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Committees and Inspections

Guidance on triggers for inspections of bioequivalence trials: Quick scan

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

Adopted by Co-ordination Group for Mutual Recognition & Decentralised Procedures – Human (CMDh)	November 2016
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This guidance replaces EMA/244111/2013 "Guidance on triggers for inspections of bioequivalence trials".

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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 potentially have an impact on the quality of the data, the assessor is advised in the first instance to have a discussion with their good clinical practice (GCP) inspectorate.

This document represents 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. This list is to be considered a quick scan. The topics listed in this document are intended to assist the assessor in deciding on whether to consult or to seek input from their GCP inspectorate on the need for a GCP inspection and on the best way forward.

Where concerns appear, this may warrant a triggered study-specific or even a systems inspection. Multiple triggers may be identified; however, even one trigger may be sufficient reason for a GCP inspection.

Where concerns are low-medium risk and are only raised in isolated areas, alternative mechanisms of reassurance such as a discussion with GCP 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 of an old bioequivalence trial, i.e. performed more than 5 years ago, before requesting an inspection it should be checked that the trial complies with current requirements.

In case there are identified triggers for inspection for a particular site or CRO, the assessor or GCP inspectorate should check if the site is included as part of the European programme for inspection of the CROs more often used in the conduct of bioequivalence (BE) trial submitted in marketing authorisation applications (MAAs) 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 planned inspection.

1. General check		
Question	**General considerations**	**Specific assessor's comment**
1. Has this **BE trial** been previously inspected by EU/EEA inspectors?	If the trial has been previously inspected by an EU/EEA authority with a positive outcome 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 (Article 15.1 of Directive 2001/20/EC). In case the trial has been previously inspected with a negative outcome, this should in principle result in rejection of the application.	
2. Have the **trial site(s)** (clinical, analytical) previously been inspected by inspectors of EU/EEA?	If the trial site has been inspected by an EU/EEA authority with a positive outcome (no critical and few major findings) within the last 3 years, no new inspection should be requested and the results of the initial inspection should be accepted, unless new information has become available, triggers in the actual trial are identified, or the scope of the previous inspection did not cover the whole trial (Article 15.1 of Directive 2001/20/EC) In case the trial site has been previously inspected with a negative outcome, the consequences of that inspection for acceptability of the current study or the need for a GCP inspection should be discussed with the inspectorate. For this purpose, the critical period	

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	for which the site inspection is relevant, as determined by CMDh or CHMP, should be checked. In case the trial site has never been inspected by an EU/EEA authority, the consequences for acceptability of the current study or the need for a GCP inspection should be discussed with the inspectorate. Of note, at CMDh it has been agreed that solely the fact that no inspection has been conducted is not a trigger for inspection. However, on the absence of triggers, the CRO involved may be put on the list for routine inspection via the CMDh/IWP.	
3. Was this inspection more than 3 years ago?	This issue should be discussed with the inspectorate in relationship with other potential triggers that are identified. Solely the fact that an inspection was conducted more than 3 years ago is not a trigger for inspection.	

2. Data check		
Question	**General considerations**	**Specific assessor's comment**
4. Does this product present specific characteristics? E.g.: • challenging formulation (e.g. transdermal patches); • complex PK profile.	In this case the individual PK results should be thoroughly evaluated, e.g. with respect to deviating individual concentrations, timing of pharmacokinetic analysis, reported plasma concentrations at the start and end of the analysis period etc.	
5. Does the answer that has been submitted regarding missing information (e.g. missing validation and/or analytical and/or clinical report(s), method SOP and other relevant SOPs, representative chromatograms) cast doubts on the compliance with current requirements and guidelines?	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.	
6. 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; • data/results in contradiction to published and known data (e.g. distribution and/or characteristics of volunteers) on this product/active substance; • conflicting results between studies regarding	Although response to these questions may not always be easily found, the issues raised should be taken seriously. Issues should generally be judged based on proper knowledge on bioequivalence testing methodologies. In case it is known, the conduct and outcome of the study may be compared with previous studies in order to check for potential issues.	

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pharmacokinetic parameters or overall/intra-subject variability; • presence of another BE study conducted shortly before or after the presented BE study. This study can either be a positive or failed one.		

3. Specific check		
Question	**General considerations**	**Specific assessor's comment**
7. 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; • adverse event frequencies and severities (profiles) not consistent with the known profile for the product; • deviations from dosing regimens are not described adequately, dietary and exercise restrictions are not adhered to (where applicable).		
8. 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 repeated 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;	Although a number of the issues raised may be resolved by requesting additional information, in case the issues result in an overall perception of poor compliance with current requirements this should be discussed with the inspectorate.	

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• re-analysis of samples for PK reasons; • indications of inappropriate manual re-integration of chromatograms.		
9. 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; • 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.	In case QC are samples excluded from statistical analysis in the first instance, recalculate with all results (or ask the applicant for it), rather than ask for an inspection.	
10. 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.	Although a number of the issues raised may be resolved by requesting additional information, in case the issues result in an overall perception of poor compliance with current requirements this should be discussed with the inspectorate.	

FINAL COMMENTS FROM THE ASSESSORS: