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4 Reflection paper on guidance for laboratories that perform
5 the analysis or evaluation of clinical trial samples
6 Draft

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7 Comments should be provided using this [template](#). The completed comments form should be sent to
8 GCP@ema.europa.eu

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11 the analysis or evaluation of clinical trial samples

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44 **1. Executive summary**

45 The purpose of this guidance document is to provide laboratories that perform the analysis of samples
46 collected as part of a clinical trial, with information that will help them develop and maintain quality
47 systems which will comply with relevant European Union Directives, national regulations and
48 associated guidance documents. It will also provide information on the expectations of the inspectors
49 who may be assigned by national monitoring authorities to inspect facilities that perform work in
50 support of human clinical trials.

51 **2. Introduction**

52 Article 15 of EU Clinical Trials Directive 2001/20/EC provides provision for the inspection of laboratories
53 that perform the analysis or evaluation of samples collected as part of a clinical trial and expects
54 Member States to appoint inspectors to verify compliance with good clinical practice.

55 The analysis of samples collected from subjects participating in clinical trials forms a key part of the
56 clinical trials process. Sample analysis or evaluation provides important data on a range of endpoints
57 which is used, for example, to assess the pharmacokinetic profile of investigational medicinal products
58 and to monitor their safety and efficacy. Consequently, it is essential that sample analysis or
59 evaluation is performed to an acceptable standard which will ensure patient safety is not compromised
60 and that data is reliable and accurately reported.

61 To date no detailed guidance has been produced which outlines the expectations of national monitoring
62 authorities with respect to the analysis or evaluation of samples collect as part of a clinical trial. In the
63 absence of guidance, some laboratories apply the principles of good laboratory practice when
64 conducting clinical analysis.

65 **3. Scope**

66 This reflection paper is designed to provide guidance to laboratories and other facilities that perform
67 the analysis or evaluation of samples collected as part of a clinical trial. The guidance is designed to
68 complement existing quality systems where they exist. Inspectors are encouraged to consider the
69 scope and focus of existing quality systems before performing GCP laboratory inspections in order to
70 avoid duplication of effort.

71 The guidance does not apply to non-interventional trials.

72 **4. Legal basis**

73 This document is a reflection paper (reference to [guidelines on guidelines](#)) of the GCP Inspection
74 Working Group. The paper is intended to cover the conduct of analysis or evaluation of samples
75 collected as part of a human clinical trial conducted in the EU/EEA or where clinical trial reports are
76 submitted as part of Marketing Authorisation Applications to EU/EEA regulatory authorities. The
77 guidance has its basis in Directive 2001/20/EC and Directive 2005/28/EC, and in the Note for guidance
78 on good clinical practice (CPMP/ICH/135/95).

79 **5. Definitions**

80 "Archivist" means the person responsible for the management of the archive.

81 “Clinical Kit” means the necessary components required to collect clinical trial samples prior to their
82 analysis of evaluation in a laboratory.

83 “Computerised System” is a system (consisting of one or more hardware components and associated
84 software) that is involved with the direct or indirect capture of data, processing or manipulation of
85 data, reporting and storage of data, and may be an integral part of automated equipment. Examples
86 include: a programmable analytical instrument or a personal computer linked to a laboratory
87 information management system.

88 “Clinical trial samples” means any biological sample collected from a participant of a clinical trial as
89 required by the protocol. Samples may include but are not limited to: blood, plasma, serum, urine,
90 faeces, tissues and cells.

91 “EU Directive” means Directive 2001/20/EC of the European Parliament and the Council of 4th April
92 2001 on the approximation of the laws, regulations and administrative provisions of the Member States
93 relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal
94 products for human use and Commission Directive 2005/28/EC laying down principles and detailed
95 guidelines for good clinical practice as regards investigational medicinal products for human use, as
96 well as the requirements for authorisation of the manufacturing and importation of such products.

97 “Laboratory” means a facility that conducts manipulation, analysis or evaluation of samples collected
98 as part of a clinical trial; such analysis or evaluation may include the generation of pharmacokinetic
99 data, safety data, primary efficacy data, histopathology data or data used to support any other stated
100 end point.

101 “Laboratory management” is the individual(s) having the authority and formal responsibility for the
102 organisation and functioning of a laboratory in which work that forms part of a clinical trial is
103 conducted.

104 “Master service level agreement” is an overarching contract of general terms & conditions between two
105 parties such as a laboratory and a sponsoring organisation which may be used to underpin work for a
106 number of clinical trials. Trial-specific terms, conditions, details, roles and responsibilities are then
107 further defined in other documented agreements.

108 “Quality Assurance personnel” (QA) means, the individual(s) who are responsible for maintaining the
109 laboratories quality assurance processes. (see “Quality Assurance processes”).

110 “Quality Control” (QC) means a formal process for the systematic checking of processes and data to
111 ensure accuracy.

112 “Quality assurance processes” All those planned and systematic actions that are established to ensure
113 that the trial is performed and data are generated, documented (recorded), and reported in compliance
114 with Good Clinical Practice and the applicable regulatory requirement(s)

115 “Source Data” means, all information in original records and certified copies of original records of
116 clinical findings, observation, or other activities in a clinical trial necessary for the reconstruction and
117 evaluation of the trial. Source data are contained in source documents (original records or certified
118 copies).

