EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 February 2012
EMA/INS/GCP/219642/2011
GCP Inspectors Working Group

Overview of comments received on 'Reflection paper on Guidance for laboratories that perform the analysis or evaluation of clinical samples – Draft ' (INS/GCP/532137/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA
2	AESGP
3	BQSI
4	CIMT and CIC-CRI
5	EBF
6	EQAC
7	Pfizer Inc
8	F. Hoffmann-La Roche Ltd
9	Gedeon Richter Plc.
10	Greatspur Clinical Development Ltd
11	HEXAL AG & LEK Pharmaceuticals d.d.
12	Eli Lilly & Company
13	Sanofi Pasteur
14	Servier
15	Thérèse Dupin-Spriet, consultant in clinical Pharmacology
16	H. Lundbeck A/S

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	This Reflection Paper is welcomed and overall supported. A few issues are highlighted and changes are proposed under specific comments below.	
2	It is not clear whether the document applies to clinical laboratories only (clinical laboratory is one of the key words), or whether bioanalytical laboratories analysing pharmacokinetic samples are also subjected to this document. Reference to pharmacokinetic samples is made in a few cases; however the focus seems to be on clinical laboratories and the definition of roles and responsibilities between a clinical laboratory and the sponsor. Bioanalytical laboratories are often part of the sponsor organisation, and therefore some of the sections would only apply in case the bioanalytical (pharmacokinetic) phase of a clinical trial is placed with an external bioanalytical laboratory. It is acknowledged that the fundamental GCP principles also apply to a bioanalytical laboratory. However tasks/procedures vary from a clinical lab, and therefore the focus of the reflection should be clear.	
3	The BQSI Expert Working committee is a group of professionals working in the Pharmaceutical Industry (Pioneer, Generic and Contract) whose work focuses on Bioanalytical support for clinical trials (Scientists, Quality and Regulatory, Program Managers and Test Facility Management). The group, established in February 2008, has actively worked to bring attention to the need for a global quality standard addressing the current regulatory gap, one that both regulatory agencies and industry agree benefit the public through	

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	timely review and approval of safe and effective drugs. In September 2009, the BQSI submitted a draft guidance document, entitled Quality Management System for BioAnalysis Supporting Clinical Trials, version 4 to the US FDA (Division of Dockets Management – Docket No. FDA-2009-D-0428) for consideration. During the same time frame, the MHRA issued the guideline for analysis or evaluation of clinical trial samples, which the subject document closely reflects. In discussions with the contribution authors of the MHRA document, it is clear that the focus of the guideline is to enhance the existing GLP regulations with increased attention to patient or trial subject safety; a very important and necessary improvement. However, the subject document does not include the necessary measures to ensure data accuracy and study integrity, which is the focus of the BQSI. Since the initial submission of the guidance document, the BQSI continues to receive endorsement from the leading North American BioPharmaceutical, Pharmaceutical and Generic Pharmaceutical companies who sponsor the studies, as well as the leading North American Contract Research Organizations who perform the bioanalytical work in support of the studies. I recommend that the GCP Inspectors Working Group review the content of the BQSI guidance document and give serious consideration to developing a globally harmonized document that includes the key elements ensuring data accuracy and study integrity that are addressed in the BQSI guidance document as well as the critical elements for protecting patient and trial subject safety that	

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	are included in the subject document. The BQSI guidance document may be viewed on the US FDA web site; www.regulations.gov, using the docket number provided above, or you may obtain a copy directly from the BQSI Expert Working committee chair. Submitted on behalf of the BQSI Expert Working Committee J. Kirk Smith, Ph.D., Committee Chair	
4	CIMT and CIC-CRI share the common goal of promoting safe and effective cancer immunotherapy (see information on the authors at the end of document). Cancer immunotherapy is a dynamic research area with clinical trials typically including many different types of laboratory evaluations. CIMT and CIC-CRI are both non-profit organizations and have an internationally leading role in establishing harmonization and standardization of novel immune monitoring assays with 41 and 36 laboratories participating in proficiency panels organized by CIMT and CIC-CRI, respectively. The CIMT Immunoguiding program (CIP) and the CIMT Regulatory Research Party (RRG) as well as CIC-CRI have discussed the EMA reflection paper on guidance for clinical laboratories and wish to comment it. CIMT and CIC-CRI acknowledge the high quality and excellent structure of the reflection paper and consider the document as a valuable guidance for all laboratories that perform the analysis or evaluation of clinical trial samples. This particularly relates to:	

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	• The completeness and high level of detail that allows clinical laboratories to use the future guideline, which will be based on this reflection paper as a helpful resource/checklist • Arrangements to ensure timely patient safety-related assessments • Mechanisms to ensure adherence of the performed laboratory work to the clinical study protocol and patient informed consent • Rules for data recording, handling, reporting and archiving However, CIMT and CIC-CRI also believe that several aspects of the guidance require further differentiation depending on the type of and consequences resulting from the performed assays as well as the stage of clinical development. Analyses of samples of clinical trials can relate to a broad range of purposes, such as forming the basis for (A) decision of clinical interventions, (B) patient safety, (C) surrogate for efficacy in a pivotal trial, (D) hypothesis validation as part of mechanism-of-action study endpoints or (E) exploratory analyses for hypothesis generation. A reporting of results will have very different consequences depending on the nature of the analysis. A non-differentiated (general) requirement irrespective of the development stage to always comply to all aspects stated in chapter 6.1 for all the laboratories performing analytical assays on patient specimens would have a potential to stifle clinical research and may	

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	even inhibit innovation. As a consequence, the development of new, potentially safe and efficient treatments could be unnecessary complicated, or worse, prematurely aborted. Hypothesis generation by the monitoring of samples in early, more research-driven phases of clinical development (typically phase I and phase IIa studies) should remain more flexible as the identification of novel relevant biomarkers (among many biomarker candidates) is an important dynamic research process where innovative monitoring techniques or assays may be hindered by a too high level of standardization and validation. Once a biomarker candidate has been identified and becomes a primary confirmatory study endpoint, a high degree of standardization and validation is certainly required.. In addition, flexibility in early phase biomarker discovery might lead to the development of crucial tools to identify groups of patients that will have less side effects or higher efficacy of new drug entities and therefore contribute to higher benefits for patients. It should be noted that flexibility for hypothesis generating analysis must not in any case infringe patient safety or patient rights. Overall, this indicates that a “context-specific regulation” may be necessary for distinct types of analyses performed for distinct purposes at distinct stages in the process of clinical development. Consequently, we suggest that the scope of the reflection paper differentiates among several categories of analyses (a given analysis can belong to several categories). Proposed Categories of Analyses	

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	A) Treatment-Affecting Analyses Evaluation of samples that can trigger immediate decisions / interventions for a patient in a clinical trial (such as inclusion or exclusion criteria), e.g. measuring the HLA type of a patient to determine whether a HLA-restricted peptide vaccine can be applied or not. B) Safety-Assessing Analyses Evaluation of samples relevant for the assessment of the safety of the drug, e.g. measurement of typical safety blood parameters during all phases of clinical development. C) Late Stage Surrogate Endpoint Analyses Evaluations of samples relevant for confirmatory (hypothesis-validating) study endpoints as primary endpoint of a late-stage trial (when used as surrogate for clinical efficacy of the drug). An example would be to choose a certain predefined level of antibody response to a prophylactic influenza vaccine as a confirmatory primary endpoint. D) Confirmatory Analyses Evaluations of samples relevant for confirmatory (hypothesis-validating) study endpoints (same example as for C, but as secondary endpoint or in early phases of clinical development). Often, these will be putative surrogate endpoints to show mechanistic activity of the drug. An example would be an immune response comparison according to a predefined threshold in a multi-arm Phase I or Phase IIa trial that compares different immunomodulators.	

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	E) Exploratory Analyses Evaluation of samples relevant for exploratory (hypothesis-generating) study endpoints, e.g. description of quantitative and qualitative aspects of immune responses to a vaccine in early-stage clinical research, typically without prior experience with regard to the immunogenicity of a novel immunotherapy, with the aim to identify parameters that may explain the mechanism-of-action of the novel therapy and setup first hypotheses to be validated in succeeding trials. References Britten CM, Janetzki S, Ben-Porat L, Clay TM, Kalos M, Maecker H, Odunsi K, Pride M, Old L, Hoos A, Romero P, HLA-peptide Multimer Proficiency Panel of the CVC-CRI Immune Assay Working Group. Harmonization guidelines for HLA-peptide multimer assays derived from results of a large scale international proficiency panel of the Cancer Vaccine Consortium. Cancer Immunol Immunother 2009 Oct;58(10):1701-13. Britten CM, Janetzki S, van der Burg SH, Gouttefangeas C, Hoos A. Toward the harmonization of immune monitoring in clinical trials: quo vadis? Cancer Immunol Immunother. 2008 Mar;57(3):285-8. van der Burg SH. Therapeutic vaccines in cancer: moving from immunomonitoring to immunoguiding. Expert Rev Vaccines. 2008 Feb;7(1):1-5. Lee JW, Devanarayan V, Barrett YC, Weiner R, Allinson J, Fountain S,	

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	Keller S, Weinryb I, Green M, Duan L, Rogers JA, Millham R, O'Brien PJ, Sailstad J, Khan M, Ray C, Wagner JA. Fit-for-purpose method development and validation for successful biomarker measurement. Pharm Res. 2006 Feb;23(2):312-28. Mander A, Chowdhury F, Low L, Ottensmeier CH. Fit for purpose? A case study: validation of immunological endpoint assays for the detection of cellular and humoral responses to anti-tumour DNA fusion vaccines. Cancer Immunol Immunother. 2009 May;58(5):789-800. Hoos A, Eggermont AM, Janetzki S, Hodi FS, Ibrahim R, Anderson A, Humphrey R, Blumenstein B, Old L, Wolchok J. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010 Sep 22;102(18):1388-97.	
5	EBF acknowledges and supports that EMA is preparing a document on how samples from clinical trials should be analysed and, data and information should be processed and secured. EBF as well acknowledges that EMA designed the document to complement existing quality systems such as GLP, CLIA, ISO 17025, etc in order to avoid duplication of efforts for both, laboratories as well as auditors. EBF also acknowledges that GLP is not well accommodated to take into account all aspects of patient/volunteers safety, integrity and privacy. EBF members raised in their comments the point that they got the impression that the concept paper is written under the assumption that all work is done in CROs or third party facilities rather than in sponsor's labs. We suggest that the current concept paper should be revised to reflect both scenarios, in-house as well as contracted out analysis/evaluation.	

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	EBF is seeking clarity on the scope of the current reflection paper namely if the intention is to apply the guideline to all types of labs (Bioanalytical, clinical, academic) and all types of work (PK sample analysis, Clinical chemistry, PD marker, Genotype, gene expression analysis, Metabolite profiling, 14C ADME/mass balance studies). EBF is asking for clarity whether the document is supposed to be a reflection paper as mentioned in the title or is rather supposed to be a guidance document as stated in line 45 of the executive summary.	
6	1. It is noted that the reflection paper is mostly based on the UK MHRA guidance document issued July 2009. However both documents are extremely prescriptive on the requirements of a quality system on the clinical lab. The level of guidance far outweighs any regulatory guidance for other aspects of GCP or the implementation of GLP systems within a laboratory. The guidance leaves no scope for a laboratory to implement a quality system that best meets the needs of its business, scope of work within the realms of GCP compliance. Although this is a guidance document, experience will tell us that laboratories will be inspected against this guidance by national Monitoring Authorities. 2. Rather than having two standards for GLP and GCP the guidance would be better reflecting the applicable GLP principles for the general systems within a laboratory and only including the specific requirements for the conduct of the clinical study such as patient safety, informed consent, confidentiality and blinding/unblinding requirements.	
7	Does the “scope” take into account other EU regulations such as in Human Tissue?	

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8	We thank EMA for providing instructions and proposed regulations on the handling of samples collected during clinical studies. We have these general comments on the reflection paper: • Document appears to be constructed from a collection of statements from other documents, regulations and guidances leading to some issues with general flow and instruction. Some sections include specific examples others do not. • Unclear throughout document who is being referred to under the title “investigator” – is this the laboratory investigator performing the analysis or the clinical investigator(s) conducting the clinical trial. • Protocol is used throughout the document although it sometimes applies to an assay and other times to a clinical study. We suggest that it be specific when mentioning protocol since the clinical study protocol describes procedures administered to study participants NOT so much of how samples are to be analyzed • The document is written with the assumption that all clinical trial sample analysis will be outsourced. Clarification as to which elements of the guidance do not apply (aside from contracts etc) when the analysis is performed by the Sponsor would be helpful. • The guidance document has a lot of operational details which may be unnecessary in this type of document. We would like to propose that this type of detail be removed and minimum and regulatory requirements be noted only.	
9	This guideline is tailored to CROs involved in the analysis of clinical trial samples. However, many GLP laboratories of the pharmaceutical industry perform bioanalysis of clinical trial samples as well as preclinical trial samples. Those labs are compliant with principles of GLP and regularly inspected by the	

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	national authorities. Regarding that "this guidance is designed to complement existing quality systems, what should be the status of those labs in the future - remaining a GLP laboratory? or becoming a GLP/GCP laboratory? -, and which guidance(s) on quality assurance should be referenced when conducting clinical analysis?	
10	The document is targeted as guidance to "laboratories and other facilities" performing laboratory testing and analysis for clinical trials. This implies all such facilities. However, the guidance appears to be written predominantly with dedicated service providers in mind (e.g. commercial testing facilities). Clinical trials frequently use local hospital laboratory services for sample testing, sometimes in addition to central laboratory services, sometimes exclusively. The required testing can vary from supportive safety checks before proceeding with dosing (e.g. oncology studies) to efficacy, endpoint or safety sample testing. It is also not clear whether the guidance applies in the setting of academic clinical trials conducted in hospital and university settings. It needs to be made clear whether this guidance is intended to cover such laboratories and if so, the wording needs to be clarified to allow for the heath service and institutional infrastructures that support these laboratories. The subsequent comments relate to this perspective.	
14	Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples has been issued by the MHRA on 1 July 2009 and is used by several laboratories already. We would like to propose to reference also this guidance in the present document. If we do agree that such a high standard of quality should be applied to centralised laboratories in the framework of Clinical Studies, we would like to indicate how the implementation and the maintenance	

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	of such rules in general practice of small laboratories seem difficult to arrange. Moreover, a lot of requests in this reflection paper goes further than those of ICH E6 and a lot of them are normally under the responsibility of the sponsor. Perhaps, the operating processes to be applied should be considered taking into account the kind of laboratory considered.	
15	To prevent ambiguities, and difficulties to guarantee the patients' security	

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 44-50 and 65-71	2	In the context of a clinical trial, various types of samples can be generated for different purposes, e.g. safety samples/clinical chemistry samples, pharmacokinetic samples, biomarker samples, pharmacogenomic samples, metabolite profiling, 14C mass balance etc. It is acknowledged that these experiments should be covered by the clinical trial protocol as well as the informed consent. However, since some of these samples will be analysed in bioanalytical laboratories subjected to GLP/GCP or clinical laboratories certified by CLIA etc. but other samples may be analysed by research labs such as universities, the extent of quality system expected should be defined.	The point is adopted in part. The scope of the document will be amended to make a clear distinction between the different types of clinical analysis that are performed as part of a clinical trial. In all cases the nature and purpose of the analysis must be taken into account when deciding how the information in the reflection paper should be used. The quality system needed to underpin work that is linked to the primary end points of the trial may need to be more rigorous that work which is used to gather information for research purposes.
61	15	Comment:False, a french guide exists since 1994 named “Guide de bonne execution des analyses de biologie médicale” arrêté du 26 novembre 1999 (JO France 11 december 1999) modifié par arrêté du 26 avril 2002 (JO France 4 may 2002). Chapter IV A for analysis of clinical trials samples (« cas particuliers des examens de laboratoire destinés aux recherches biomédicales » Proposed change (if any):To date ~~no~~ few detailed	Point adopted: Other European guidance will not be referenced. However, the sentence “to date no detailed guidance has been produced…” will be removed.

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		guidances has been produced which outlines the expectation of national monitoring authorities or evaluation of samples collect as part of clinical trial. In the absence of european guidance…	
61-64	14	*Comment:* The MHRA issued a document in July 2009. We would like to suggest to reference it in the present document. Proposed change (if any): to be implemented in the seventh section of the document.	Rejected – We will not reference any national guidance documents. An additional reading list may be included at the end of the document.
61-64	5	Comment: In the UK MHRA document in place (Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples.) Proposed change (if any):	Rejected – We will not reference any national guidance documents. An additional reading list may be included at the end of the document.
Lines 61-62	1	Comment: Currently, there are two additional GCLP guidance's produced by local or global health regulatory bodies or authorities (MHRA: 2009 & WHO: 2009). Proposed change (if any): " ~~To date~~ **With the exception of the document entitled ' guidance on the maintenance of regulatory compliance in laboratories that**	Rejected – We will not reference any national guidance documents. An additional reading list may be included at the end of the document.

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		perform the analysis or evaluation of clinical trial samples' published by the MHRA on 1st July 2009, *no detailed guidance has been produced which outlines the expectations of national monitoring authorities with respect to the analysis or evaluation of samples collect as part of a clinical trial".*	
Line 62	1	Comment: "Collect" should read "collected" Proposed change (if any): "…*with respect to the analysis or evaluation of samples* ~~collect~~ **collected** *as part of a clinical trial."*	Accepted
62	8	Comment: typo, change collect to collected Proposed change (if any): change "**collect**" to "**collected**"	Accepted
62-64	8	"…apply the principles of good laboratory practice when conducting clinical analysis." As long as work is not claimed to run "under GLP" there is no problem with that procedure.	Rejected - GLP does not cover a number of important issues that need to be considered when performing clinical analysis. The text has been amended to emphasis this point.
64	8	Comment: conducting clinical *sample* analysis Proposed change (if any): include the word **"sample"** as noted above	Accepted – changes have been made to the text.
Lines 62-64	1	Comment:	Accepted – the necessary changes will be made to this section

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		The Principles of Good Laboratory Practice are applicable to non clinical safety and non clinical health and environmental studies and are not meant to cover clinical trial sample analysis. It would be useful to provide this clarification in the reflection paper to avoid any misunderstanding. Proposed change (if any): "*In the absence of guidance, some laboratories apply the principles of good laboratory practice when conducting clinical analysis* **although such standards are exclusively applicable to non-clinical health and environmental safety studies required by regulations"**	of the document to emphasis this point.
66	11	Comment: It should be clarified if the reflection paper refers to laboratories used for EU submissions (e.g. laboratory work in Canada) or only to laboratories working in EU.	Accepted - The standards outlined in the paper should apply to any laboratory analysis that will be submitted to EU receiving authorities when ever it is performed section 3 will be amended to reflect this point.
66-70	12	Comment: We suggest that laboratories supporting trial endpoints be treated separately from those that are performing local analyses for the purpose of immediate monitoring of subject status, even where such monitoring is specified by the protocol. Indeed, for some oncology trials, although trial endpoint analysis is conducted by	Accepted - This point is accepted and will be addressed in changes made to section 3

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		a Central laboratory some parameters might also be analysed locally for immediate patient management. These local laboratories are often by necessity part of the hospital or institution, comply with the local healthcare system's requirements for clinical diagnosis but are unlikely to comply with all of the very specific requirements of this document, in particular due to limited resources. In addition, for such local facilities, multiple roles listed in this paper may be performed by one individual, possibly leading to "conflict of interest" within a role. If such facilities have to be included in the scope, the reflection paper should then clarify whether it is expected that sponsors will implement formal assessment/audit programmes to assure themselves of compliance with this guidance. Proposed change (if any):	
Lines 67-70	9	Comment: Please clarify. Could this mean that GLP inspectors of the national authorities may audit bioanalysis phase of a clinical study if it is performed in a GLP compliant Laboratory according to a separate "analytical protocol"? Proposed change (if any):	Acknowledged - This will vary from country to country but it is possible that GLP inspectors will perform audits of clinical analysis if they are performed in a facility that conducts GLP studies. This decision will be left to national monitoring authorities (no change required).
67	8	this would apply to all sort of analysis; also to	Yes the document would apply to biomarker analysis. (no

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		biomarker assays.	change required)
Line 71	6	Comment: It is noted that in the "scope" section where it says that it is for interventional trials only. Our question was whether the EU guidance should be in line with other EU Directives so that it was relevant for any trials involving human tissue and not limited to interventional trials. Proposed change (if any):	Rejected – The document only aimed at interventional trials.
71	8	"non-interventional trial" not defined	Accepted - Will include a definition
72-78	11	Comment: In document is stated clearly that it is a reflection paper of the GCP Inspection Working Group that performs also GCP laboratory inspections. It is clearly stated that its intend is to cover the conduct of analysis or evaluation of samples collected as part of a human clinical trial conduct. In laboratories where only samples from human clinical trials are analysed is not mandatory to follow i.e. GLP principals, is that correct?	The expressed assumption is correct. No change need.
73	8	Comment: "reference to guidelines on guidelines" is confusing.	Accepted - This reference needs to be included. Inclusion of a reference number.
Line 79	9	Comment: How to reconcile the terminology	Accepted - All definitions will be reviewed. Currently most of

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		differences between GLP and GCP in a lab which performs both clinical and preclinical trial sample analysis? E.g. would it be possible to use the terminology “raw data” instead of “source data” or different wording is necessary according to the type of study? Proposed change (if any):	these are taken directly from ICH GCP guidelines. The review will determine it is approriate to amend the definitions in the paper so that they are also consistent with GLP definitions, given that a large number of labs that perform clinical analysis are also performing pre-clinical work.
79-80	5	Comment: Proposed change (if any): please correct typo Archivist” to “Archivist” and care should be taken for GCP specific terms, please add and define the following terms if they are applicable: Bioanalyst; Scientist; Investigator; Coordinating Investigator; SOP; manager and lab manager; Sample; draft or interim data; Clinical Laboratory; Analytical laboratory; Laboratory; source documents	Acknowledged - Some of these definitions are already covered in section 5. However, a review of the document will be performed to ensure that all key words are defined. It should be noted that it will not be possible to define every term.
81	13	Comment: Replace "kit" to avoid confusion with clinical test kits. Proposed Change (if any): “Clinical test Kit” means…	Rejected – clinical kit in the context of a clinical trial is an accepted term.
81-82	5	Comment:	Rejected - evaluation covers comment.

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		Proposed change (if any): typo: analysis or evaluation or comment to line 65-70	
83-87	5	Comment: Proposed change (if any): please replace the term manipulaton by handling or another appropriate wording (manipulation has a negtive meaning with respect to data integrity and quality)	Accepted - The word manipulation will be removed or replaced.
88	15	Comment: incomplete Proposed change (if any):"Clinical trial samples" means any biological sample-collected from a participant of a clinical trial as required by the protocol (including samples collected for the trial but not conform to protocol statement) or required by the follow_up of adverse event.	Rejected - Samples collected as a result of an adverse event are not covered by this document. This is part of routine patient subject care.
97	8	Proposed change (if any): suggest changing the word "**manipulation**" to "**handling**"	Accepted - The word manipulation will be removed or replaced.
97-100	5	Comment: Proposed change (if any): please replace the term manipulaton by handling or another appropriate wording (manipulation has a negtive meaning with respect to data integrity and quality)	Accepted - The word manipulation will be removed or replaced.

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104-107	5	Comment: Proposed change (if any): Line 105: Replace “underpin” with “support,” or a similar word.”	Accepted – the word will be changed.
117	15	Comment:Incomplete Proposed change (if any):”Source data” means, all information in original records and certified copies of original records of clinical findings, observation, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial (including results of QC samples). Comment: Incomplete, to add a definition of reference value or reference interval. There are several methods whose value is not the same. One may be recommanded See: 1 IFCC-CLSI - Determining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition CLSI Document C28-A3,Wayne, PA, 2008 2 Spriet A, Dupin-Spriet T. Good practice of clinical drug trials. Third edition. Basle:Karger 2004 : **p166** Proposed change (if any):There are several 1 A reference interval is established by collecting samples from a sufficient number of qualified reference individuals to yield a minimum of 120 samples for	Rejected - The definitions have to be broard. This suggestion would add unnecessary detail.

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		analysis, by nonparametric means, for each partition (eg, sex, age range); 2 Either periodic determination of a range values obtained on a group of normal subjects (students, laboratory staff or other volunteers); 3 Determination from certain selected sick patients, excluding laboratory parameters altered by the disease; 4 Limits of usual values determined in sick patients without screening : for example, all tests run during a certain time period by a laboratory, or quintiles from 2.5% to 97.5% of these tests.	
122-124, 128-130	8	Comment: Assume that these lines are only intended for when sample analysis is contracted out to a CRO and does not apply when the work is conducted by the Sponsor itself. Also, need a period at the end of line 124.	Rejected - This is not a correct assumption. Often sponsor laboratories will use work instructions etc. Lines 128-130 apply to CRO's and sponsors a like. Accepted - Full stop will be included.
127,156, 177, 258, 312, 373, 406, 420, 487, 557, 562	4	2.2 Recommendations referring to the organizational details of the laboratory work (including SOPs, equipment, training, contracts, logistics, QA and QC) This relates to document chapters 6.1.1., 6.1.2., 6.1.3., 6.1.6., 6.1.9., 6.1.11., 6.1.14., 6.1.15., 6.1.17., 6.1.18., 6.1.19. To facilitate differentiation between distinct categories of analysis, it could be considered to include an additional chapter at the end	Acknowleged - This comment suggests there should be different standards or requirments depending on the nature of the clinical analytical work that is being performed. It is accepted that clinical anlysis takes many different forms and that the guidance in this document may not apply in its entirety to all types of clinical analysis. This will be covered in the revised scope section but not in the level of detail requested here.

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		of the guidance that describes context-specific regulation. We fully agree that these organizational regulations listed here are mandatory to prevent the generation of missing or incorrect data in situations where patient safety, a clinical decision potentially affecting patient health or the primary outcome of a late-stage study may be affected (categories A-C). For other laboratory assessments (categories D-E), we suggest a gradient of organizational requirements, as such requirements pose a substantial burden on early-stage clinical research. Category E: We suggest that exploratory work to generate hypotheses (category E) should require as a minimum a description of the appropriateness of the facilities (6.1.14.) and CVs and other documentation demonstrating the appropriate expertise and sufficient level of training of the key personnel. Procedures, logistics and equipment used for the study should be documented in a descriptive way. Written agreements (but not necessarily fully legally binding contracts at this stage) should be made to define the scope and type of the performed assays and to ensure that	

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		collaborators adhere to the study protocol and that patients' rights are fully considered. At this early stage of development, it may be sufficient to use assays that have undergone • a certain level of standardization, i.e. the use of protocols or SOPs for assay performance and analysis, auditing of all final results and use of only well trained personnel (per lab SOP) and • ideally (but not mandatory) participation within internal or external quality assurance programs (e.g. proficiency panels) which provide data-based evidence about robustness and overall performance of the analytical assays in the hand of the respective investigator as compared to the community and create a large awareness how important such qualification measures are. • Ensuring full quality assurance including regular audits (as for categories A-D) should not be required at this stage. However, processes and methods used should be scientifically sound and it should be ensured that they are principally suitable for the chosen purpose. Category D: We agree that confirmatory studies (category D) should have additional regulations in place to ensure	

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		robustness. In addition to standards for exploratory studies, this would require standardized logistics (6.1.9.), rules for repeat analysis (6.1.11.), maintenance of equipment (6.1.15.), documented staff training (6.1.2.), local QA processes (6.1.17.) and quality control checks (6.1.18.). Key activities related to the laboratory processes should be covered by SOPs (6.1.19.).	
128 vs 243-245	8	not clear if work instruction (= bioanalytical protocol/study plan) is mandatory or not. Line 128 leaves it open, 243-245 demands it. In particular, while outsourced work is normally performed after the CRO representative prepares a protocol that is approved by the sponsor, in case of experimental activities performed in-house does the Agency	Rejected - Lines 243-245 just refer to "documented procedures".
130	15	Comment:Incomplete Proposed change (if any):(To add) An organisation chart would be documented.	Rejected – This requirement is too prescriptive. The reflection paper is designed to allow a level of flexibility in the way laboratories organise their quality systems.
133	15	Comment: consistency with lignes 142, 158, 160, 161… Proposed change (if any):Laboratory management should ensure that each individual involved in the analysis" or evaluation "of clinical trial samples …	Regected – no need to change, meaning is clear.
134	8	Proposed change (if any): Suggest changing "**is**	Accepted - Text will be amended.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		provided by" to "**has a**"	
133-135	5	Comment: Proposed change (if any): Suggest replacing "is provided" by "has a"	Accepted - Text will be amended.
Line 137	1	Comment: Proposed change (if any): suggest changing word as follows: "…*designated personal and* ~~assure~~ **ensure**…"	Accepted - Change will be made to the text.
Lines 139-141	9	Comment: Please clarify, in which documents should the terminology "principal investigator" be avoided? Would it be acceptable according to this guideline if usage of the title PI would be limited to the preclinical studies? Proposed change (if any):	Clarification provided - The term PI will be used in GLP documentation and clinical protocols. In these two situations the term will have a different meaning, however, both terms are accepted in the context of the types of study they are associated with. The reflection paper encourages laboratory management not to refer to analysts that perform clinical work as a PI as this may lead to confusion.
139-141	8	Comments: • Is the agency suggesting that a PI cannot be an analyst? • It would be helpful if the Agency can provide examples of acceptable terminology if "Principal Investigator" "Study Director", etc. are already reserved for the exclusive meanings in GCP, GLP or other guidances.	Point acknowledged - Any suitably qualified person can be an analyst. The section has been reviewed and the example deleted. Point acknowledged - The section has been reviewed and the example deleted.
144-145	8	Comment: all laboratory work is performed in	Accepted - Protocol refers to the clinical protocol. The text will

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		compliance with the protocol (technical/assay protocol?), any associated work instruction and standard operating procedures Proposed change (if any): specify if the intent is the assay protocol	be amended to clarify this point.
144-151	8	recommend to define "protocol" shortly in chapter 5. Guideline probably refers to "clinical protocol" whereas we should avoid confusion with "bioanalytical protocol".	Accepted - Protocol refers to the clinical protocol. The text will be amended to clarify this point.
142-145	5	Comment: In order to avoid misunderstanding please specify the type of protocol in line 144, i.e write clinical trial protocol instead of protocol" Proposed change (if any):	Accepted - Protocol refers to the clinical protocol. The text will be amended to clarify this point.
146-148	7	Comment: When a local lab in the hospital is used, at present it is unlikely that the lab would report anything directly to the sponsor. The results would normally be just sent to the investigator/clinic. Of course, the sponsor would get the results when collecting the CRFs from the site.	Acknowleged
146-148	11	Comment: In the case of bioequivalence studies, deviations occurring during the bioanalysis of pharmacokinetic	Acknowledged – The text will be changed to indicate that results should be reported to the investigator when appropriate. Any data that has an impact of the trial subjects

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		samples are usually not reported to the investigator. As the investigator is usually a physician and may be not an expert in pharmacokinetics, this does not seem to be necessary. Proposed change (if any): "The named individual(s) is responsible for reporting the results of the analysis or evaluation and any deviations from the work instruction or protocol to the sponsor or their representative and to the investigator, if deemed necessary."	well being must be reported to the investigator. Some PK date, for example data that indicated miss dosing, may have safety implications and consequently should be reported to the investigator.
146-148	5	Comment: requirements are different for different types of samples e.g. safety and pharmacokinetic samples Proposed change (if any): please consider and add the following sentence after line 148: Depending on the type of work the reporting lines as well as the time point of reporting will vary, and not all parties listed above have to be informed in all cases.	Accepted – The text will be changed accordingly.
146-148	8	Comment: CROs do not normally report data to the investigators, as this sentence seems to imply. CROs report data to sponsors only, who in turn report the data to investigators	Accepted in part – CRO's would be expected to make provision for the expedited reporting of anomalous results which may impact on subject safety to relevant people, which may include the investigator. The text will be reviewed to provide more detail on when it would be appropriate to report

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): remove "…and to the investigator."	information to the investigator.
148	13	Comment: The testing lab might not always be the direct link with the investigator. Proposed change (if any): The named individual(s) is responsible for reporting the results of the analysis or evaluation and any deviations from the work instruction or protocol. Reporting could be to the sponsor, investigator, or their representatives..	Accepted - See above comments.
150-151	8	how is this to be documented? Should an official document be prepared that indicates all the roles within the study, as it is done in pre-clinical study plans?	Acknowleged (no change needed) – The reflection paper is not designed to be overly prescriptive. Laboratories must implement processes that are effective and transparent. How this is done will vary from facility to facility. Using the GLP model would be a satisfactory way of dealing with this issue.
153-155	8	Comment: too general, and we suggest is unnecessary unless it is referring to outsourcing to a 3rd party, and then it should have language to that effect Proposed change (if any): suggest removing this paragraph unless if is referring to outsourcing to a 3rd party, and then we suggest adding this language at the end of line 155: "if analytical work is outsourced to a third party contract organization."	Reject - The reflection paper is not designed to be overly prescriptive

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
153-155	5	Comment: Proposed change (if any): add to the end of the paragraph "....laboratory analysis, if analytical work is outsourced to a third party contract organization."	Rejected - Lines of communication may still need to be established if the work is conducted by a large pharmaceutical company which is also the study sponsor.
159	8	this is usually given and documented in facilities which are GLP compliant. When GLP compliance is not given, what kind of supplemental documentation should be given?	Point rejected - the current wording sets a general principle and leaves the laboratory full flexibility on how to achieve it.
161-162	13	Comment: Laboratory staff involved in testing of clinical trial samples do not typically receive GCP training, but rather are GMP , GLP or GCLP trained. Proposed change (if any): More clearly define "all staff involved in the analysis or evaluation of…" so that testing personnel are not included in the group. Suggest to use "GxP" instead of GCP and define in glossary it stands for GCP or GCLP as applicable.	Point rejected - although it is acknowledged that all testing personnel may not need to be fully trained in GCP, a basic level of understanding of specific GCP requirements is expected. The proposed wording allows to adapt the level of this training depending on the involvement of each member of staff.
161-164	8	Text: All staff involved in the analysis or evaluation of clinical trial samples should receive GCP training commensurate with their roles and responsibilities. It is appropriate for laboratory staff to receive periodic GCP refresher training. Such training is especially	Point rejected - this reflection paper precisely aims at highlighting aspects of GCP which need to be taken into account when analysing samples from clinical trials.

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		important following changes to regulations and associated guidance documents. Comment: It would be helpful if Agency can identify specific parts of GCP guidance pertaining to the analysis of clinical samples.	
161	8	Says analyst should have GCP training. Is GCP training different from GLP training? If not would it be OK to have GLP or GCP training?	Point rejected - this reflection paper precisely aims at highlighting aspects of GCP which need to be taken into account when analysing samples from clinical trials and which are not covered by GLP.
161 - 164	10	Comment: Where samples are tested by local hospital laboratories, consideration is needed on the cost and burden to the institutions/health authorities to provide the laboratory staff with the relevant level of GCP training Proposed change (if any):	Point rejected - although it is acknowledged that all testing personnel may not need to be fully trained in GCP, a basic level of understanding of specific GCP requirements is expected. The proposed wording allows to adapt the level of this training depending on the involvement of each member of staff.
161-164	8	Comment: How GCP training could be conducted in a GLP environment? Can this task taken over by a GLP facility?	Point rejected - this reflection paper precisely aims at highlighting aspects of GCP which need to be taken into account when analysing samples from clinical trials and which are not covered by GLP.
172-174	8	Comment: To what details an individual laboratory personnel should maintain the training records from previous employment? A training certificate or more detailed outline of what have been trained. We suggest that a CV is sufficient	Point aknoweglged: the paper states the requirement for training records which would provide evidence of competence
173	8	Comment: What constitutes a record of experience	Same answer as above

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		gained from previous employment?	
175-176	8	Comment: This section is too prescriptive. Proposed change (if any): Remove the need to for signing and dating but include the management is responsible for ensuring proper training	Point adopted - change made to allow more flexibility in the way the review is documented. A statement on the responsibility of management is already included in section 6.1.1. and does not need to be repeated here.
Line 175-176	2	It is recommended that training records are periodically reviewed by laboratory management. This review should be documented to ensure the information they contain is up to date and remains relevant.	Point adopted - change made.
Line 177	9	Comment: It might be worth mentioning that parts of this section are not relevant to industrial laboratories belonging to the sponsor.	Point adopted - specific paragraph added at the end of this section.
Line 177-294	2	Comments: sections are written assuming that all work is placed with an external laboratory. However, quite often pharmacokinetic or pharmacodynamic (biomarker) samples are analysed in house by company (sponsor) labs. Those laboratories may assume that requirements in these sections generally do not apply for them. Proposed change (if any): Since some of the topics reflect basic GCP principles independent of type of laboratory performing the work, it should be made clear which topics apply to both external as well as in house analysis, and which topics	Point adopted - specific paragraph added at the end of this section.

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		solely apply in case sample analysis is performed by an external laboratory.	
177	8	Comment: Contracts and agreements are company specific and cannot be covered in a guidance, it is business related Proposed change (if any): Take out	Point rejected - contracts and agreements are not limited to financial or business-related issues, but may include information on tasks, responsibilities, communication channels, specific guidance or guidelines to be followed, etc.
178-207	8	Comments: • The intent of this section is unclear with regards to contractual agreements with BA CROs. Such agreements are of a strictly financial nature and do not in any way affect the procedures implemented for study conduct. • We suggest that this section is too prescriptive and most are recommendations for good business practices as opposed to regulatory requirements. Suggest that this section only include truly regulated requirements (e.g. 186-191) and that it be written with less detail. Proposed change (if any): Suggest high level wording on oversight vs. the details of contracts and agreements. If analysis is contracted out, ensure that the contract lab is following the appropriate regulations and regulatory guidances. Sponsor should provide adequate oversight to ensure quality. Also, recommend, a paragraph on when analysis is outsourced to a third party laboratory.	Point rejected - contracts and agreements are not limited to financial or business-related issues, but may include information on tasks, responsibilities, communication channels, specific guidance or guidelines to be followed, etc.

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Lines 177-207	1	Comment: Section 6.1.3 on Contracts and Agreements suggests that it is assumed that all types of laboratory analysis work are outsourced by the sponsor. This is not always the case, especially with respect to bioanalytical laboratories where PK/PD samples are usually run by the company's (sponsor's) laboratory. In order to avoid any misunderstanding it would be appropriate to recognise that where the sponsors own internal laboratories are concerned a formal contract or agreement is not needed provided all the elements are addressed in sponsor internal lab SOP and policy documents. Proposed change (if any):	Point adopted - specific paragraph added at the end of this section.
Line 183	1	Comment: Contractual agreements between relevant parties should be in place prior to the initiation of <u>any work.</u> Propose change to allow separate contractual agreements where needed to allow preliminary and method development work prior to contractual agreement on the definitive safety study. Proposed change (if any):	Point rejected - preliminary and method development work not involving the analysis of clinical trial samples is not under the scope of this Reflection Paper.
183	8	Comment: too restrictive! how to handle cases when	Point adopted - specific paragraph added at the end of this

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		analyses are done in the internal laboratories of the sponsor's firm? Proposed change (if any): Suggest adding the following to the beginning of line 183 "**If work is outsourced to a third party laboratory,**"	section.
Line 183	2	Comments: contractual agreements only necessary if work package is placed with an "external" laboratory which is not part of the sponsor organisation Proposed change (if any): Please **replace** "Contractual agreements..." **by** "For work packages placed with an external laboratory/service provider, contractual agreements..."	Point adopted - specific paragraph added at the end of this section.
183 - 185	10	Comment: In a hospital setting, the contract will often or usually be between the institution's management organisation and the sponsor, not with the laboratory directly Proposed change (if any): change to "with the laboratory or institution's management" in line 185	Point rejected: The reflection paper is not designed to be overly prescriptive and the contract section refers to "relevant parties"
183-185	11	Comment: Please clarify: Is a CRO a representative of a sponsor?	Point rejected - already cleary defined in the Note for Guidance on good clinical practice (§ 5.2), no need for further clarification.

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183-185	5	Comment: Proposed change (if any): Suggest adding the following to the beginning of line 183 “If work is outsourced to a third party laboratory,...”	Point adopted - specific paragraph added at the end of this section.
184-185	13	Comment: move "(or their delegated representative)" to the end of the sentence since applicable to both parties. Proposed change (if any): This will usually take the form of a legally binding contract which is signed by the sponsor and laboratory management (or their delegated representative).	Point rejected: The reflection paper is not designed to be overly prescriptive and the contract section refers to “relevant parties”.
198-202	5	Comment: Proposed change (if any): “...where...-“	Point adopted- change made
198-199	10	Comment: The procedure for contract drafting might lie with the institution, in which case the lab’s quality management system should refer to this Proposed change (if any): add “or reference to the institution’s process” at the end of the sentence	Point acknowleged: The reflection paper is not designed to be overly prescriptive and the contract section refers to “relevant parties”.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
201, 220	8	Comment: couple of typos in lines 201, 220 “were” needs to be replaced by “where”	Point adopted- change made
201-202	10	Proposed change (if any): add “or reference the institution’s process” at the end of the sentence	Point acknowleged: The reflection paper is not designed to be overly prescriptive and the contract section refers to “relevant parties”.
203-207	5	Comment: remove this paragraph, too detailed and not needed at all Proposed change (if any):	Point rejected: the section was reviewed to better describe the process
203-207	8	Proposed change (if any): This section covers an area of purely business nature. Please delete	
208	8	Comment: “Trial conduct” is misleading Proposed change (if any): “Analysis/evaluation conduct” more appropriate	Point rejected: the statement is clear as it is.
208	4	2.3. Further (minor) Comments Chapter 6.1.4. (trial conduct), chapter 6.1.18. (informed consent) and chapter 6.1.19. (SOPs) are partially overlapping. For clarification, we suggest to focus chapter 6.1.4. on the conduct according to the clinical study protocol and to integrate the other parts into the respective other chapters.	Point acknowledged: the various sections mentioned in the comment have been reveiwed for clarity.
208-245	8	Proposed change (if any): Suggest adding a	Point rejected - this section applies also in the case when the

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		paragraph to differentiate between when a sponsor analyzes samples and when conducted by a 3rd party laboratory	laboratory is part of the sponsor company.
211-213	5	Comment: Proposed change (if any): replace “have been contracted to” by “are to”	Point adopted- change made
211-213 229-232	11	Comment: “… laboratory will be provided with a copy of the full protocol… or relevant sections …” Information in study protocol are limited to sample preparation in the clinic and shipment of those samples to the bioanalytical laboratory and some basic information regarding analytical method. Specific information regarding sample analysis should be described in analytical study protocol.	Point rejected - the protocol will also include information on the trial flow chart, number of subjects or patients, samples to be analysed, tests to be performed, concimitant medication or disease state that may affect the performance of the tests, etc. This information is relevant to the work to be performed by the laboratory.
212	13	Comment: Instead of "sections" of the protocol, suggest to say "relevant details" since we may not actually provide the protocol; e.g. we provide analytical plan per GCLP. Proposed change (if any): As a minimum the laboratory should be provided with the relevant details of the protocol which are relevant to the work…	Point adopted- change made

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213	8	Proposed change (if any): remove the words "**have been contracted to**" with "**are to**"	Point adopted- change made
Lines 216-217	1	Comment: it would be helpful to clarify the meaning of "relevant". Proposed change (if any): "*A mechanism should be agreed with the sponsor or their representative to ensure that ~~any relevant~~ amendments to the protocol are supplied to the analytical laboratory* **if they affect its work".**	Point adopted- change made
218-221	5	Comment: typo in lines 220 "were" needs to be replaced by "where Proposed change (if any):	Point adopted- change made
218 – 221	10	Comment: A further exception would be where a "local" hospital laboratory is testing safety samples using routine analytes. In this case the laboratory would already have its own procedures for conducting the analysis and study-specific procedures would not be required, unless the protocol requirements differed from the lab's routine methodology. Proposed change (if any): add this example to line 221.	Point Acknowledged: the scope of the paper was reviewed to further define the applicability fo the reflection paper

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 218-221	2	Comments: Requirements differ for in house analysis and analysis placed with an “external” laboratory Proposed change (if any): Replace section by (Changes underlined): “Prior to…to conduct the analysis and evaluation, <u>especially if work package is placed with an external service provider/laboratory</u>.” Exceptions will include…in the <u>clinical</u> protocol or the contract <u>or a SOP</u>.	Point rejected - also applies to "in-house" laboratories.
218-221	8	Comment: Recommend the use of SOPs instead of work instruction as proposed in this paragraph.	Point adopted- change made and the term “SOP” has been used in the paper.
Line 220	1	Comment: Replace “were” with **<u>“where”</u>** Proposed change (if any): “*Exceptions will include situation ~~were~~* **<u>where</u>** *all the relevant information…”*	Point adopted- change made
Line 222-227	6	Comment: It is noted that in the “scope” section where it says that it is for interventional trials only. Our question was whether the EU guidance should be in line with other EU Directives so that it was relevant for any trials involving human tissue and not limited to	Point rejected – the comment is not relevant to this section

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		interventional trials. Proposed change (if any):	
227-228	7	Comment: Clarification is sought on whose responsibility is to check that the work instruction only includes work that is covered by the informed consent document (ICD) - the sponsor or the laboratory, and how this can be achieved, e.g. does the laboratory have to obtain/receive a copy of the consent form.	Point adopted: section on informed consent was reviewed.
227-228	8	Comment: • The burden of correspondence between informed consent form and the work instructions can not be put on analytical laboratory since the informed consent form either general or signed by particular patient is not communicated to the laboratory, thus providing no means to accomplish this mandate. As indicated in lines 229-232, the protocol should be used as a basic document for compiling the work instruction. This is also emphasized in line 247. The correspondence of the work scope to the informed consent should be the solely responsibility of sponsor.	Point adopted: section on informed consent reviewed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		• looks like confusion of work instruction for bioanalytical work and work instruction for rather clinical handling of samples? • Suggest that these lines refer to the clinical protocol instead of the informed consent or patient information leaflet.	
229-230	8	Comment: Clarification is needed when the protocol is reference, is it the assay protocol or clinical protocol?	Point acknowledged: clinical trial protocol used throughout the document
229-232	5	Comment: typo in line 230 been" Proposed change (if any):	Point adopted- change made
Line 230	1	Comment: Replace "be" with "**been**" Proposed change (if any): "*If a protocol has not ~~be~~ **been** provided by the sponsor…"*	Point adopted- change made
242	15	Comment: Incomplete as far as the safety of patients may be concerned Proposed change (if any): representative immediately and to the investigator if necessary for the patient's safety.	Point adopted- change made
247	11	Comment: It is stated that labs should not perform any work that	Point rejected, because it is already stated in the section 6.1.5 that the original protocol should be amended in case of

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		is not specified in the original protocol. Proposed change (if any): It should be clarified how cases should be handled, where samples for PK analysis from a bioequivalence study should be used for additional analysis not planned in the study protocol. Examples: - It was planned in the protocol to measure only the parent compound. Due to a deficiency letter, the metabolite should also be measured. - It was planned in the protocol to use an achiral method. Due to a deficiency letter, the samples are planned to be re-analyzed using the chiral method. - It was not planned to measure samples of drop-out subjects, but this is requested in a deficiency letter. At that stage, subjects may no longer be available to give an additional informed consent.	additional work.
247-252	8	Comment: Suggest a change in wording so that Sponsor (instead of the laboratories) is accountable for ensuring that additional work does not conflict with the protocol.	The point is adopted
258-261	5	Comment: The word “to” is missing in line 259 ….. prior to its initiation …	The point is adopted

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		please stipulate whether this subcontracting is delegated by the laboratory or the sponsor Proposed change (if any):	
259	8	not clear what is meant: does “sub-contracted to another laboratory” mean, that the chosen bioanalytical lab further contracts bioanalytical work to another lab?	
Line 262	1	Comment: Proposed change (if any): Suggest inserting comma after ‘sub-contractor’	The point is adopted
266	15	Comment: Incomplete Proposed change (if any): responsibilities and the scope and nature of the work that will be undertaken by the sub-contractor including data archiving).	The point is adopted. The section on record retention was reviewed.
269-275	5	Comment: typo out **of** range instead of out **or** range Proposed change (if any):	The point is adopted
271-273	8	Comment: It should be responsibility of sponsor to communicate with investigators for at least two	The point is rejected. The lines of communication could be done in parallel to make sure that both investigators and sponsor get the same information. Information flow to the

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		reasons: 1. The study can involve several hundreds of investigator at different clinical sites, so the burden of establishing communication with all of them is excessive for the analytical laboratory; 2. Direct line of communication of analytical laboratory and investigator can inadvertently create dangerous bypass when the sponsor is excluded from this line. It is automatically avoided if all communications go through the sponsor.	investigator(s) must not be delayed by the sponsor.
272 282-286	11	Comment: It is requested that a line of communication is established between the lab and the investigator. However, this does not seem applicable to bioanalytical labs in bioequivalence studies. The bioanalytical work is only started after the clinical part of the study for the subject has been completed. Therefore, even if the pharmacokinetic results are unexpected or very high, this information does usually not have safety implications. Proposed change (if any): … and with the investigator (in case of safety labs) …	The point is rejected. The lines of communication could be done in parallel to make sure that both investigators and sponsor get the same information. Information flow to the investigator(s) must not be delayed by the sponsor.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
272	15	Comment: Incomplete Proposed change (if any): with the sponsor, or their representative, with the laboratory, and with the investigators, to ensure that any issues that…	The point is rejected, The sentence is referring to the laboratory.
274	15	Comment: printing error Proposed change (if any): limited to, the reporting of unexpected or out of range results and …	The point is adopted
274	8	Comment: typo out **of** range instead of out **or** range. Also, it should be noted that the lab must ensure that the reporting of these results does NOT accidentally unblind sponsor staff blinded to the study, if applicable.	Make sure that this is reflected here as part of the agreement regarding reporting results without unblinding.
278	15	Comment: to take into account that clinical trials concern ill patients with some "logically abnormal" biological values. In these circumstances normalisation may be "anomalous" and critical. Proposed change (if any): under mot circumstances ~~normal ranges~~ reference values (and critical values if relevant) should be established for safety tests prior to the start of analysis. If clinically significant deviations from these ranges (even anomalous trend profile	The point is rejected because the proposed change can not be used in every trial. Therefore the individual trials must be described in the contract specifying the needs for the trial.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		among the normal range) or unexpected worsening results are recorded a mechanism should be in place to communicate to the sponsor or their representative and to the investigator as quickly as possible.	
278-281	8	Comment: • Need to better differentiate safety vs. general (e.g. PK analyses) The analytical laboratory should maintain the responsibility of communication with the sponsor only unless specifically indicated in the contract (see comments for the lines 271-273).	The point is rejected because the proposed change can not be used in every trial. Therefore the individual trials must be described in the contract specifying the needs for the trial.
282-286	8	Comment: Instructions should include consideration of "blind to the trial"	The point is considered when establishing the lines of communications between the parties.
Line 282-289	2	Comments: Apart from first- in-men studies and rising dose studies pharmacokinetic samples are often stored frozen for quite a while before they are analysed because the result is not needed for safety assessment. Procedure therefore differs from safety samples. Terms "out of specification" and "anomalous" do not apply to pharmacokinetic samples but may only be used for calibration standards and quality control samples with a known nominal concentration. Proposed change (if any): Replace line 282-286 by :	Point partly acknowledged: added text "unexpected in in section 6.1.7.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"It is always appropriate to consider the need to expedite the reporting of results regardless of the nature of analysis/sample type or evaluation that is being conducted, especially in case potential safety implications may arise."	
287	11	Comment: Please define "(…) appropriately qualified person (…)"	The point is rejected as it is not up to the authorities to define the level of experience /education. The persons performing this task should be qualified to perform the task.
287-289	11	Comment: It is requested that the results should be reviewed by an appropriately qualified person to identify any anomalous data. However, when it comes to bioanalysis in bioequivalence studies, anomalous data do not have any implications: - They are not relevant with regard to the subject´s safety, because when the results become available, the clinical part has already been completed for this subject. - According to the draft Guideline on Validation of Bioanalytical Methods (EMEA/CHMP/EWP/192217/2009, 19 Nov 2009), it is normally not possible to re-analyze them ("Normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable"). - According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 20 Jan 2010), it is normally not	The point is rejected because the proposed change can not be used in every trial. Therefore the individual trials must be described in the contract specifying the needs for the trial.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		possible to exclude anomalous values ("Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone"). Therefore, in case of bioanalysis of bioequivalence samples, this review does usually not seem to be necessary. Proposed change (if any): "If relevant for subject safety, results and observations should be reviewed by an appropriately qualified person …"	
287-289	5	Comment: Wording needed to permit additional analyses to determine if result is real or truly anomalous Proposed change (if any):	The point is rejected because the section refers to review and not re-analysis.
288	8	Comment: "anomalous or out of specification data"- need clarification. For example, if pk or ADA result, this is not applicable.	The point partly acknowledged: the term "unexpected" has been added.
289	15	Comment:Incomplete Proposed change (if any):The review must be documented. The investigator is responsible for	The point is rejected because the section covers the quality control step performed at the laboratory before sending the

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		ensuring that any subject enrolled in a clinical trial get his/her laboratory results in his/her medical file ;these results must be either nominatives or attributable with no doubt.	results to the investigator and sponsor.
290-294	8	Comment: seems to be too much level of detail Proposed change (if any): suggest removing this section	The point is rejected
294	13	Comment: "hour's" – context requires plural, not possessive form. Proposed change (if any): implementation of an agreed and tested out of hours communication policy.	The point is adopted
Lines 293-294	1	Comment: Quotation mark Proposed change (if any): "*In such situations the laboratory should consider the implementation of an agreed and tested 'out of hours' communication policy."*	Point is rejected – sentence changed
295-311	8	Comment: It seemed too much for the laboratory to exercise due diligence to ensure the work performed is under informed consent. The process should be adequate if the sponsor takes full responsibility and inform the lab of any change with patient's consent	Point adopted: section rephrased

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		status in timely manner.	
296-306	8	See comment for the lines 271-273.	Refer to answer above
296-306	13	Comment: To be challenged: it basically states that the analytical lab must verify informed consent for the testing to be done. Since the lab is bound by a contract or agreement (see previous sections) to execute what the sponsor requests, it is up to the sponsor and not the analytical lab to ensure informed consent coverage, not at least since the sponsor is the "closest" to the trial subject. This allows the sponsor to react the fastest to any change in informed consent and keeps the overall process in a simpler form.	Point adopted: section rephrased
299 - 301	10	Comment: Since the informed consent documentation and informed consent process are the responsibility of the investigator, the responsibility for ensuring this is included in the consent also lies with the investigator rather than the laboratory. In a multinational trial, if the lab were responsible for the confirming consent content in this respect, a central lab would be required to review all consent forms from the trial (each country, each site), including the associated burden of translation into the lab's local language. Proposed change (if any): The responsibility for checking that the consent documentation covers the laboratory tests should lie with the investigator. A better way to ensure this is done would be to	Point adopted: section rephrased

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		specifically include a reference to laboratory tests in any future guidance on consent or ICH GCP, specifically section 4.8.10 (d).	
299 - 301	10	There is a risk of misinterpretation resulting in the laboratory expecting to receive copies of patient consent forms, which would breach confidentiality in the setting of commercial laboratories. Proposed change (if any): Clarify that signed informed consent documents should not be provided to the laboratory.	Point adopted: section rephrased
Lines 299-301	1	Comment: Investigators are responsible for managing consent form issues. While the sentence reading *"However laboratory management personnel must exercise due diligence to ensure that the work they have been contacted to conduct is covered by the consent given by the trial subjects"* is probably not intended to suggest that laboratory management personnel should check the consent forms (this would raise personal data protection issues) but rather to check that samples can be appropriately managed should for example a patient withdraw his/her consent, the sentence may be misinterpreted. It is suggested that this sentence be deleted. Proposed change (if any): Delete ~~"However laboratory management personnel~~	Point adopted: section rephrased

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~must exercise due diligence to ensure that the work they have been contacted to conduct is covered by the consent given by the trial subjects"~~	
299-303	11	Comment: Providing the protocol to the safety laboratory is general practice in phase III studies, but for bioequivalence phase I study it is inflated. Proposed change (if any): For bioequivalence studies a comparison of informed consent form and subcontracted work has not to be done by the safety lab. The investigator/CRO should be responsible to look whether the same haematological and urinary parameters are listed in the ICF and in the contract with the laboratory.	The point is rejected because the proposed change can not be used in every trial. Therefore the individual trial must be described in the contract specifying the needs for the trial.
Lines 301-306	1	Comment: With reference to the above comment in relation to the likely intended purpose of the section 6.1.8 it is proposed to replace the text of lines 302-306 with following one: Proposed change (if any): ~~"Mechanisms implemented to address this concern may include a review of the approved protocol, or a documented dialogue with the sponsor to confirm that~~	Point adopted: section rephrased

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~the consent process covers the work that will be undertaken by the laboratory. It may also be appropriate to include a clause in the contractual agreement between the sponsor and the laboratory which stipulates the need for informed consent to cover any laboratory analysis or evaluation.~~ ***The Laboratory Management should ensure there is a clause in the contractual agreement which stipulates the need for appropriate informed consent and that the sponsor, or sponsor representative, is responsible for ensuring that only samples from suitably consented patients are sent to the laboratory for analysis."***	
307-308	11	Comment: It is mentioned that there should be a mechanism in place to ensure that the lab is informed in a timely manner if consent is withdrawn to ensure that no further data is generated or collected. However, according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 20 Jan 2010): "Drop-out and withdrawal of subjects should be fully documented. If available, concentration data and pharmacokinetic parameters from such subjects should be presented in the individual listings, ...". Proposed change (if any): It should be clarified if already taken (plasma) samples	Point acknowledged - Section rephrased

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		of subjects withdrawing consent can be analyzed or not.	
Lines 307-308	1	Comment: The sentence reading “there should be a mechanism to ensure that the laboratory is informed in a timely manner if consent is withdrawn to ensure that no further data is **generated or collected**" somewhat contradicts the FDA guidance on data retention. In some instances the clinical samples are stored frozen in the hospital until a batch shipment to the central laboratory is organized. In addition, sample analysis may be performed in batches and sometimes at the end of the study. Therefore further data will be generated from samples already obtained during the time the subject was enrolled. The sentence should be understood as "no new data would be obtained from the subject". To prevent lab deleting samples collected prior to the consent removal and not yet analyzed we would propose to remove "generated" from line 308. This would be in alignment with FDA Guidance for sponsors, clinical Investigators, and IRBs "data retention when subjects withdraw from the FDA-Regulated Clinical Trials" and the OHRP guidance on	Point acknowledged: The section on Informed Consent has been reviewed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		withdrawal of subjects from Research: data retention and other related issues. Proposed change (if any): *"There should be a mechanism to ensure that the laboratory is informed in a timely manner if consent is withdrawn to ensure that no further data is ~~generated or~~ collected".*	
307-308	8	Comment: • The mechanism mentioned in this document should also address samples inadvertently collected without an additional consent. • It is not clear what specifically Agency is suggesting in these lines. The statement regarding withdrawal of informed consent saying "…the responsibility for providing this information primarily resides with the sponsor" should be sufficient and adequate for the intended purpose of this section.	Point rejected: refer to section on informed 6.1.8 and answer above
Lines 310-311	1	Comment: It is suggested to simplify the wording as follows: Proposed change (if any): ~~While the responsibility for providing this information primarily resides with the sponsor, the clinical laboratory must exercise due diligence. It is therefore recommended that these factors be considered and~~	Point acknowledged: see section on inform consent

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~documented in the contractual agreement or other relevant documentation prior to the initiation of any analytical work.~~ ***"The Laboratory Management should ensure there is a clause in the contractual agreement which stipulates the need for the laboratory management to be notified in a timely manner by the sponsor, or sponsor representative, of the withdrawal of patient consent for any sample the laboratory is analyzing or storing."***	
Lines 312	16	Propose to add a paragraph with a description of procedure for confirming receipt (by the laboratory) of the samples to the investigator. Particularly in cases where the sponsor collects samples which test results are not provided to the investigator. **"According to ICH GCP 8.3.25 (Essential documents for the conduct of a Clinical Trial) the investigator and sponsor needs to have records of retained body fluids/tissue samples to document location and identification of retained samples."**	Point acknowleged: A mechanism to track the movement of each sample from arrival to analysis or evaluation should be implemented and maintained.
312-317	5	Comment: add "**and storage**" to title of section Proposed change (if any):	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
312	8	Comment: section also describes storage Proposed change (if any): add "**and storage**" to title of section	Point adopted
312-360	8	Comment: Section 6.1.9 did not address samples received beyond stability, how this should be handled, addressed and documen ted? It is not uncommon that clinical sites collect samples but do not sent them in the clinical protocol specified time.	Point adopted
313	15	Comment: Incomplete Proposed change (if any):A clinical trial sample must be labelled by the individual who does sampling. Samples should be...	Point adopted
313-321	8	Since the analytical laboratory has practically no control over the sponsor and investigator operations on samples collection and transportation, the scope of this section should be limited to the issues that can be implemented and controlled by laboratory, essentially starting with the arrival of the samples.	Point rejected – the laboratory may collaborate with the sponsor to define samples collection and shipment procedures as these would influence directly the integrity of the samples.
315-317	8	thinking of plasma/urine – there should be no transfer at ambient temperature!	Point adopted
315	15	Comment:to prevent contamination during transportation	Point rejected – shipment of samples can be performed using various means and it is the intend to keep the a general

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): <u>if samples are shipped the shipping should be organised in suche a way that any pollution is avoided, according to IATA guidelines (International Air Transport Association).</u>	approach rather than mentioning all the various shipment requirements.
318-321	8	Comment: using data loggers to monitor temperature during transit is not standard and maybe considered as overkill (presence of dry ice at the time of arrival is sufficient proof of appropriate temperature during shipment). Proposed change (if any):change "**data loggers**" to "**devices**"	Point adopted
318-321	5	Comment: To detailed. Suggested to leave it at 'documented proof' , delete sentence "Best practice..." Proposed change (if any):	Point adopted
Lines 320-321	1	Comment: Data loggers for monitoring temperature during sample transport are not a requirement and are not always used. In order to avoid that reference to the use of data loggers in the Reflection Paper is not misinterpreted the sentence should be deleted or modified to reflect that this is not a requirement but only one example of good practice when close monitoring is needed.	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Recommend either removing data logger sentence or adding clarification that data loggers are not a requirement.	
Line 323	16	Proposed change Recommend adding: "*sponsor* **or their representative and the investigator** sho*uld be notified promptly."*	Point adopted
324-331	5	Comment: to allow for sample accounting with large sets of samples, suggest a slight change in wording Proposed change (if any): change "**on receipt**" to " **As soon as possible**" Comment: to allow for analytical systems that do not allow for destruction of results we suggest adding language about excluding Proposed change (if any): should be destroyed "**or excluded"**	Point related to "On receipt" rejected – the timeframe of the receipt procedure is expected to be documented at the laboratory and it is not the intent to define the timeframe for receipt in this paper. Point adopted – "destroyed" to be replaced by "reported"
324	8	Comment: to allow for sample accounting with large sets of samples, suggest a slight change in wording Proposed change (if any): change "**on receipt**" to " **As soon as possible**"	Point rejected: the timeframe of the receipt procedure is expected to be documented at the laboratory and it is not the intent to define the timeframe for receipt in this paper.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
325-326	8	Comment: In case of sample discrepancies, laboratory should only contact sponsor or their representative, and avoid direct contact with the investigator. Proposed change (if any): delete ", or the investigator,"	Point rejected: the lines of comminication are dependent on the study design.
325-327	8	Comment: if lab personal assign unique identifier, it is trackable to analyze poorly labelled samples, and confirm identity after analysis	Point noted and covered by the next sentence
327	8	may delay analysis of samples, especially in Ph III studies.	Point noted and covered by the next sentence
328-331	8	sounds not like the best practice to create data and to decide later if they can be used or not.	Point rejected- consideration to stability of samples has to be taken into account – this is covered by the next statement
329	13	Comment: "samples identity" context requires possessive, not plural form Proposed change (if any): "sample's identity"	Point adopted - replace by "sample's identity"
330	13	Comment: "If the identity of the sample can not be established the results should be destroyed." Add a provision that it should be clearly documented as to the reason behind any destruction of results. Proposed change (if any): Any sample destruction should be recorded and justified as appropritae.	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
330	13	Comment: "if the identity" is too nonspecific and not realizable. As written here it would require to remove the results from the database (doable) but also from lab notebooks and/or other information carriers which might be paper-based. Proposed change (if any): Remove the line. "	Point rejected: in the event that a sample has been analysed but that its identity cannot be ascertained, the result should be excluded and not provided to the sponsor.
330	8	Comment: to allow for analytical systems that do not allow for destruction of results we suggest adding language about excluding Proposed change (if any): should be destroyed "**or excluded"**.	Point adopted
330	3	Comment: one concern was line 330, the requirement to "destroy results"; We suggest that a reword is necessary to emphasize that results will not be "destroyed" but do not need to be reported. Proposed change (if any):	Point adopted
Line 330	1	Comment: Use of the word "destroyed" in this sentence may not be appropriate. Proposed change (if any): Perhaps, the sentence can be modified to indicate that the data where the identity of the sample cannot be identified it is not appropriate to report the results.	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"*If the identity of the sample can not be established the results should* ~~*be destroyed*~~ **not be reported or assigned as rejected."**	
Line 330	2	Proposed change (if any): If the identity of the sample cannot be established the results should not be reported or assigned as rejected.	Point adopted
332	13	Comment: Remove the word "robust" since nonspecific; can be interpreted very differently. Proposed change (if any): A mechanism to track the movement of each sample from arrival to analysis…	Point adopted - "robust" removed
335-339	5	Comment: Proposed change (if any): Please delete "strongly"	Point adopted - "strongly" removed
340-341	15	Comment: to respect local regulations Proposed change (if any):On arrival, or prior to processing, each sample and requisition form should be examined to ensure that its label does not display information which may identify the trial subject, otherwise the patient should have consent to the contrary according to local regulations.	point rejected: the reflection is written in such a way to allow flexibility and do not detail the local requirements.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
340-344	5	Comment: - It might be useful to have guidelines of what constitutes identification i.e. name, date of birth etc - Information on a label should not be deleted Proposed change (if any): If information is recorded on the label which may compromise the trial subject's right to privacy, it should be masked **but not deleted**.	Point adopted
340-344	12	Comment: There are situations where local Health Service/ Hospital laboratories require that all samples are directly attributable to a named patient and these laboratories do not have facility to accept anonymised samples. If a sample is being analysed at the institution where a patient is also receiving medical care, it may additionally be desirable that the results form a part of the patient's normal medical record (e.g. a cancer patient participates in a trial at the hospital where he is being treated). Proposed change (if any): We suggest that the privacy requirements in this section be restricted to samples transferred outside of the study site/hospital/institution.	Point adopted –statement included "unless it is permitted by the hospital procedure (e.g. local laboratory) and it does not contradict the sample handling as specified in the protocol (e.g. blinded study)"
340-341	8	Subject numbers (although not clear individual IS) is usually given on tubes. Trial subject identification is	Point noted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		therefore easily possible, isn't it?	
341	13	Comment: Make more specific; the trial subject needs to be identified in some way; for example a number or code to be differentiated from other trial subjects.	Point rejected: the traceability of the samples is discussed in line 324
Lines 341-342	1	Comment: In the event it is found that information which may identify a trial subject is displayed on a label action should be taken to make sure this information is not visible/accessible. A small change in the wording of the sentence describing this action is suggested below: Proposed change (if any): *If information is recorded on the label which may compromised the trial subject's right to privacy, it should be masked or ~~deleted~~* ***obscured.***	Point adopted
Lines 349-350	1	Comment: Investigator sites are always the primary contacts in such situations Proposed change (if any): "*The* **sender including the** *sponsor or their representative should be notified of all instances of inappropriate labelling of clinical trial samples as soon as is practically possible*	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
351 - 353	10	Comment: This statement should be clarified to indicate that it refers to long term storage of samples rather than transit from the clinic to the laboratory. Proposed change (if any):	Point adopted – this statement refer to the storage of samples as per protocol has been included
Lines 361-370	1	Comment: This section on method validation should include guidance on the expectation and good practice approaches to method validation in the exceptional circumstances that are defined on line 371. Technical constraints and/or patient population constraints can pose great and in some cases insurmountable challenges to demonstrating method accuracy, precision, sensitivity, specificity and range etc., per the currently available guidance documents. Consideration should also be given to allowing flexibility and judgement in these cases and the extent to which full validation or qualification is required dependant on such factors as the clinical phase of the study, and whether the assay/test relates to primary, secondary or exploratory endpoints. Proposed change (if any):	Point rejected: a degree of flexibility already exists in the paper in the section method validation.
361 Section 6.1.10	13	Comment: A paragraph needs to be added to differentiate the use of qualified and validated methods and how "validated" is different from "qualified".	Point rejected: a degree of flexibility already exists in the paper in the section method validation

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
361, 434	4	CIMT and CIC-CRI would like to specifically comment on following sections: Please see the overview table in Appendix 1 for our proposal with regard to a context-specific regulation. 2.1 Validation of analysis methods, validation of storage stability of samples and validation of computerized systems This relates to document chapters 6.1.10., 6.1.16. We welcome this guideline text necessary to prevent generation of imprecise data in situations where patient safety, a clinical decision potentially affecting patient health or the primary outcome of a late-stage study may be affected but recommend that this is applied as proposed by EMA only for categories A-C as defined above. For categories D-E, we suggest: • a full validation approach is not a prerequisite for these analysis categories, because exploratory studies often support the development of new assays, which cannot be validated or qualified at inception. With repeat use of an exploratory assay, a basic	Point rejected: a degree of flexibility already exists in the paper in the section method validation

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		qualification of the method, such as showing robustness and state of the art within internal or external quality assurance programs (e.g. proficiency panels), for example as recommended by the CIMT Immunoguiding Program and the CIC-CRI (Britten et al., 2009) for immune monitoring, should be sufficient at the early stage of clinical research. A conceptually similar “fit-for-purpose” validation approach for biomarkers was also suggested by Lee et al., 2006. • the technical feasibility of classical validation approaches should also be considered here, such as taking into account the principal non-availability of true reference standard samples or gold-standard assays for e.g. the quantification of lymphocytes expressing hypervariable receptors or analyzing functionally diverse cellular subsets. • importantly, the actual validation status at the time of analysis should be accurately documented to allow a complete interpretation of the results.	
361-362	13	Comment: Should reference guidelines on validation… ICH, CBER, etc.	Point rejected – there are multiple references however a reading list will be provided
362	13	Comment: "circumstances*" - * is not referenced.	Point adopted
365	15	Comment: to be factual and because of a possible	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		immediate lability Proposed change (if any):Relevant storage stability data must be available if samples are to be stored ~~for extended periods~~ of time prior to analysis.	
365-366	11	According to the draft Guideline on Validation of Bioanalytical Methods (EMEA/CHMP/EWP/192217/2009, 19 Nov 2009) it is recommended that evaluation of long term stability is determined before the start of analysis. Proposed change (if any): It is recommended to obtain relevant storage stability data prior to analysis if samples are stored for extended periods of time.	Point rejected – please refer to the overview of comments on draft Guideline on Validation of Bioanalytical Methods
361	8	In chapter 6.1.10 or in References (Chapter 7, Line 651) add citation for EMA “GUIDELINE ON VALIDATION OF BIOANALYTICAL METHODS”	Point adopted
362 (371-372)	8	Comments: • "In all but exceptional circumstances*, analysis should be performed using appropriately validated methods with defined acceptance criteria, where appropriate." The guidance is not clear on what the exceptional circumstances are and the "*" in this sentence needs to be referenced - think it refers to lines 371-372. We don't think validated assays are	Point adopted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		necessary for exploratory PK analysis, for example, urine PK or cold metabolite profiling. • Review to guidance documents on assay validations, as appropriate • "*" at "circumstances" is explained nowhere, please add.	
365	8	"extended periods" should be defined more precisely.	Point adopted
Line 365-366	2	Comments: Relevant storage stability data must be available in any case Proposed change (if any): Replace current sentence by: Relevant storage stability data must be available	Point rejected – the current statement addresses the issue
365-366	5	Comment: Proposed change (if any): If samples are to be stored for extended periods of time prior to analysis, relevant storage stability data must be generated.	Point rejected – the current statement addresses the issue
367-368	13	Comment: Opportunity here to cite guidance documents on analytical method development.	Point adopted – reference added
369-370	8	Carry-over sentence makes not much sense (PK labs are usually unblinded for blinded trials).	Point accepted: line deleted

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
369	15	Comment:incomplete Proposed change (if any):affect clinical trial results are considered (including possible interactions with tested medicinal product metabolites).	Point rejeted – the statement is clear enough
370	15	Comment:Incomplete Proposed change (if any): any reagent prepared or diluted in advance should be labelled with preparation date, shelf life, and batch number. Purchased reagents should bear reception date. As much as possible the same analytical methods should be used throughout the trial.	Point rejected – the proposal is not relevant to this section
370	11	…Where the laboratory is blinded it is very important that the presence of carry over is assessed. Comment: According to the draft Guideline on Validation of Bioanalytical Methods (EMEA/CHMP/EWP/192217/2009, 19 Nov 2009) carry over should be addressed and minimised during method development. This is valid for all bioanalytical methods.	as above

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 371-372	1	Comment: There is an * missing from Line 371 which defines exceptional circumstances as “leading edge research analysis. For example – the identification of potential clinical markers in specific patient groups where the method is validated as part of the clinical trial”. In addition this text should be moved to the end of Line 364. Proposed change (if any): As mentioned above under “Comment.”	Point acknowledged
375	15	Comment: Incomplete Proposed change (if any):…should be clearly defined and documented.	Point acknowledged- change made
389	8	Comment: used “changed” instead of “manipulated”	Point acknowledged – change made to “corrected”
394	11	Comment: In case of bioequivalence studies outsourced to a full service provider CRO, the CRO is normally responsible for agreeing on the data format with both the safety and the bioanalytical work. Proposed change (if any):	Point acknowledged – change made

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"… with the sponsor or their representative …"	
395	8	Comment: Typical contracts with CROs do not specify the means of data reporting. Data reporting may be governed by SOPs, verbal agreements, company/study policies, etc.	Point rejected – the current statement allows enough flexibility on how to agree the reporting of the data
400	15	Comment:incomplete Proposed change (if any):accurate, ~~and~~ complete, validated by a suitably qualified and identified person and reported with the relevant reference value if any.	Point rejected – the intend is to ensure that the data reported are accurate and complete. The process on how there are reported (validated by a suitably qualified person…) is not purpose of this statement.
401	11	Comment: Results of the bioanalytical lab in bioequivalence studies do not necessarily need to be reported to the investigator. Proposed change (if any): "… and to the investigators (for safety lab results) …"	Point rejected – the suggestion made is too specific and the intend of the statement is to keep a general approach to the reporting procedure.
402	8	Comment: Please define what is meant by the term "full data sets."	Point acknowledged – change made
404	8	Comment: The word "**draft**" has many different interpretations and implications. Proposed change (if any): Suggest changing the word "**draft**" to "**interim**"	Point acknowledged – change made
410-413	8	These lines are of very general nature and do not contain specific recommendations or requirements.	Point rejected – the intention is to provide general guidance

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		They should be deleted.	on the laboratory facility
415-416	8	Comment: The myth of cross contamination during storage! Does this mean that predose samples and placebos should be separated from other samples? Not practicable e.g. if the bioanalyst is blinded. Carry over is more likely during sample preparation but there is no instruction to perform separate analytics. This is not consistent!	Point rejected – the intention is to provide general guidance on storage of samples
418	15	Comment:incomplete Proposed change (if any):and disposal. Appropriate procedures are in place that protect personnel's hygiene and security during laboratory work. Procedures for decontaminating laboratories …	Point rejected – the intention is to provide general guidance on the need for decontamination procedures wich in principle include sampling handling by personnel – the hygiene procedure in a laboraotry goes beyond the scope of this reflection paper
421-423	8	Comment: There is also equipment which does not need to be maintained	Point noted. No changes made
424	8	Comment: Prior to use implies – every time is used, to avoid confusion suggest the following word changes Proposed change (if any): change "**prior to use"** to "**prior to commissioning"**	Point rejected: "prior to use" encompasses "prior to commissioning"
Line 424-428	6	Comment: This section requires user acceptance testing of 'analytical equipment'. The guidance does not take into account the different types of equipment used some of which may not require such level of	Point rejected: the statement "..is fit for its intended purpose" already is included.

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		testing. It is suggested that the guidance only states that equipment should be demonstrably fit for its intended purpose. Proposed change (if any):	
Line 434	16	The Guidance lack description of requirement regarding back-up procedure / business continuity plan for laboratory analysis and evaluation. This is relevant to ensure compliance with the protocol and ensure patient safety. Paragraph 6.1.16 covers computerised system back up but not laboratory test equipment.	point acknowledged: focus is given to CT samples
434-438	5	Comment: Proposed change (if any): Replace manipulation by e.g. handling, because manipulation has a rather negative touch	
435-486	8	Comment: Computerized systems section does not appear to address electronic signatures and their meaning. Suggest Reference 21 CFR Part 11	point rejected; the issue is addressed elsewhere
Line 439	6	Comment: This section requires that a responsible person should be identified to act as the administrator for each computerised system. Whilst this may be a good idea there are other ways in which adequate controls on computer systems can be exercised	Point rejected : the concept of adminstrator /person responsible for a computer system is essential to ensure maintenance of a system
455-456	8	Comment: It is unclear what the agency is requesting. Is the agency suggesting that whenever a new system	Point noted and no changes made ; the intention is to provide guidance on the need to assess the impact if a validated

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		is interfaced with LIMS one should assess its impact on the LIMS system, or is it sufficient to assess the particular new interface?	system (e.g. LIMS)
463 - 465	10	Comment: In a hospital infrastructure it might not be feasible for the laboratory to conduct retrospective validation on its existing systems if the ownership of the system lies with another department (e.g. Technology department) and the budgetary constraints do not allow clinical trials work to be prioritised amongst routine support of patient systems. In such cases, is it the expectation that the hospital laboratory would decline to test clinical trial samples? This could significantly affect the ability of those hospitals to host clinical trials. The ideal is clearly that retrospective validation would be done, but in the current economic climate this might not be achievable and might be outside the laboratory's control. Proposed change (if any):	Point noted- no changes made – the intention of this reflection paper is to provide guidance and for this particular aspect, a retrospetive validation should be done if applicable
487	8	Is GLP QA (staff/SOP/audit procedures) fit for GCP?	Point noted – no changes made - the intention of this section si to present the principles of quality assurance processes to would be applied to a laboratory involved in the analysis or evaluation of clincial trial samples
Line 487	2	Comments: Quality assurance processes are not commonly standardized in research laboratories. Proposed change (if any): Clearly state whether research labs, e.g. universities,	Point noted – refer to the scope

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		are also subjected to these QA processes	
488-556	8	Comment: QA process does not include audit and oversight of a sub-contracted lab, suggest that this be addressed	Point rejected: the ability of the sub-contractor to perform the work must be assessed prior to its initiation. This requirement is included in the section on sub-contracting.
515	8	Comment: typo, add an "s" to resource	Point acknowledged
523-535	5	Comment: Line numbers seems to show up in text Proposed change (if any):	Point noted
Line 531	16	Proposed change: Recommend adding: "*to all trials such as; sample receipt,* **sample storage**, *temperature monitoring, pipette and balance controls, and"*	Point acknowledged – changes made
Lines 536-539	1	Comment: 536-539 confuses the role and purpose of QA and QC. Requiring QA review of completed data sets before they are sent to the sponsor will delay the release and risk patient safety and expedited reporting. The QC check (558-561) is or should be an immediate and authoritative check of the assay conditions, acceptance criteria and validity of result(s) prior to lab acceptance & authorisation for their release. To address this issue a series of changes are suggested Proposed changes: • Remove lines 536-539	Point rejected – QA has a function to check the data produced by the lab

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		~~It would be appropriate for quality assurance personnel to review completed data sets and reports before they are sent to the sponsor to confirm that the analysis or evaluation of the clinical trial samples has been conducted and reported in accordance with the protocol, the contract/agreement, the work instruction and in compliance with the principles of GCP.~~ • Add to 558-561 the requirement for peer and lab manager real time QC check and signing prior to results acceptance and release. • Add to 558-561 the requirement (for the more standard assay/tests), to include implement internal QC and External Quality schemes (e.g. NEQUAS, CAP etc.) for review of key indicators of quality of laboratory operations and review of the laboratory's performance and results against external peers group laboratories and benchmarks, trended over time.	
540-546	5	Comment: CAPA is a term relevant for GMP environment, but not well applicable in a laboratory environment Proposed change (if any): "Quality assurance departments will usually take	Point rejected – the term is relevant to quality assurance processes

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		responsibility for monitoring the progress of follow-up activities to be performed after an audit"	
Lines 555-556	1	Comment: Proposed change (if any): "*A system should be implemented to ensure that the quality assurance personnel are working in accordance with their own procedures and in compliance with the principles of GCP* **where applicable."**	Point rejected: the reflection paper applies to laboratories involved in the analysis or evaluation of clinical trials samples and the principles of GCP therefore would need to be complied with.
557	8	QC procedures insufficiently described	Point acknowledged – changes made
Lines 558-561	1	Comments: As mentioned in comments in relation to lines 536-539, the following are suggested: • Please add to 558-561 the requirement for peer and lab manager real time QC check and signing prior to results acceptance and release. • Please add to 558-561 the requirement (for the more standard assay/tests), to include implement internal QC and External Quality schemes (e.g. NEQUAS, CAP etc.) for review of key indicators of quality of laboratory operations and review of the laboratory's performance and results against external peers	

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		group laboratories and benchmarks, trended over time. Proposed change (if any):	
570	8	SOP on contracts is not needed, take out	Point rejected – the need of such SOP could be relevant
570-581	8	Comment: suggest that an SOP on contracts is unnecessary and should be removed. Also, remove the word "**organised**" from line 571.	Point acknowledged – changes made
Line 576	16	Proposed change: Add: "Pr*ocedures for the receipt, storage,* **destruction** *and , processing of samples and reference materials"*	Point acknowlegded: as before
594-595	8	statement not correct. Tube labels always contain either subject ID number or barcode – if data are delivered with either of these IDs, study blinding is compromised. That has nothing to do with the unblinding code.	Point acknowledged – changes made
594-597	11	Comment: During analysis of samples from bioequivalence study the personnel in bioanalytical laboratory should be blinded.	To be discussed with the team
605	15	Comment:incomplete Proposed change (if any):…stored securely and only be accessed by authorised laboratory personnel. Each	Point acknowlegded – change made

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		access should be documented.	
606-608	5	Comment: Typo: ...with the sponsor... Proposed change (if any):	Point acknowledged: section re-phrased
608	10	Comment: Proposed change (if any):correct “responsible” to “responsibility”	Point acknowlegded
608	13	Comment: responsible should be responsibility Proposed change (if any): […] the laboratory should agree with sponsor who will take responsibility for archiving trial data.	Point acknowleged: section re-phrased
608	8	Proposed change (if any): change word responsible to responsibility	Point acknowlegded
613	15	Comment: Incomplete Proposed change (if any):Archive facilities should be available for secure storage of clinical trial data (including source data). Facilities should be …	Point acknowlegded – changes made
627	13	Comment: Remove word "robust"; simply "mechanism" covers the point. Proposed change (if any): In small organisations where separation of responsibilities is not possible,	Point acknowlegded

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		mechanisms should be adopted which ensure that the integrity of records is not compromised.	
631-632	13	Comment: A detailed log of removal of archived material should be kept to insure chain of custody of results. Proposed change (if any): Add requirement for archival check-out log book.	Point rejected – the process by which the laboratory manages loan is not the purpose of this reflection papaer
633-637	5	Comment: Considering rapid change in hardware/software being not always compatible please rephrase: o Long-term access to, and readability of, electronic information choosing an appropriate data format such as PDF, XML, etc Proposed change (if any):	Point acknowledged – changes made
638	8	Kit preparation can be taken out (not primarily the task of analytical lab)	Point rejected: the section is phrased in such a way to allow flexibility
651	8	References on important documents (BA method validation, CSV etc.) are missing	Point acknowledged – inspectors to suggest
662 - 664	14	*Comment:* We suggest to reference the MHRA guidance. *Proposed changes :* "Guidance on the maintenance of regulatory	Point rejected - Other European guidance will not be referenced. However, the sentence "to date no detailed guidance has been procedures…" in section 2. will be amended to take in account national guidances within the

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		compliance in laboratories that perform the analysis or evaluation of clinical trial samples. GCP, MHRA, issue 1 July 2009"	EU/EEA.
References	15	Comment: incomplete Proposed change (if any): IATA Dangerous Goods Regulations (DGR) Regular Bound Manual – 2011 (52nd edition)	Point rejected: reference to IATA not be included