnotes for adding additional information. Fields that do not apply should be completed as "Not applicable" together with an explanatory footnote if needed.

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

The tables should not be scanned copies and their content should be searchable. It is strongly recommended that applicants 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 "Comparative BA and Bioequivalence (BE) Study Reports". A summary of the data should be provided in Module 2.7.1 with a justification for the BCS-based biowaiver and a list of relevant references.

1. BIOWAIVER REQUEST for DIFFERENT STRENGTHS

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 (w/w) of the total core or coating weight or w/v % for solutions*

Instructions

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

Table 1.2 In vitro dissolution data for biowaiver request.

Dissolution testing Site		Study Report Location <vol/page, link>
Dissolution Conditions	Apparatus	
	RPM	
	Medium	
	Volume	
	Temperature	
	Surfactant	

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

[1] Only if the medium intended for drug product release is different from the buffers above

Instructions

Fill this table only if biowaiver is requested for additional strengths besides the strength tested in the bioequivalence study. Only the mean percent dissolution values should be reported but denote the mean by star (*) if the corresponding RSD is higher than 10% except the first point where the limit is 20%. Expand the table with additional columns according to the collection times. If more than 3 strengths are requested then add additional rows. f2 values should be computed relative to the strength tested in the bioequivalence study. Justify in the text if not f2 but an alternative method was used.

2. BIOEQUIVALENCE TRIAL INFORMATION

Table 2.1 Test and reference product information

Product Characteristics	**Test product**	**Reference Product**
Name		
Strength		
Dosage form		
Manufacturer		
Batch number		
Batch size (Biobatch)		
Measured content(s)[1] (% of label claim)		
Commercial Batch Size		
Expiry date (Retest date)		
Location of Certificate of Analysis	<Vol/page, link>	<Vol/page, link>
Member State where the reference product is purchased from:		
This product was used in the following trials:	<Study ID(s)>	<Study ID(s)>

[1]List for each active substance for fixed combinations

Instructions

If more than one batch of the Test or Reference products were used in the bioequivalence trials then fill out Table 2.1 for each Test/Reference batch combination.

Table 2.2 Study Site(s) of <Study ID>

	Name	Address	EU Authority Inspection	
			Year	Authority
Clinical Study Site				
Bioanalytical Study Site				
PK and Statistical Analysis				
Sponsor of the study				

Table 2.3 Study description of <Study ID>

Study Title:

Report Location:	<vol/page, link>
Study Periods	
Clinical:	<DD Month YYYY> - <DD Month YYYY>
Bioanalytical:	<DD Month YYYY> - <DD Month YYYY>
Design	
Dose:	
Single/Multiple dose:	
Number of periods:	
Two-stage design:	(yes/no)
Fasting/ Fed:	
Number of subjects	
- dosed:	<##>
- completed the study:	<##>
- included in the final statistical analysis of AUC:	<##>
- included in the final statistical analysis of Cmax:	<##>

Instructions

Fill out Tables 2.2 and 2.3 for each study.

3. RESULTS

Table 3.1 Pharmacokinetic data for <analyte> in <Study ID>

Pharmacokinetic parameter	[4]Arithmetic Means (±SD)	
	Test product	**Reference Product**
$AUC_{(0-t)}$ [1]		
$AUC_{(0-\infty)}$ [2]		
Cmax		
tmax[3]		

[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. Only for immediate release products.
[2] $AUC_{(0-\infty)}$ does not need to be reported when $AUC_{(0-72h)}$ is reported instead of $AUC_{(0-t)}$.
[3] Median (Min, Max)
[4] Arithmetic Means (±SD) may be substituted by Geometric Mean (±CV%)

Table 3.2
Additional pharmacokinetic data for <analyte> in <Study ID>

Plasma concentration curves where	**Related information**
- $AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$[1]	<subject ID, period #, F[2]>
- Cmax is the first point	<subject ID, period #, F>
- Pre-dose sample > 5% Cmax	<subject ID, period #, F, pre-dose concentration>

[1] Only if the last sampling point of $AUC_{(0-t)}$ is less than 72h
[2] F = T for the Test formulation or F = R for the Reference formulation

Table 3.3
Bioequivalence evaluation of <analyte> in <Study ID>

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Ref**	**Confidence Intervals**	**CV%[1]**
$AUC^{2}_{(0-t)}$			
Cmax			

[1]Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.
[2] In some cases $AUC_{(0-72)}$

Instructions

Fill out Tables 3.1-3.3 for each relevant analyte.

4. Bioanalytics

Table 4.1 Bioanalytical method validation

Analytical Validation Report Location(s)	<Study Code> <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>	
Biological matrix	<e.g. Plasma, Whole Blood, Urine>	
Analyte Location of product certificate	<Name>, <vol/page, link)>	
Internal standard (IS)[1] Location of product certificate	<Name> <vol/page, link>	
Calibration concentrations (Units)		
Lower limit of quantification (Units)	<LLOQ>, <Accuracy%>, <Precision%>	
QC concentrations (Units)		
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 (MF) (all QC)[1] IS normalized MF (all QC)[1] C.V.% of IS normalized MF (all QC)[1] % of QCs with >85% and <115% n.v.[1,4] % matrix lots with mean <80% or>120% n.v[1,4]	Low QC <Mean> <Mean> <C.V.%> <%> <%>	High QC <Mean> <Mean> <C.V.%> <%> <%>
Long term stability of the stock solution and working solutions[2] (Observed change %),	Confirmed up to <Time> at <°C> <%, Range or by QC>	
Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to <Time> <%, Range or by QC>	
Long term stability in biological matrix (Observed change %) Location	Confirmed up to <Time> at < °C> <%, Range or by QC> <vol/page, link>	
Autosampler storage stability (Observed change %)	Confirmed up to <Time> <%, Range or by QC>	
Post-preparative stability (Observed change %)	Confirmed up to <Time> <%, Range or by QC>	
Freeze and thaw stability (Observed change %)	<-Temperature °C, # cycles, > <Range or by QC>	
Dilution integrity	Concentration diluted <X-fold> Accuracy <%> Precision <%>	
Partial validation[3] Location(s)	<Describe shortly the reason of revalidation(s)> <vol/page, link>	
Cross validation(s) [3] Location(s)	<Describe shortly the reason of cross-validations> <vol/page, link>	

[1]Might not be applicable for the given analytical method
[2] Report short term stability results if no long term stability on stock and working solution are available
[3] These rows are optional. Report any validation study which was completed after the initial validation study,
[4] n.v. = nominal value

Instruction

Many entries in Table 4.1 are applicable only for chromatographic and not ligand binding methods. Denote with NA if an entry is not relevant for the given assay. Fill out Table 4.1 for each relevant analyte.

Table 4.2 Storage period of study samples

Study ID[1] and analyte	Longest storage period
	<#> days at temperature < C° >
	<#> days at temperature < C° >

[1] Only pivotal trials

Table 4.3 Sample analysis of <Study ID>

Analyte	<Name>
Total numbers of collected samples	<#>
Total number of samples with valid results	<#>
Total number of reassayed samples[1,2]	<#>
Total number of analytical runs[1]	<#>
Total number of valid analytical runs[1]	<#>
Incurred sample reanalysis	
Number of samples	<#>
Percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays	<%>

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

Instructions

Fill out Table 4.3 for each relevant analyte.