119 “Source Documents” means, original documents, data, and records.

120 “Validation of a computerised system” is a documented process that demonstrates that a computerised
121 system is suitable for its intended purpose.

122 “Work instruction” is a written plan which will include, but is not limited to, the purpose of the analysis
123 and the methodology that will be used to perform the analysis. This may also be referred to as an
124 “analytical protocol” or an “analytical plan”

125 **6. Main guideline text**

126 **6.1. Guidance for Good Clinical Practice (GCP) Laboratories**

127 **6.1.1. Organisation**

128 Roles and responsibilities within a laboratory should be established and documented prior to the
129 initiation of analytical work. These will include but not be limited to identifying personnel that are
130 responsible for laboratory management, quality assurance, scientific analysis, reporting and archiving.

131 It is the responsibility of laboratory management to ensure that laboratory personnel are appropriately
132 trained to perform the roles and responsibilities assigned to them.

133 Laboratory management should ensure that each individual involved in the analysis of clinical trial
134 samples is provided with a current job description detailing the individual’s role and responsibilities
135 within the laboratory.

136 Laboratory management should ensure that there is a Quality Assurance programme with designated
137 personnel and assure that the quality assurance responsibility is being performed in accordance with
138 regulatory requirements.

139 Care should be taken not to confuse terminology. For example, a principal investigator has a specific
140 meaning in the context of a clinical trial or a GLP study. Consequently, this title should be avoided
141 when describing the position held by a scientist responsible for conducting laboratory analysis.

142 The analysis or evaluation of clinical trial samples should be overseen by a named individual(s) who
143 assumes responsibility for the conduct and reporting of the work. This individual(s) should ensure that
144 all laboratory work is performed in compliance with the protocol, any associated work instruction and
145 standard operating procedures.

146 The named individual(s) is responsible for reporting the results of the analysis or evaluation and any
147 deviations from the work instruction or protocol to the sponsor or their representative and to the
148 investigator.

149 Prior to the initiation of any analysis, the persons designated as “laboratory management” should
150 make provision to ensure that sufficient resources are available for the timely and proper conduct of
151 the analysis in accordance with the protocol, work instructions, associated methods and standard
152 operating procedures.

153 Prior to the initiation of analytical work, lines of communication should be established and documented
154 between the sponsor or their representative and the individual who is responsible for coordinating the
155 laboratory analysis.

156 **6.1.2. Personnel**

157 Procedures and systems should be implemented to ensure that individuals involved in the organisation
158 and conduct of the analysis or evaluation of samples collected as part of a clinical trial are
159 appropriately educated, experienced and trained. Laboratory personnel should be fully aware of their
160 roles and responsibilities with respect to the analysis or evaluation they are performing.

161 All staff involved in the analysis or evaluation of clinical trial samples should receive GCP training
162 commensurate with their roles and responsibilities.

163 It is appropriate for laboratory staff to receive periodic GCP refresher training. Such training is
164 especially important following changes to regulations and associated guidance documents.

165 Laboratory personnel must receive an appropriate level of technical training prior to their participation
166 in the analysis or evaluation of clinical trial samples. Specifically, laboratory management should
167 ensure that staff are competent to perform the techniques required by the protocol, work instructions
168 or associated methods.

169 A record of training should be maintained for each individual involved in the analysis or evaluation of
170 clinical trial samples. Laboratory management should ensure a copy of this information is retained
171 when staff leave the organisation.

172 If an individual has relevant experience that has been gained through previous employment, they
173 should maintain a record of this experience in addition to a record of training provided by their current
174 employer.

175 It is recommended that training records are periodically reviewed by laboratory management, signed
176 and dated to ensure the information they contain is up to date and remains relevant.

177 **6.1.3. Contracts and Agreements**

178 The analysis or evaluation of clinical trial samples may be organised in a number of different ways
179 depending on the requirements of the protocol, the type of data that is being generated, the volume of
180 samples that are received and the time lines within which data is required. In all circumstances the
181 analysis should be organised and conducted in such a way that the findings are transparent and stand
182 up to retrospective verification.

183 Contractual agreements between relevant parties should be in place prior to the initiation of any work.
184 This will usually take the form of a legally binding contract which is signed by the sponsor (or their
185 delegated representative) and laboratory management.

186 Contracts and agreements between the laboratory and the sponsor should not conflict with the
187 requirements outlined in the protocol or work instruction. It is advisable to review the contract, the
188 relevant sections of the protocol and (where applicable) the work instruction prior to the initiation of
189 laboratory analysis or evaluation in order to ensure that the documents are not contradictory and that
190 their requirements are not incompatible. It is also appropriate to ensure these agreements comply with
191 local legal regulatory and ethical requirements, and again that there are no conflicting terms.

