3 July 2013
EMA/244111/2013
Compliance and Inspection

Guidance on triggers for inspections of bioequivalence trials

GCP Inspectors Working Group (GCP IWG) / Mutual Recognition & Decentralised Procedures - Human (CMDh)

Adopted by GCP Inspectors Working Group (GCP IWG)	24 February 2010
Adopted by Mutual Recognition & Decentralised Procedures - Human (CMDh)	16 March 2013
Date of coming into effect	01 May 2010
Revision: A disclaimer was included to say that the list of triggers mentioned in the document are not exhaustive.	April 2013
Adopted by the GCP Inspectors Working Group (GCP IWG)	23 April 2013
Adopted by Mutual Recognition & Decentralised Procedures - Human (CMDh)	24 April 2013
Adopted by Committee for Medicinal Products for Human Use (CHMP)	17 June 2013

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1. Introduction

The following checklist is designed to be used by assessors when reviewing bioequivalence studies. Missing documentation should first be solved through questions to the applicant. If triggers are identified after the completion of the checklist which have a major impact on the quality of the data and may result in a potential serious risk to public health, the assessor is advised to have further discussions with their GCP Inspectorate.

This document re-presents a non-exhaustive overview of issues which are taken into account during the assessment phase. Identification of other triggers not mentioned in this document is possible.

1.1. How to complete the checklist

Score each answer Yes, No or Not Known; (in case the answer to any other question is not applicable please enter N/A in the comment field) then provide an overall total and determine if the outcome of the review is low, medium or high risk. The overall profile of low, medium and high scores in each section (general check, data check, and specific check) should also be used to consider the need to seek input from the GCP Inspectorate.

1.2. What the scores mean

Following completion of the above checklist, where concerns appear to be high risk and many areas give rise to assessment concerns, this may warrant a triggered study-specific inspection.

Where the concerns appear to be medium to high risk and there are sufficient areas of assessment concern, advice should be sought from the GCP Inspectorate on whether an inspection is warranted.

Where concerns are low-medium risk and are only raised in isolated areas, alternative mechanisms of reassurance such as a discussion with Inspectors or enquiries to the MA applicant about routine system information for the concerned organisation may be beneficial to progression of the application.

In case there are identified triggers for inspection for a particular site or CRO, the assessor or GCP Inspectorate should first of all check if the site is included as part of the European programme for inspection of the CROs more often used in the conduct of BE trial submitted in MAA before deciding on the need for an inspection. If so, the assessor should liaise with their Inspectorate to verify if the concerns can be included in the scope of the inspection of such programme.

1.3. What do the asterisk means in some of the questions?

For those questions with an asterisk if the answer is yes the assessor should always discuss further with the Inspectorate.

1. General check:

Question	Answer	Score	Comment
1. Will the present application for the marketing authorisation be followed by other applications with the same study data in the EU MS?	☐ **Yes**	**1**	
	☐ **No**	**0**	
	☐ **Not known**	**1**	
2. Is this the first application for a specific group of generics?	☐ **Yes**	**1**	
	☐ **No**	**0**	
	☐ **Not known**	**1**	
3. Is there any information from other regulatory authorities or other sources related to the **applicant, sponsor, CRO** etc regarding known problems (e.g. business changes, bankruptcy) and/or GCP quality/adherence?	☐ **Yes**	**1**	If the answer is YES, what kind of information? Any negative information could be a trigger for a GCP inspection.
	☐ **No**	**0**	
	☐ **Not known**	**1**	
4. Is this an old BE trial i.e. performed more than 5 years ago?	☐ **Yes**	**1**	Before requesting an inspection on this ground it should be checked that the trial complies with current requirements and that the test IMP used in the trial is still representative of the product for which the application is made.
	☐ **No**	**0**	

5. Has this **BE trial** been previously inspected by MS/EU/EEA inspectors?	☐ **Yes**	**0 or1 (see comment)**	If the trial has been previously inspected by a EU/EEA authority no new inspection should be requested and the results of the initial inspection should be accepted, unless new information has become available or the scope of the inspection did not cover the whole trial (Directive 2001/20/EC, art. 15.1). In which case score this question as 1.
	☐ **No**	**1**	
	☐ **Not known**	**1**	
6. Have the **trial site(s)** (clinical, analytical) previously been inspected by inspectors of MS/EU/EEA? Was this inspection more than 3 years ago?	☐ **Yes**	**0**	
	☐ **No**	**1**	
	☐ **Not known**	**1**	
7. Were positive (compliant) results achieved regarding previous inspections of the BE study and/or trial site(s) (no critical and few major findings)?	☐ **Yes**	**0**	**BE study inspection**: If the answer is **NO**, the MAA should be immediately rejected, without any further assessment or inspection. **Trial Site(s) inspection**: Any critical or several major findings may be a trigger for a GCP inspection.
	☐ **No**	**1**	
	☐ **Not known**	**1**	
	☐ **N/A**	**0**	
8. Is/are there sites located outside Europe (third country, non-ICH country)?	☐ **Yes**	**1**	If the answer is **yes** and the site has never been inspected with a positive outcome then assessor should discuss with inspectorate.
	☐ **No**	**0**	

Total Score:	**Minimum 0, Maximum 8** ☐ **Low 0-3** ☐ **Medium 4-5** ☐ **High 6-8**	**Comments from the assessors on this section:**