192 If a laboratory performs analysis or evaluation of samples associated with more than one clinical trial
193 for the same sponsor, it may be appropriate to conduct the work under a "master service level
194 agreement". In such circumstances it is important to ensure that the terms and conditions stipulated in
195 the master service level agreement are applicable to all the work conducted for the sponsor in
196 question. Care must be taken to ensure that any trial-specific schedules or appendices are not over-
197 ridden by the terms of the master service level agreement.

198 The laboratory's quality system should include a documented procedure for the drafting, agreement,
199 review and revision of contracts. All contracts and agreements, including master service level
200 agreements, should be subject to periodic review to ensure that they remain up to date and relevant.
201 In cases where the contract is provided by the sponsor, the laboratory's quality system should include
202 procedures for agreement and review of contracts.

203 There is an expectation that a contract or agreement will be implemented between the laboratory and
204 any company or individual that provides a service linked to the analysis or evaluation of clinical trial
205 samples. These agreements will stipulate the nature of the service(s) provided. Examples may include:
206 companies that provide maintenance services for analytical equipment through to scientific experts
207 who are contracted to read pathology slides.

208 **6.1.4. Trial conduct**

209 Clinical analyses must be conducted in accordance with relevant EU Directives, applicable guidance and
210 the Declaration of Helsinki.

211 Under most circumstances the laboratory will be provided with a copy of the full protocol (and
212 amendments). As a minimum the laboratory should be provided with the sections of the protocol which
213 are relevant to the work that they have been contracted to perform.

214 The laboratory should be able to verify with the sponsor that the protocol (or part there of) provided is
215 current and has not been subject to amendments.

216 A mechanism should be agreed with the sponsor or their representative to ensure that any relevant
217 amendments to the protocol are supplied to the analytical laboratory.

218 Prior to the initiation of sample analysis or evaluation, it is often necessary to prepare a work
219 instruction detailing the procedures which will be used to conduct the analysis or evaluation.
220 Exceptions will include situations where all the relevant information is detailed in the protocol or the
221 contract.

222 Work instruction may take a number of different forms. However, care should be taken to ensure that
223 the work instruction contains sufficient detail for the analyst to perform their duties and to allow the
224 reconstruction of techniques used to perform the analysis or evaluation. Checks should be made to
225 ensure that the work instruction does not contradict other documents associated with the laboratory
226 analysis or evaluation, such as the contract and the protocol.

227 It is critical that the work instruction only includes work that is covered by the informed consent or
228 patient information leaflet.

229 All analysis or evaluation of clinical trial samples must be performed in accordance with the protocol. If
230 a full protocol has not been provided by the sponsor, it would be appropriate for the sponsor to confirm
231 that they have reviewed the work instruction and it does not exceed or contradict the requirements set
232 out in the full protocol.

233 Appropriate procedures should be implemented to ensure effective and timely communication with the
234 sponsor or their representative, regarding any serious deviations from the work instruction, protocol or
235 contract/agreement. Timely reporting will ensure that the sponsor or their representative are able to
236 determine the significance and impact of the deviation on the safety and well being of the trial subjects
237 and on the integrity and reliability of the trial data.

238 The impact of any deviations from the laboratory's standard operating procedures or documented
239 policies should be assessed and documented. Where there is potential for a deviation to impact on the
240 integrity or reliability of the trial data, patient or subject confidentiality, consent or safety, appropriate
241 procedures should be implemented to ensure the issue is reported to the sponsor or their
242 representative immediately.

243 Regardless of the way in which clinical analysis is organised and performed, activities should be driven
244 by documented policies or procedures. In all cases sufficient documentation must be available to
245 confirm that the conduct of the analysis is performed in a manner which assures its quality.

246 **6.1.5. Requests for additional work**

247 Laboratories should not perform any work that is not specified in the original protocol. If additional
248 work is requested by the sponsor or their representative all relevant documentation must be amended
249 prior to the initiation of the additional analysis or evaluation. The laboratory should seek a documented
250 assurance from the sponsor that the additional work does not conflict with the requirements of the
251 protocol, compromise the informed consent given by the trial subjects or impact on the ethics
252 committee approval and/or the authorisation given by the competent authority.

253 It should be noted that patient/subject safety is of primary importance. Consequently, if unscheduled
254 analysis or evaluation is required for urgent clinical reasons, for example, as a result of adverse
255 events, then it should not be delayed because it is not stipulated in the protocol, the work instruction
256 or the contract. Laboratories should maintain a documented policy detailing how they would address
257 this type of situation.

258 **6.1.6. Sub-contracting laboratory analysis**

259 If analysis or evaluation of clinical trial samples is sub-contracted to another laboratory, the ability of
260 the sub-contractor to perform the work must be assessed prior its initiation. Particular attention should
261 be paid to staff training.

262 Before placing work with a sub-contractor the sponsor, or their representative, must be informed and,
263 if necessary, the contract with the sponsor amended.

264 A contract or service level agreement must be implemented between the two laboratories prior to the
265 initiation of any work. Any such contract or service level agreement should clearly state roles and
266 responsibilities and the scope and nature of the work that will be undertaken by the sub-contractor.
267 Care should be taken to ensure that contracts do not conflict with the requirements of the protocol,
268 work instruction or the contract between the analytical laboratory and the sponsor.

269 **6.1.7. Patient/subject safety**

270 The safety of trial patients or subjects takes precedence over any other aspect of the trial.
271 Consequently, prior to the initiation of laboratory work, lines of communication should be established
272 with the sponsor, or their representative, and with the investigators, to ensure that any issues that
273 may impact on patient/subject safety are reported without delay. These may include, but are not
274 limited to, the reporting of unexpected or out of range results and significant deviations from the
275 protocol or work instructions.

276 The need to expedite the reporting of results should always be considered and discussed with the
277 sponsor or their representative prior to the initiation of any laboratory work.

278 Under most circumstances normal ranges should be established for safety tests prior to the start of
279 analysis. If clinically significant deviations from these ranges are recorded, a mechanism should be in
280 place to communicate this information to the sponsor or their representative and to the investigator as
281 quickly as possible.

282 It is always appropriate to consider the need to expedite the reporting of results regardless of the
283 nature of analysis or evaluation that is being conducted. For example, anomalous results or
284 unexpected values associated with pharmacokinetic analysis may indicate incorrect dosing or marked
285 differences in a subject's ability to metabolise an investigational medicinal product which may
286 potentially have safety implications.

287 In all cases, results and observations should be reviewed by an appropriately qualified person to
288 identify any anomalous or out of specification data. This review should be performed in a timely
289 manner.

290 In situations where the clinical laboratory, the sponsor, or their representative, and the investigators
291 are operating in different time zones or in countries with different (public) holiday allocations,
292 consideration should be given to how the laboratory would expedite the reporting of issues that may
293 impact on patient safety or well being. In such situations the laboratory should consider the
294 implementation of an agreed and tested out of hours' communication policy.

295 **6.1.8. Informed consent**

296 Prior to the initiation of a clinical trial, informed consent must be obtained from all trial subjects or
297 their legal representatives. The investigators are responsible for ensuring that the subjects enrolled on
298 a trial (and/or their legal representatives) have been provided with an appropriate level of information
299 concerning the nature of the trial and that consent has been obtained. However, laboratory
300 management personnel must exercise due diligence to ensure that the work they have been contracted
301 to conduct is covered by the consent given by the trial subjects. Mechanisms implemented to address
302 this concern may include a review of the approved protocol, or a documented dialogue with the
303 sponsor to confirm that the consent process covers the work that will be undertaken by the laboratory.
304 It may also be appropriate to include a clause in the contractual agreement between the sponsor and
305 the laboratory which stipulates the need for informed consent to cover any laboratory analysis or
306 evaluation.

307 There should be a mechanism to ensure that the laboratory is informed in a timely manner if consent
308 is withdrawn to ensure that no further data is generated or collected. While the responsibility for
309 providing this information primarily resides with the sponsor, the clinical laboratory must exercise due
310 diligence. It is therefore recommended that these factors be considered and documented in the
311 contractual agreement or other relevant documentation prior to the initiation of any analytical work.

312 **6.1.9. Sample receipt and chain of custody**

313 Samples should be transported in such a way that their integrity and viability remains unaffected. This
314 requirement should apply to all samples whether they are being transported over long distances or
315 between different departments within the same organisation. If samples are transferred from the trial
316 site to the laboratory at ambient temperature particular attention should be paid to the time the
317 samples remain in transit and the climatic conditions at the time of transit.

318 Where there is a requirement for samples to be refrigerated or frozen during transportation, measures
319 should be taken to positively confirm that the samples were maintained at an appropriate temperature
320 for the duration of time they were in transit. Best practice would include the use of data loggers to
321 monitor temperature during transit.

322 All samples received by the laboratory should be assessed on arrival to check their physical integrity. If
323 samples have been compromised in transit the sponsor should be notified promptly.

324 On receipt, laboratory staff should ensure that all samples are accounted for, this process should be
325 documented. If samples are poorly labelled, missing or if unexpected samples are received, the
326 sponsor or their representative, or the investigator, should be contacted in order to investigate and
327 resolve the issues. In most cases samples should not be analysed until their identity is confirmed.
328 However, if a delay in analysis is likely compromise the integrity of the sample as a result of instability
329 etc. the sample should be analysed and the result quarantined until the samples identity has been

330 established. If the identity of the sample can not be established the results should be destroyed.
331 Policies for dealing with missing, unexpected or poorly labelled samples should be documented.

332 Each sample received at the laboratory should be appropriately and uniquely identified. A robust
333 mechanism to track the movement of each sample from arrival to analysis or evaluation should be
334 implemented and maintained.

335 It is strongly recommended that sample receipt is subject to regular quality control checks.
336 Additionally, it is advisable to include an audit of the sample receipt processes as part of the QA
337 programme to ensure it is performed in accordance with laboratory policy. Failure to monitor the
338 receipt and accurate "booking in" of samples may have a significant impact on the integrity of data
339 produced by the laboratory.

340 On arrival, or prior to processing, each sample and requisition form should be examined to ensure that
341 its label does not display information which may identify the trial subject. If information is recorded on
342 the label which may compromise the trial subject's right to privacy, it should be masked or deleted.
343 Care should be taken not to obliterate other information which may be needed to identify the sample
344 during analysis or evaluation.

345 It would not be appropriate to permanently delete information on a label if there was no other way of
346 identifying the sample. In such cases the trial subject's personal details should be masked and a
347 unique identifier assigned to the sample by the laboratory.

348

349 The sponsor or their representative should be notified of all instances of inappropriate labelling of
350 clinical trial samples as soon as is practically possible.

351 The required sample storage conditions should be included in the work instruction or associated trial
352 documentation. These conditions must be monitored in order to provide evidence that the samples
353 have been stored in a way that ensures they remain fit for purpose.

354 Refrigerators or freezers used for the storage of clinical samples should be monitored to ensure they
355 are operating within acceptable parameters. Procedures should be implemented to ensure that prompt
356 action is taken if the acceptable parameters are breached. Evidence of monitoring and action taken in
357 the event of any excursions from the specified ranges should be documented and retained. Equipment
358 used to monitor temperature should be subject to periodic calibration.

359 Adequate provision should be made to ensure that laboratories have sufficient spare capacity for the
360 storage of chilled and frozen samples, should a refrigerator or freezer malfunction.

361 **6.1.10. Method validation**

362 In all but exceptional circumstances*, analysis should be performed using appropriately validated
363 methods with defined acceptance criteria, where appropriate. The validation of methods should be
364 documented and, on completion, this documentation should be archived.

365 Relevant storage stability data must be available if samples are to be stored for extended periods of
366 time prior to analysis.

367 Routine system suitability tests, such as the analysis of QC samples, should be considered and included
368 in the analytical methodology as required. It is important that analytical factors that may potentially
369 affect clinical trial results are considered. For example, where the laboratory is blinded it is especially
370 important that the presence of carry over is assessed.

371 *“Leading edge research analysis”. For example - the identification of potential clinical markers in*
372 *specific patient groups where the method is validated as part of the clinical trial.*

373 **6.1.11. Repeat analysis**

374 Acceptance criteria for each method of analysis and the circumstances that allow repeat analysis
375 should be clearly defined.

376 Repeat analyses should only be undertaken in accordance with a documented policy. Such a policy
377 may be detailed in a standard operating procedure, or if there are specific requirements for a particular
378 trial, this information may form part of the contract or work instruction. It is never acceptable to
379 selectively report data; consequently, the rationale for performing the repeat analysis and the reason
380 for the selection of the data points that will be reported should be transparent and must be
381 documented.

382 **6.1.12. Data recording**

383 All data should be recorded directly, promptly, accurately, and legibly. It should be possible to
384 determine the date on which the analysis or evaluation was performed and the identity of the person
385 who conducted the work.

386 It is good practice to implement a quality control procedure to ensure that all data generated in a
387 laboratory during the course of a trial is accurate and complete.

388 Any change to the data should be made so as not to obscure the previous entry. If data is generated,
389 recorded, manipulated and stored or archived electronically, it is strongly recommended that (where
390 possible) an electronic audit trail is maintained. The reason for any changes to the data should be
391 justified and the justification documented. It should be possible to determine who made the change,
392 when the change was made and for what reason.

393 **6.1.13. Reporting**

394 The way in which data will be reported should be agreed with the sponsor prior to initiation of the
395 work. This agreement should be documented in the contract or the work instructions.

396 Depending on the circumstances, it is acceptable to report data in a number of different ways. These
397 may include, a report which contains data, interpretation of results and conclusions or alternatively,
398 the results of clinical analysis may simply be supplied as electronic source data or printouts from the
399 analytical equipment used to perform the testing. Regardless of how data is reported it must be
400 accurate and complete.

401 Data may be sent to the sponsor or their representative and to the investigators as hard paper copy or
402 electronically. Which ever method is used it is advisable to ensure that full data sets have been
403 received, especially if results are sent using, for example, e-mail attachments or internet portals.

404 Draft datasets or reports which are used to make either patient-specific or trial-related decisions
405 should be retained so that the basis upon which the decisions were made can be verified.

406 It is appropriate to indicate in trial reports or other supporting documentation that the analysis or
407 evaluation of samples has been performed in compliance with the relevant national and international
408 regulations and guidance.

409 **6.1.14. Facilities**

410 Laboratories which conduct work in support of a clinical trial should be of suitable size, construction
411 and location to meet the requirements of the work being performed.

412 The design of the facility should provide an adequate degree of separation of different activities to
413 assure the proper conduct of the work.

414 In order to maintain sample integrity, consideration should be given to arrangements for sample
415 receipt, tracking and storage. It is essential that adequate and appropriate storage conditions are
416 maintained that will protect sample integrity and prevent cross-contamination.

417 Facility personnel should ensure that appropriate procedures are in place for waste storage, collection
418 and disposal. Procedures for decontaminating laboratories and their equipment should be considered
419 where relevant.

420 **6.1.15. Equipment maintenance**

421 All equipment used to conduct clinical analysis should be fit for its intended purpose. As a minimum,
422 equipment should be regularly maintained by suitably qualified persons and any maintenance
423 documented.

424 Prior to use, analytical equipment should be subject to an appropriate level of user acceptance testing,
425 by a suitably qualified person to demonstrate that the equipment is fit for its intended purpose. Any
426 such tests should be documented and the records retained as long as the trial records to which the
427 sample analyses relate (i.e. it may be necessary to retain the records beyond the decommissioning and
428 retirement of the equipment).

429 Apparatus should be periodically inspected, cleaned, maintained and calibrated according to standard
430 operating procedures or the manufacturer's manuals. Records of these activities should be maintained.
431 Calibration should, where appropriate, be traceable to national or international standards of
432 measurement. Calibration frequency will be determined by management or their representatives and
433 should be designed to ensure that all equipment remains fit for purpose.

434 **6.1.16. Computerised systems**

435 All computerised systems used for the capture, processing, manipulation, reporting and storage of data
436 should be developed, validated and maintained in ways which ensure the validity, integrity and
437 security of the data. The following points should be considered in relation to the use of computerised
438 systems:

439 A responsible person should be identified who will act as the administrator for each computerised
440 system.

441 Prior to use, all computerised systems should be subject to an appropriate level of validation. The
442 primary aim of any validation process will be to demonstrate that the computerised system is fit for its
443 intended purpose and can produce reliable and reproducible data. The scope of the validation should
444 be linked to the level of functionality that will be utilised. Validation should be performed in accordance
445 with a documented plan. All key aspects of the validation process should be documented and on
446 completion, results should be assessed by a suitably qualified person. When a computerised system is
447 deemed fit for use the decision should be documented and authorised by laboratory management or
448 their designated representative. Any limitations of the system should be clearly described in laboratory
449 procedures.

450 For each computerised system, the components (e.g. hardware and software) which constitute the
451 system should be clearly defined. This information should be documented with the associated
452 validation package.

453 If additional functionality is utilised which is beyond the scope of the original validation the need to
454 perform additional validation must be considered and, in most cases, will be required.

455 If additional computerised systems are interfaced with an existing laboratory information management
456 system (LIMS) the impact of the new equipment on the functionality of the LIMS should be assessed.

457 Following changes to computer software such as a system upgrade, or the installation of "patches", the
458 need to re-validate the computerised system should be determined. It may be appropriate to perform
459 a documented risk assessment which will determine what level of re-validation is required. Following
460 any re-validation activities, if it is deemed that the computerised system remains fit for use this
461 decision should be documented and authorised by laboratory management or their designated
462 representative.

463 If a computerised system has been in use for some time, but has never been subject to any formal
464 validation, a retrospective assessment of its suitability should be performed. The scope of any
465 retrospective validation will vary, but should always be justified and documented.

466 If the validation of a computerised system has been performed at a remote location it will usually be
467 necessary for laboratory management or their designated representative to review the validation
468 records to confirm that the system is fit for purpose. In most situations, an appropriate level of
469 validation should be performed to ensure that the system operates appropriately, following its
470 installation in the laboratory. This assessment should be documented and retained.

471 On completion, all records associated with the validation of a computerised system should be archived.

472 Computerised systems should be sited in appropriate locations. Consideration should be given to
473 environmental conditions and other external factors which may adversely impact on the systems
474 performance.

475 Disaster recovery procedures should be considered for all computerised systems. In most cases it will
476 be necessary to maintain documented policies which will describe the procedures that would be
477 followed in the event of a system failure. Such procedures may, for example, describe the measures
478 that would be taken to recover data.

479 Laboratory policies should clearly define what constitutes source documents. Source documents may
480 take a number of forms including electronic primary source data or paper hard copies. Source
481 documents must always be archived and be sufficiently detailed to ensure they can be used to
482 reconstruct the analysis, and any subsequent manipulation of data performed, during or after the
483 analysis.

484 Access to computerised systems should be controlled. The identity of those with specific access rights
485 to computerised systems should be documented and subject to periodic review to ensure that the
486 access restrictions remain current and appropriate.

487 **6.1.17. Quality Assurance (QA) processes**

488 The following guidance on quality assurance is provided to assist in the development of quality systems
489 and to provide examples of best practice.

490

491 Commission Directive 2005/28/EC require that; “the necessary procedures to secure the quality of
492 every aspect of the trials shall be complied with”. Consequently, quality systems should be developed
493 which include in-process quality control procedures and independent quality assurance audits designed
494 to ensure data integrity and safeguard patient safety and confidentiality.

495 It is strongly recommended that facilities assess and document their approach to the implementation
496 of quality assurance processes. Factors to consider in this assessment include, but are not limited to,
497 the nature of the work performed, the number of trials conducted (or samples analysed) and the
498 resources available to support the laboratory’s operations.

499 The frequency, duration and content of quality assurance checks will vary depending on the nature of
500 the work conducted by the laboratory. However, QA programmes should always be designed to assure
501 compliance with the relevant European Union Directives, associated guidance and the facility’s internal
502 policies and SOPs.

503 Quality assurance processes should be developed to ensure that:

- 504 • Patient safety and confidentiality are not compromised.
- 505 • The analysis or evaluation of clinical trial samples is conducted in accordance with the
506 principles of GCP.
- 507 • Analysis or evaluation of samples is performed in accordance with the protocol and,
508 where applicable, the contract/agreement, the work instruction and associated
509 methods.
- 510 • The laboratories policies and SOPs are adhered to.
- 511 • Trial data is recorded and reported accurately, legibly, completely and in a timely
512 manner.
- 513 • Trial data is archived.

514

515 Laboratories may appoint dedicated quality assurance personnel or alternatively resource may be
516 drawn from other areas of the organisation. However, it would be inappropriate for members of the
517 organisation who are directly involved in generating trial data to be involved in a quality assurance
518 programme. Consequently, before appointing quality assurance personnel, consideration should be
519 given to any potential conflict of interest which may undermine their effectiveness or the independence
520 of quality assurance processes.

521 Quality assurance personnel should be appropriately qualified and trained to perform the tasks
522 assigned to them. A record of their qualifications and relevant experience should be maintained.

523 It is recommended that quality assurance activities include, but are not limited to the following:

- 524 i. Regular facility audits to ensure that the laboratory and associated equipment used to conduct
525 analysis or evaluation of clinical trial samples remain fit for purpose.
- 526 ii. Periodic review of the laboratory’s quality systems, including control of standard operating
527 procedures and/or laboratory policies, archiving and the maintenance of training records.
- 528 iii. The audit of technical procedures and methodologies used to conduct the analysis or evaluation
529 of clinical trial samples.
- 530 iv. Audits performed to assess the conduct of routine and repetitive processes which are common
531 to all trials such as; sample receipt, temperature monitoring, pipette and balance controls, and

532 cleaning procedures. The most robust audit schedules will ensure that all key functions,
533 personnel and procedures are reviewed over the course of one audit cycle.

534 v. The audit of documentation generated during the validation of computerised systems or
535 analytical equipment.

536 It would be appropriate for quality assurance personnel to review completed data sets and reports
537 before they are sent to the sponsor to confirm that the analysis or evaluation of the clinical trial
538 samples has been conducted and reported in accordance with the protocol, the contract/agreement,
539 the work instruction and in compliance with the principles of GCP.

540 Quality assurance personnel should report audit findings to both laboratory management and other
541 relevant personnel within agreed timelines. Quality assurance departments will usually take
542 responsibility for monitoring the progress of corrective and preventative actions (CAPA) identified
543 during audits. It is appropriate to implement a process for escalating the requirement to perform
544 corrective actions should quality assurance personnel encounter delays or resistance from those
545 concerned. Escalation policies should be agreed with, and supported by, laboratory management if
546 they are to be effective.

547 A mechanism for informing the sponsor and the concerned investigator or coordinating investigator (as
548 appropriate) of significant deviations (those that may impact on data integrity, patient safety etc.)
549 should be agreed prior to the initiation of laboratory work.

550 Quality assurance personnel will normally require the underlying cause of a deficiency to be addressed
551 as well as the specific deficiency itself. The most effective quality assurance programmes will include a
552 documented CAPA procedure.

553 All routine quality assurance activities should be documented in standard operating procedures or
554 laboratory policies.

555 A system should be implemented to ensure that the quality assurance personnel are working in
556 accordance with their own procedures and in compliance with the principles of GCP.

557 **6.1.18. Quality Control (QC)**

558 The accuracy of data and/or specific processes, such as clinical kit preparation, should be subject to an
559 appropriate level of quality control checks. The frequency and nature of these checks will vary
560 depending on individual circumstances, but in all cases should be designed to minimise the risk of
561 mistakes which could lead to the mis-reporting of data or may compromise other key trial functions.

562 **6.1.19. Standard Operating Procedures (SOPs) and facility policies**

563 A laboratory should have written procedures that are designed to underpin the quality and integrity of
564 the data it generates. It is expected that these procedures will be periodically reviewed and authorised
565 by an appropriately qualified person. Revisions to procedures should be controlled, documented and
566 authorised. If new procedures are issued, or existing ones reviewed, the need to provide additional
567 training should be considered and where appropriate addressed and documented.

568 Standard operating procedures or documented policies should cover all key activities; examples
569 include, but are not limited to the following:

- 570 • The preparation and review of contracts and agreements.
- 571 • The way in which the analysis or evaluation of clinical trial samples is organised, performed
572 and reported.

- 573 • Issues linked to patient safety and confidentiality such as expedited reporting of results, issues
574 associated with unblinding and blinding samples and procedures for dealing with the receipt of
575 unexpected, unscheduled or poorly labelled samples.
- 576 • Procedures for the receipt, storage and processing of samples and reference materials.
- 577 • Policies that control the installation, validation, calibration, maintenance and servicing of
578 apparatus, equipment and computerised systems.
- 579 • The retention of trial data and non trial-specific records.
- 580 • Quality assurance and quality control functions.
- 581 • Clinical kit preparation.

582 Each area of the laboratory should have access to the procedures relevant to the activities being
583 conducted within that area. Published text books, analytical methods and manuals may be used to
584 supplement procedures written by the laboratory. However, consideration should be given to the
585 retention of these documents for historical reconstruction and verification purposes.

586 **6.1.20. Blinding/unblinding**

587 In many cases clinical trials will be blinded. Maintaining the integrity of the blinding process is an
588 essential part of conducting a clinical trial. If the blinding is compromised the validity of the trial may
589 be put at risk.

590 The sponsor is responsible for ensuring that appropriate measures are implemented to ensure blinded
591 individuals are not party to information which will compromise the blinding. Laboratories that perform
592 the analysis or evaluation of clinical trial samples must exercise due diligence to ensure they do not
593 inadvertently compromise the blinding process.

594 In situations where samples from blinded trials are supplied to a laboratory without an unblinding
595 code, there is little danger that the laboratory will be in a position to compromise the blinding process.
596 However, it is still important that data is only sent to an established point of contact at the sponsoring
597 organisation.

598 It is not uncommon for analytical laboratories to be asked to unblind trials so that analysis is not
599 performed on samples collected from trial subjects that have been given a placebo treatment. In such
600 cases, it is imperative that the laboratory has a documented policy(ies) detailing how results will be
601 communicated to the sponsor or their representative. Such policies may cover the reblinding of
602 samples and safeguards that have been implemented to ensure that unblinded results are not
603 disseminated in a manner that may comprise the integrity of the trial.

604 If laboratories are supplied with the codes necessary to unblind trial samples this information should be
605 stored securely and only be accessed by authorised laboratory personnel.

606 **6.1.21. Retention of data**

607 Prior to the initiation of experimental work the laboratory should agree with sponsor who will take
608 responsible for archiving trial data.

609 If the sponsor requests that source documents are returned to them on completion of the work for
610 archiving, the laboratory should retain verified copies of the source documents for at least one
611 inspection cycle (an inspection cycle will be dictated by each member states inspection frequency) in
612 order to demonstrate that they are operating in compliance with the GCP regulations.

613 Archive facilities should be available for the secure storage of clinical trial data. Facilities should be
614 suitably designed and constructed to accommodate the types of material that will be archived. Archive
615 design and environmental conditions should protect contents from untimely deterioration and should
616 safeguard the confidentiality of any trial participants.

617 Archives may take a number of different forms including a building or room specifically designated for
618 the retention of trial materials, a fireproof safe or lockable cabinet. All archive facilities must be secure
619 to prevent unauthorised access to the retained materials.

620 Non trial-specific data such as equipment validation and maintenance records, staff training records,
621 quality assurance reports, SOPs etc. should be retained in a secure archive to facilitate the
622 reconstruction of clinical trials and also provide evidence of compliance, with the GCP regulations,
623 during regulatory inspections.

624 Access to the archive should be restricted to designated member(s) of staff. In most instances a
625 dedicated archivist will be appointed. Personnel responsible for the archive will normally not be
626 involved with the generation of data or supporting records that are passed into their care. In small
627 organisations where separation of responsibilities is not possible, robust mechanisms should be
628 adopted which ensure that the integrity of records is not compromised.

629 Procedures for the removal of material from the archive and its subsequent return should be
630 documented.

631 If materials are removed from the archive they should be returned in a timely manner. On their return
632 adequate checks should be performed to verify that all loaned material has been accounted for.

633 Requirements for the archiving of electronic records are the same as those for other record types.
634 However there are a number of specific issues which should be considered such as:

- 635 • Long-term access to, and readability of, electronic information
- 636 • The shelf-life of the storage medium where appropriate (CD-ROM, DVD, floppy disks etc.)
- 637 • QC checks following data migration to a secure server or other storage medium.

638 **6.1.22. Preparation and distribution of clinical kits**

639 It is not uncommon for analytical laboratories to prepare and distribute clinical kits used for the
640 collection of trial samples. If such activities are undertaken the following points should be considered.

641 A documented agreement should be implemented between the sponsor and the laboratory which
642 includes: information on the content of each kit, shipment details (destination names and address) and
643 the number of kits required.

644 Areas designated for the preparation of clinical kits should be fit for purpose. They should be large
645 enough to allow a clear separation of activities and environmental conditions should be monitored.

646 Kit components must be stored in conditions that assure the integrity of any active ingredients.
647 Particular attention should be paid to expiry dates.

648 Kit preparation must be subject to an acceptable level of quality control monitoring which will ensure
649 that each kit contains the correct components and that associated labelling is accurate and readable.

650 The laboratory must make appropriate provision for the resupply of clinical kits at short notice.

651 **7. References**

652 Directive 2001/20/EC of the European parliament and of the Council of 4 April 2001 on the
653 approximation of the laws, regulations and administrative provisions of the Member States relating to
654 the implementation of good clinical practice in the conduct of clinical trials on medicinal products for
655 human use.

656 Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for
657 good clinical practice as regards investigational medicinal products for human use, as well as the
658 requirements for authorisation of the manufacturing or importation of such products.

659 Note for guidance on good clinical practice (CPMP/ICH/135/95)

660 Declaration of Helsinki adopted by the World Medical Assembly in June 1964, and subsequent
661 amendments as referenced in Directive 2005/28/EC, Chapter 2, Article 3.

662 Guidelines on guidelines:

663 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC50000401
664 [1.pdf](#)