2. Data check:

Question	Answer	Score	Comment
9. Is this a product with particular difficulties or is there any specific risk for patients if the product would be wrongly assessed as bioequivalent? E.g.: • challenging formulation (e.g. transdermal patches); • complex PK profile; • narrow therapeutic margin; • risk of lack of efficacy (e.g. antibiotics); • protectable population (children, elderly, subjects renal/hepatic impairment).	☐ **Yes**	**1**	
	☐ **No**	**0**	
10. Is there missing documentation (e.g. missing validation and/or analytical and/or clinical report(s), method SOP and other relevant SOPs, representative chromatograms)?	☐ **Yes**	**1**	Missing documentation should first be solved through questions to the applicant. This issue may only grow to be an inspection trigger once an answer has been submitted and doubts are raised on the new documentation submitted.
	☐ **No**	**0**	
11. Is the Protocol clear/well written and adhered to? • Are the priority of clinical assessments specified, are the procedures described in detail? • Are deviations listed and has the impact been assessed?	☐ **Yes**	**0**	
	☐ **No**	**1**	

12. Is the CRF design adequate to capture all required information? Is all necessary information included?	☐ **Yes**	**0**	
	☐ **No**	**1**	
13. Are there any obvious conflicts of interest for the key named staff?	☐ **Yes**	**1**	
	☐ **No**	**0**	
14. Are there any observations which raise concerns about the quality or validity of the reported study data in general? E.g.: • study data too clean / too messy; • the amount of missing values/drop outs not meet the reviewer's expectation for the active substance or the type of measurement; • implausibility/inconsistency of clinical or analytical data provided; • conflicting results between studies regarding pharmacokinetic parameters or overall/intra-subject variability; • data/results in contradiction to published and known data (e.g. distribution and/or characteristics of volunteers) on this product/active substance;	☐ **Yes**	**1**	Score this section according to the extent of the issues identified; for example a lot of missing/inconsistent data score **Yes** (1), however, if the pattern of errors or omissions is no greater than expected for a study of this nature, score **No** (0).
	☐ **No**	**0**	

15. Are there any observations which raise concerns whether the BE trial was conducted in compliance with ICH-GCP or legislative requirements?	☐ **Yes**	**1**	Any critical or several major findings may be a trigger for a GCP inspection.
	☐ **No**	**0**	
Total Score:	**Minimum 0, Maximum 7** ☐ **Low 0-2** ☐ **Medium 3-4** ☐ **High 5-7**		**Comments from the assessors on this section:**

3. Specific check:

Score this section according to the extent of the issues identified; for example a lot of missing or inconsistent data score **Yes** (1), however, if the pattern of errors or omissions is no greater than expected for a study of this nature, score **No** (0).

Question	Answer	Score	Comment
16. Are there any observations which raise concerns about the quality or validity of the **subject-related data** ? E.g.: • inclusion and exclusion criteria not adhered to; • dosing schedules and visits not adhered to; • adverse event frequencies and severities (profiles) not consistent with the known profile for the product;	☐ **Yes**	**1**	
	☐ **No**	**0**	
17. Are there any observations which raise concerns about the quality or validity of the **product-related data**? E.g.: • deviations from dosing regimens are not described adequately, dietary and exercise restrictions are not adhered to (where applicable).	☐ **Yes**	**1**	
	☐ **No**	**0**	

18. Are there any observations which raise concerns about the quality or validity of the **sampling process or study sample analyses**? E.g.: • inconsistencies between the numbers of samples collected, analysed and reported; • insufficient information to confirm the integrity of the samples (e.g. regarding storage, shipment and stability); • management of repeat sample analyses and missing samples is not described adequately; • timing for taking the samples; • large number of samples re-assay; • re-injection of QC or calibrators; • samples not injected at constant intervals; • re-analysis of samples for PK reasons; • indications of inappropriate manual re-integration of chromatograms.	☐ **Yes**	**1**	
	☐ **No**	**0**	
19. Are there any observations which raise concerns about the quality or validity of the **Analytical method validation**? E.g.: • bioanalytical method has not been fully validated before study sample analyses;	☐ **Yes**	**1**	Concerning QC samples excluded from statistical analysis in the first instance re-calculate with all results (or ask the applicant for it), rather than ask for an inspection.
	☐ **No**	**0**	

• the method validation data and the acceptance criteria are inadequate; • the data presented are inconsistent with the described and planned methodologies (for example retention times, chromatogram identifiers, run sequence/order); • QC samples excluded from statistical analysis.			
20. Are there any observations which raise concerns about the quality or validity of the **statistical analysis**? E.g.: • a separate report governing PK and statistical analysis has not been presented. Output files have not been included; • the software used for the PK and statistical analysis is inappropriate (not well known, not from a commercial source); • summaries presented in the text do not match the tabulated summaries and individual data.	☐ **Yes** ☐ **No**	**1** **0**	
Total Score:	**Minimum 0, Maximum 5** ☐ **Low 0-1** ☐ **Medium 2-3** ☐ **High 4-5**		**Comments from the assessors on this section:**

4. Summary:

Total Score – Section 1 General check :	Total Score – Section 2 Data check :	Total Score – Section 3 Specific check :
Minimum 0, Maximum 8 ☐ **Low 0-3** ☐ **Medium 4-5** ☐ **High 6-8**	**Minimum 0, Maximum 7** ☐ **Low 0-2** ☐ **Medium 3-4** ☐ **High 5-7**	**Minimum 0, Maximum 5** ☐ **Low 0-1** ☐ **Medium 2-3** ☐ **High 4-5**

FINAL COMMENTS FROM THE ASSESSORS: