

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

DRAFT CONSENSUS GUIDELINE

**GOOD MANUFACTURING PRACTICE GUIDE FOR
ACTIVE PHARMACEUTICAL INGREDIENTS**

Released for Consultation
at *Step 2* of the ICH Process
on 19 July 2000
by the ICH Steering Committee

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

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Draft ICH Consensus Guideline

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GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS

1. INTRODUCTION

1.1 Objective

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to ensure that all APIs meet requirements for quality and purity which they purport or are represented to possess.

In this Guide “manufacturing” is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this Guide the term “should” indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms “current good manufacturing practices” and “good manufacturing practices” are equivalent.

The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This Guide is not intended to define registration/filing requirements or modify pharmacopeial requirements. This Guide does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.

1.2 Regulatory Applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be produced according to this Guide.

1.3 Scope

This Guide applies to the manufacture of APIs for use in human drug (medicinal) products including sterile APIs only up to the point immediately prior to the API being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities.

This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, or by recovery from natural sources, or any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18. The intermediates and API's produced by recombinant DNA technology will be included for the purpose of this Guide provided they are proteinacious materials.

This Guide excludes all vaccines, whole cells, whole blood and plasma, and APIs derived from them (plasma fractionation). However, it does include APIs that are

45 produced using blood or plasma as raw materials. Note that cell substrates
46 (mammalian, plant, or microbial cells, tissue or animal sources including
47 transgenic animals) and early process steps may be subject to GMP but are not
48 covered by this Guide. In addition, the Guide does not apply to medical gases,
49 bulk-packaged drug (medicinal) products, and manufacturing/control aspects
50 specific to radiopharmaceuticals.

51 Section 19 contains guidance that only applies to the manufacture of APIs used in
52 the production of drug (medicinal) products specifically for clinical trials
53 (investigational medicinal products).

54 An "API Starting Material" is a material used in the production of an API which is
55 incorporated as a significant structural fragment into the structure of the API. An
56 API Starting Material may be an article of commerce, a material purchased from
57 one or more suppliers under contract or commercial agreement, or it may be
58 produced in-house. API Starting Materials normally have defined chemical
59 properties and structure.

60 The company should designate and document the rationale for the point at which
61 production of the API begins. For synthetic processes this is known as the point at
62 which "API Starting Materials" are entered into the process. For other processes
63 (e.g. fermentation, extraction, purification, etc), this rationale should be
64 established on a case by case basis.

65 From this point on appropriate GMP as defined in this Guide should be applied to
66 these intermediate and/or API manufacturing steps. This would include the
67 validation of critical process steps determined to impact the quality of the API.
68 However it should be noted that the fact that a company chooses to validate a
69 process step does not necessarily define that step as critical.

70 The guidance in this document would normally be applied to the steps shown in
71 gray in the table on the next page. The table is an example; it does not imply that
72 all steps shown must be completed. The stringency of GMP in API manufacturing
73 should increase as the process proceeds from early API steps to final steps,
74 purification, and packaging. Physical processing of APIs such as granulation,
75 coating or physical manipulation of particle size (e.g. milling, micronizing) should
76 be conducted at least to the standards of this Guide.

77 This GMP Guide does not apply to steps prior to the introduction of the defined
78 "API Starting Material".

79

Type of Manufacturing	Application of this Guide to steps used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Biotech/ fermentation cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging

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86 **2. QUALITY MANAGEMENT**

87 **2.1 Principles**

88 2.10 Quality should be the responsibility of all persons involved in manufacturing.

89 2.11 Each manufacturer should establish, document, and implement an effective
90 system for managing quality that involves the active participation of
91 management and appropriate manufacturing personnel.

92 2.12 The system for managing quality should encompass the organisational
93 structure, procedures, processes and resources, as well as activities
94 necessary to ensure confidence that the API will meet its intended
95 specifications for quality and purity. All quality related activities should be
96 defined and documented.

97 2.13 All quality related activities should be recorded at the time they are
98 performed.

99 2.14 Any deviation from established procedures should be documented and
100 explained. Critical deviations should be investigated, and the investigation
101 and its conclusions should be documented.

102 2.15 Procedures should exist for notifying responsible management in a timely
103 manner of regulatory inspections, serious GMP deficiencies, product defects
104 and related actions (e.g. quality related complaints, recalls, regulatory
105 actions, etc.).

106 2.16 There should be a quality unit(s) which is independent of production, and
107 which fulfills both quality assurance (QA) and quality control (QC)
108 responsibilities. This may be in the form of separate QA and QC units or a
109 single individual (or group), depending upon the size and structure of the
110 organization.

111 2.17 No materials should be released or used before the satisfactory completion of
112 evaluation by the quality unit(s) unless there are appropriate systems in
113 place to allow for such use (e.g. release under quarantine as described in
114 Section 10.20 or the use of raw materials or intermediates pending
115 completion of evaluation).

116 2.18 The persons authorised to release intermediates and APIs should be
117 specified.

118 **2.2 Responsibilities of the Quality Unit(s)**

119 2.20 The quality unit(s) should be involved in all quality-related matters.

120 2.21 The quality unit(s) should review and approve all appropriate quality related
121 documents.

122 2.22 The main responsibilities of the independent quality unit(s) / should not be
123 delegated. These responsibilities should be described in writing, and should
124 include but not necessarily be limited to:

- 125 1. Releasing or rejecting all APIs;
- 126 2. Establishing a system to release or reject raw materials, intermediates,
127 packaging and labelling materials;

- 128 3. Reviewing completed manufacturing records for critical process steps
129 before release of the API for distribution;
- 130 4. Making sure that critical deviations are investigated and resolved;
- 131 5. Approving all specifications and master production instructions;
- 132 6. Approving all procedures potentially impacting the quality of
133 intermediates or APIs;
- 134 7. Making sure that internal audits (self-inspections) are performed;
- 135 8. Approving intermediate and API contract manufacturers;
- 136 9. Approving changes that potentially impact intermediate or API quality;
- 137 10. Reviewing and approving validation protocols and reports;
- 138 11. Making sure that quality related complaints are investigated and
139 resolved;
- 140 12. Making sure that effective systems are used for maintaining and
141 calibrating critical equipment;
- 142 13. Making sure that materials are appropriately tested and the results are
143 reported;
- 144 14. Making sure that there is stability data to support retest or expiry dates
145 and storage conditions on intermediates and/or APIs where appropriate;
146 and
- 147 15. Performing product quality reviews (as defined in Section 2.5)

148 **2.3 Responsibility for production activities**

149 The responsibility for production activities should be described in writing, and
150 should include but not necessarily be limited to:

- 151 1. Preparing, reviewing, approving and distributing the instructions for the
152 production of intermediates or APIs according to written procedures;
- 153 2. Producing APIs and, when appropriate, intermediates according to pre-
154 approved instructions;
- 155 3. Reviewing all production batch records and ensuring that these are
156 completed and signed;
- 157 4. Making sure that all production deviations are reported and evaluated and
158 that critical deviations are investigated and the conclusions are recorded;
- 159 5. Making sure that production facilities are clean and when necessary
160 disinfected;
- 161 6. Making sure that the necessary calibrations are performed and records
162 kept;
- 163 7. Making sure that the premises and equipment are maintained and records
164 kept;
- 165 8. Making sure that validation plans, protocols and reports are reviewed and
166 approved;
- 167 9. Evaluating proposed changes in product, process or equipment; and

168 10. Making sure that new and, when appropriate, modified facilities and
169 equipment are qualified.

170 **2.4 Internal Audits (Self Inspection)**

171 2.40 In order to verify compliance with the principles of GMP for APIs, regular
172 internal audits should be performed in accordance with an approved
173 schedule.

174 2.41 Audit findings and corrective actions should be documented and brought to
175 the attention of responsible management of the firm. Agreed corrective
176 actions should be completed in a timely and effective manner.

177 **2.5 Product Quality Review**

178 2.50 Regular quality reviews of APIs should be conducted with the objective of
179 verifying the consistency of the process. Such reviews should normally be
180 conducted and documented annually and should include at least:

- 181 - A review of critical in-process control and critical API test results;
- 182 - A review of all batches which failed to meet established specifications;
- 183 - A review of all critical deviations or non-conformances and related
184 investigations;
- 185 - A review of any changes carried out to the processes or analytical methods;
- 186 - A review of results of the stability monitoring program;
- 187 - A review of all quality related returns, complaints and recalls; and
- 188 - A review of adequacy of corrective actions.

189 2.51 The results of this review should be evaluated and an assessment made of
190 whether corrective action or any revalidation is necessary. The necessity for
191 such corrective action should be documented. Agreed corrective actions
192 should be completed in a timely and effective manner.

193 **3. PERSONNEL**

194 **3.1 Personnel Qualifications**

195 3.10 There should be an adequate number of personnel qualified by appropriate
196 education, training and/or experience to perform and supervise the
197 manufacture of intermediates and APIs.

198 3.11 The responsibilities of all personnel engaged in the manufacture of
199 intermediates and APIs should be specified in writing.

200 3.12 Training should be regularly conducted by qualified individuals and should
201 cover at a minimum the particular operations that the employee performs
202 and GMP as it relates to the employee's functions. Records of training should
203 be maintained. The practical effectiveness of the training should be
204 periodically assessed.

205 **3.2 Personnel Hygiene**

206 3.20 Personnel should practice good sanitation and health habits.

207 3.21 Personnel should wear clean clothing suitable for the manufacturing activity
208 with which they are involved and this clothing should be changed when
209 necessary. Additional protective apparel, such as head, face, hand, and arm
210 coverings, should be worn when necessary, to protect intermediates and APIs
211 from contamination.

212 3.22 Personnel should avoid direct contact with intermediates or APIs.

213 3.23 Smoking, eating, drinking, chewing and the storage of food should be
214 restricted to certain designated areas separate from the manufacturing areas.

215 3.24 Personnel suffering from an infectious disease or having open lesions on the
216 exposed surface of the body should not engage in activities, that could result
217 in compromising the quality of APIs. Any person shown at any time (either by
218 medical examination or supervisory observation) to have an apparent illness
219 or open lesions that may adversely affect the safety or quality of APIs should
220 be excluded from direct contact with APIs until the condition is corrected or
221 qualified medical personnel determine that the person's inclusion would not
222 jeopardize the safety or quality of the APIs.

223 **3.3 Consultants**

224 3.30 Consultants advising on the manufacture and control of intermediates or
225 APIs should have sufficient education, training, and experience, or any
226 combination thereof, to advise on the subject for which they are retained.

227 3.31 Records should be maintained stating the name, address, qualifications, and
228 type of service provided by these consultants.

229 **4. BUILDINGS AND FACILITIES**

230 **4.1 Design and Construction**

231 4.10 Buildings and facilities used in the manufacture of intermediates and APIs
232 should be located, designed, and constructed to facilitate cleaning,
233 maintenance, and operations as appropriate to the type and stage of
234 manufacture. Facilities should also be designed to minimize potential
235 contamination. Where microbiological specifications have been established
236 for the intermediate or API, facilities should also be designed to limit
237 exposure to objectionable microbiological contaminants as appropriate.

238 4.11 Buildings and facilities should have adequate space for the orderly placement
239 of equipment and materials to prevent mix-ups and contamination.

240 4.12 Where the equipment itself (e.g., closed or contained systems) provides
241 adequate protection of the material, such equipment may be located outdoors.

242 4.13 The flow of materials and personnel through the building or facilities should
243 be designed to prevent mix-ups or contamination.

244 4.14 There should be defined areas or other control systems for the following
245 activities:

246 - Receipt, identification, sampling, and quarantine of incoming materials,
247 pending release or rejection;

248 - Quarantine before release or rejection of intermediates and APIs;

249 - Sampling of intermediates and APIs;

- 250 - Holding rejected materials before further disposition (e.g., return,
251 reprocessing or destruction);
- 252 - Storage of released materials;
- 253 - Production operations;
- 254 - Packaging and labelling operations; and
- 255 - Control and laboratory operations.

256 4.15 Adequate and clean washing facilities should be provided for personnel.
257 These washing facilities should be equipped with hot and cold water as
258 necessary, soap or detergent, air driers or single service towels. The washing
259 and toilet facilities should be separate from, but easily accessible to,
260 manufacturing areas. Adequate facilities for showering and/or changing
261 clothes should be provided when appropriate.

262 4.16 Laboratory areas/operations should normally be separated from production
263 areas. Some laboratory areas, in particular those used for in-process controls,
264 may be located in production areas, provided the operations of the production
265 process do not adversely affect the accuracy of the laboratory measurements,
266 and the laboratory and its operations do not adversely affect the production
267 process or intermediate or API.

268 **4.2 Utilities**

269 4.20 All utilities that could impact on product quality (e.g. steam, gases, and
270 compressed air) should be qualified and appropriately monitored to ensure
271 that specifications are met and action is taken when limits are exceeded.

272 4.21 Adequate ventilation and exhaust systems should be provided, where
273 necessary. These systems should be designed and constructed to minimise
274 risks of contamination and cross-contamination and should include
275 equipment for control of air pressure, microorganisms (if appropriate), dust,
276 humidity, and temperature, as appropriate to the stage of manufacture.
277 Particular attention should be given to areas where APIs are exposed to the
278 environment.

279 4.22 If air is recirculated to production areas, appropriate measures should be
280 taken to control risks of contamination and cross-contamination.

281 4.23 Permanently installed pipework should be appropriately identified. This can
282 be accomplished by identifying individual lines, documentation, computer
283 control systems, or alternative means. Pipework should be located to avoid
284 risks of contamination of the intermediate or API.

285 4.24 Drains should be of adequate size and should be provided with an air break or
286 a suitable device to prevent back-siphonage, when appropriate.

287 **4.3 Water**

288 4.30 Water used in the manufacture of APIs should be demonstrated to be suitable
289 for its intended use.

290 4.31 Unless otherwise justified, process water should, at a minimum, meet
291 national standards for potable water that have been documented as at least
292 equivalent to World Health Organization (WHO) guidelines. In the absence
293 of national standards, WHO guidelines should be used.

294 4.32 If potable water standards are insufficient to assure API quality and tighter
295 chemical and microbiological water quality specifications are necessary,
296 appropriate specifications for physical/chemical attributes, total microbial
297 counts, objectionable organisms and/or endotoxins should be established.

298 4.33 Where water used in the process is treated by the manufacturer to achieve
299 defined quality, the treatment process should be validated and monitored
300 with appropriate action limits.

301 4.34 Where the manufacturer of a non-sterile API either intends or claims that it
302 is suitable to be used in further processing to produce a sterile drug
303 (medicinal) product, then water used in the final isolation and purification
304 steps should be monitored and controlled for total microbial counts,
305 objectionable organisms, and endotoxins.

306 **4.4 Containment**

307 4.40 Dedicated production areas, which may include such facilities as air handling
308 equipment and/or process equipment, should be employed in the production
309 of each type of highly sensitizing material (e.g., penicillins or cephalosporins).

310 4.41 Dedicated production areas should also be considered when material of an
311 infectious nature or high pharmacological activity or toxicity is involved (e.g.,
312 certain steroids or cytotoxic anti-cancer agents) unless validated inactivation
313 and/or cleaning procedures are established and maintained.

314 4.42 Appropriate measures should be established and implemented to prevent
315 cross-contamination from personnel, materials, etc. moving from one
316 dedicated area to another.

317 4.43 Any production activities (including weighing, milling, or packaging) of
318 highly toxic non-pharmaceutical materials such as herbicides and pesticides
319 should not be conducted using the buildings and/or equipment being used for
320 the production of APIs. Handling and storage of these highly toxic non-
321 pharmaceutical materials should be separate from APIs.

322 **4.5 Lighting**

323 4.50 Adequate lighting should be provided in all areas to facilitate cleaning,
324 maintenance, and proper operations.

325 **4.6 Sewage and Refuse**

326 4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products
327 from manufacturing) in and from buildings and the immediate surrounding
328 area should be disposed of in a safe, timely, and sanitary manner. Containers
329 and/or pipes for waste material should be clearly identified.

330 **4.7 Sanitation and Maintenance**

331 4.70 Buildings used in the manufacture of intermediates and APIs should be
332 properly maintained and repaired and kept in a clean condition.

333 4.71 Written procedures should be established assigning responsibility for
334 sanitation and describing the cleaning schedules, methods, equipment, and
335 materials to be used in cleaning buildings and facilities.

336 4.72 When necessary, written procedures should also be established for the use of
337 suitable rodenticides, insecticides, fungicides, fumigating agents, and
338 cleaning and sanitizing agents to prevent the contamination of equipment,
339 raw materials, packaging/labelling materials, intermediates, and APIs.

340 **5. PROCESS EQUIPMENT**

341 **5.1 Design and Construction**

342 5.10 Equipment used in the manufacture of intermediates and APIs should be of
343 appropriate design and adequate size, and suitably located for its intended
344 use, cleaning, sanitization (where appropriate), and maintenance.

345 5.11 Equipment should be constructed so that surfaces that contact raw materials,
346 intermediates, or APIs do not alter the quality of the intermediates and APIs
347 beyond the official or other established specifications.

348 5.12 Production equipment should only be used within its qualified operating
349 range.

350 5.13 Major equipment (e.g., reactors, storage containers) and permanently
351 installed processing lines used during the production of an intermediate or
352 API should be appropriately identified.

353 5.14 Any substances necessary for the operation of equipment, such as lubricants,
354 heating fluids or coolants, should not contact intermediates or APIs so as to
355 alter their quality beyond the official or other established specifications. Any
356 deviations from this should be evaluated to ensure that there are no
357 detrimental effects upon the fitness for purpose of the material. Wherever
358 possible food grade lubricants and oils should be used.

359 5.15 Closed or contained equipment should be used whenever appropriate. Where
360 open equipment is used, or equipment is opened, appropriate precautions
361 should be taken to minimize contamination.

362 5.16 A set of current drawings should be maintained for equipment and critical
363 installations (e.g., instrumentation and utility systems).

364 **5.2 Equipment Maintenance and Cleaning**

365 5.20 Schedules and procedures (including assignment of responsibility) should be
366 established for the preventative maintenance of equipment.

367 5.21 Written procedures should be established for cleaning of equipment and its
368 subsequent release for use in the manufacture of intermediates and APIs.
369 Cleaning procedures should contain sufficient details to enable operators to
370 clean each type of equipment in a reproducible and effective manner. These
371 procedures should include, but should not be limited to:

- 372 - Assignment of responsibility for cleaning of equipment;
- 373 - Cleaning schedules, including, where appropriate, sanitizing schedules;
- 374 - A complete description of the methods and materials, including dilution of
375 cleaning agents used to clean equipment;
- 376 - When appropriate, instructions for disassembling and reassembling each
377 article of equipment to ensure proper cleaning;

- 378 - Instructions for the removal or obliteration of previous batch
379 identification;
- 380 - Instructions for the protection of clean equipment from contamination
381 prior to use;
- 382 - Inspection of equipment for cleanliness immediately before use, if
383 practical; and
- 384 - Establishing the maximum time that may elapse between the completion of
385 processing and equipment cleaning, when appropriate.
- 386 5.22 Equipment and utensils should be cleaned, stored, and, where necessary,
387 sanitized or sterilized to prevent contamination or carry-over of a material
388 that would alter the quality of the intermediate or API beyond the official or
389 other established specifications.
- 390 5.23 Where equipment is assigned to continuous production or campaign
391 production of successive batches of the same intermediate or API, equipment
392 should be cleaned at appropriate intervals to prevent build-up and carry-over
393 of contaminants (e.g. degradants) or objectionable levels of micro-organisms.
- 394 5.24 Non-dedicated equipment should be cleaned between production of different
395 materials to prevent cross-contamination.
- 396 5.25 Acceptance criteria for residues and the choice of cleaning procedures and
397 cleaning agents should be defined and justified.
- 398 5.26 Equipment should be identified as to its contents and its cleanliness status by
399 appropriate means.
- 400 **5.3 Calibration**
- 401 5.30 Control, weighing, measuring, monitoring and test equipment that is critical
402 for assuring the quality of intermediates or APIs should be calibrated
403 according to written procedures and an established schedule.
- 404 5.31 Equipment calibrations should be performed using standards traceable to
405 certified standards, if existing.
- 406 5.32 Records of these calibrations should be maintained.
- 407 5.33 The current calibration status of critical equipment should be known and
408 verifiable.
- 409 5.34 Instruments that do not meet calibration criteria should not be used.
- 410 5.35 Deviations from approved standards of calibration on critical instruments
411 should be investigated to determine if these could have had an impact on the
412 quality of the intermediate(s) or API(s) manufactured using this equipment
413 since the last successful calibration.
- 414 **5.4 Computerized Systems**
- 415 5.40 GMP related computerized systems should be validated. The depth and
416 scope of validation depends on the diversity, complexity and criticality of the
417 computerized application.

- 418 5.41 Appropriate installation qualification and operational qualification should
419 demonstrate the suitability of computer hardware and software to perform
420 assigned tasks.
- 421 5.42 Commercially available software that has been qualified does not require the
422 same level of testing. If an existing system was not validated at time of
423 installation, a retrospective validation may be conducted if appropriate
424 documentation is available.
- 425 5.43 Computerized systems should have sufficient controls to prevent
426 unauthorized access or changes to data. There should be controls to prevent
427 omissions in data (e.g. system turned off and data not captured). There should
428 be a record of any data change made, the previous entry, who made the
429 change, and when the change was made.
- 430 5.44 Written procedures should be available for the operation and maintenance of
431 computerized systems.
- 432 5.45 Where critical data are being entered manually, there should be an additional
433 check on the accuracy of the entry. This may be done by a second operator or
434 by the system itself.
- 435 5.46 Incidents related to computerized systems that could affect the quality of
436 intermediates or APIs or the reliability of records or test results should be
437 recorded and investigated.
- 438 5.47 All changes to the computerized system should be made according to a change
439 procedure and should be formally authorized, documented and tested.
440 Records should be kept of all changes including modifications and
441 enhancements made to the hardware, software and any other critical
442 component of the system to demonstrate that the final system is maintained
443 in a validated state.
- 444 5.48 If system breakdowns or failures would result in the permanent loss of
445 records then a back-up system should be provided. A means of ensuring data
446 protection should be established for all computerized systems.
- 447 5.49 Recording data by a second means in addition to the computer system is
448 acceptable to provide a backup data source.

449 **6. DOCUMENTATION AND RECORDS**

450 **6.1 Documentation System and Specifications**

- 451 6.10 All documents related to the manufacture of intermediates or APIs should be
452 prepared, reviewed, approved and distributed according to written
453 procedures. Such documents may be in paper or electronic form.
- 454 6.11 The issuance, revision, superseding and withdrawal of all documents should
455 be controlled with maintenance of revision histories.
- 456 6.12 A procedure should be established for retaining all appropriate documents
457 (e.g., development history reports, scale-up reports, technical transfer
458 reports, process validation reports, training records, production records,
459 control records, and distribution records). The retention periods for these
460 documents should be specified.

- 461 6.13 All production, control, and distribution records should be retained for at
462 least one year after the expiry date of the batch. For APIs with retest dates,
463 records should be retained for at least three years after the batch is
464 completely distributed.
465
- 466 6.14 When entries need to be made in records, these should be made indelibly in
467 spaces provided for such entries, directly after performing the activities (in
468 the order performed), and should identify the person making the entry.
469 Corrections to entries should be dated and signed and leave the original
470 entry still readable.
- 471 6.15 All records or copies of such records, should be readily available during the
472 retention period at the establishment where the activities described in such
473 records occurred. Records that can be promptly retrieved from another
474 location by electronic or other means are acceptable.
- 475 6.16 Specifications, instructions, procedures, and records may be retained either
476 as originals or as true copies such as photocopies, microfilm, microfiche, or
477 other accurate reproductions of the original records. Where reduction
478 techniques such as microfilming or electronic records are used, suitable
479 retrieval equipment and a means to produce a hard copy should be readily
480 available.
- 481 6.17 Specifications should be established and documented for raw materials,
482 intermediates where necessary, APIs and labelling and packaging materials.
483 In addition, specifications may be necessary for certain other materials, such
484 as process aids, gaskets, or other materials used during the production of
485 intermediates or APIs that would critically impact on quality. Acceptance
486 criteria should be established and documented for in-process controls.
- 487 6.18 Electronic signatures on documents are acceptable, provided they are
488 authenticated and secure.

489 **6.2 Equipment Cleaning and Use Record**

- 490 6.20 Records of major equipment use, cleaning, sanitization and/or sterilization
491 and maintenance should show the date, time (if appropriate), product, and
492 batch number of each batch processed in the equipment, and the person who
493 performed the cleaning and maintenance.
- 494 6.21 If equipment is dedicated to manufacturing one intermediate or API, then
495 individual equipment records are not necessary if batches of the intermediate
496 or API follow in traceable sequence. In cases where dedicated equipment is
497 employed, the records of cleaning, maintenance, and use may be part of the
498 batch record or may be maintained separately.

499 **6.3 Records of Raw Materials, Intermediates, API Labelling and** 500 **Packaging Materials**

- 501 6.30 Records should be maintained including:
- 502 - The name of the manufacturer, identity and quantity of each shipment of
503 each batch of raw materials, intermediates or labelling and packaging
504 materials for API's; the name of the supplier; the supplier's control

- 505 number(s), if known, or other identification numbe; the number allocated
506 on receipt; and the date of receipt;
- 507 - The results of any test or examination performed and the conclusions
508 derived from this;
- 509 - Records tracing the use of materials;
- 510 - Documentation of the examination and review of API labelling and
511 packaging materials for conformity with established specifications; and
- 512 - The final decision regarding rejected raw materials, intermediates or API
513 labelling and packaging materials.
- 514 6.31 Master (approved) labels should be maintained for comparison to issued
515 labels.

516 **6.4 Master Production Instructions (Master Production and Control**
517 **Records)**

518 6.40 To ensure uniformity from batch to batch, master production instructions for
519 each intermediate and API should be prepared, dated, and signed by one
520 person and independently checked, dated, and signed by a person in the
521 quality unit(s).

522 6.41 Master production instructions should include:

- 523 - The name of the intermediate or API being manufactured and an
524 identifying document reference code, if applicable;
- 525 - A complete list of raw materials and intermediates designated by names or
526 codes sufficiently specific to identify any special quality characteristics;
- 527 - An accurate statement of the quantity or ratio of each raw material or
528 intermediate to be used, including the unit of measure. Where the
529 quantity is not fixed, the calculation for each batch size or rate of
530 production should be included. Reasonable variations are permitted
531 provided they are justified;
- 532 - The production location and major production equipment to be used;
- 533 - Detailed production instructions, including the:
- 534 - sequences to be followed,
- 535 - ranges of process parameters to be used,
- 536 - sampling instructions and in-process controls with their acceptance
537 criteria, where appropriate,
- 538 - time limits for completion of individual processing steps and/or the
539 total process, where appropriate; and
- 540 - expected yield ranges at appropriate phases of processing or time;
- 541 - Where appropriate, special notations and precautions to be followed, or
542 cross-references to these; and
- 543 - The instructions for storage of the intermediate or API to assure its
544 suitability for use, including the labelling and packaging materials and
545 special storage conditions with time limits where appropriate.

546 **6.5 Batch Production Records (Batch Production and Control**
547 **Records)**

548 6.50 Batch production records should be prepared for each intermediate and API
549 and should include complete information relating to the production and
550 control of each batch. The batch production record should be checked before
551 issuance to assure that it is the correct version and a legible accurate
552 reproduction of the appropriate master production instruction. If the batch
553 production record is produced from a separate master document, that
554 document must include a reference to the current master production
555 instruction being used.

556 6.51 These records should be numbered with a unique batch or identification
557 number, dated and signed when issued. In continuous production the product
558 code together with the date and time may serve as the unique identifier until
559 the final number is allocated.

560 6.52 Written procedures should be established and followed for investigating
561 critical deviations or the failure of a batch of intermediate or API to meet
562 specifications. The investigation should extend to other batches that may
563 have been associated with the specific failure or deviation.

564 6.53 Intermediates and APIs failing to meet established specifications should be
565 identified as such and quarantined. Written procedures should be followed if
566 these materials are reprocessed or reworked. The final disposition of rejected
567 materials should be recorded.

568 6.54 Documentation of completion of each significant step in the batch production
569 records (batch production and control records) should include:

- 570 - Dates and, when appropriate, times;
- 571 - Identity of major equipment (e.g., reactors, driers, mills, etc.) used;
- 572 - Specific identification of each batch, including weights, measures, and
573 batch numbers of raw materials, intermediates, or any reprocessed
574 materials used during manufacturing;
- 575 - Actual results recorded for critical process parameters;
- 576 - Any sampling performed;
- 577 - Signatures of the persons performing and directly supervising or checking
578 each critical step in the operation;
- 579 - In-process and laboratory test results;
- 580 - Actual yield at appropriate phases or times;
- 581 - Description of packaging and label for intermediate or API;
- 582 - Representative label of API or intermediate if made commercially
583 available;
- 584 - Any deviation noted, its evaluation, investigation conducted (if
585 appropriate) or reference to that investigation if stored separately; and
- 586 - Results of release testing.

587 **6.6 Laboratory Control Records**

588 6.60 Laboratory control records should include complete data derived from all
589 tests necessary to ensure compliance with established specifications and
590 standards, including examinations and assays, as follows:

- 591 - A description of samples received for testing, including the material name
592 or source, batch number or other distinctive code, date sample was taken,
593 and, where appropriate, the quantity and date the sample was received for
594 testing;
- 595 - A statement of or reference to each test method used;
- 596 - A statement of the weight or measure of sample used for each test as
597 described by the method; data on or cross-reference to the preparation and
598 testing of laboratory reference standards, reagents and standard solutions,
- 599 - A complete record of all raw data secured during each test, in addition to
600 graphs, charts, and spectra from laboratory instrumentation, properly
601 identified to show the specific material and batch tested;
- 602 - A record of all calculations performed in connection with the test,
603 including, for example, units of measure, conversion factors, and
604 equivalency factors;
- 605 - A statement of the test results and how they compare with established
606 specifications;
- 607 - The signature of the person who performed each test and the date(s) the
608 tests were performed; and
- 609 - The date and signature of a second person showing that the original
610 records have been reviewed for accuracy, completeness, and compliance
611 with established standards.

612 6.61 Complete records should also be maintained for:

- 613 - Any modifications to an established analytical method,
- 614 - Periodic calibration of laboratory instruments, apparatus, gauges, and
615 recording devices;
- 616 - All stability testing performed on APIs; and
- 617 - Out-of-specification (OOS) investigations.

618 **6.7 Batch Production Record Review**

619 6.70 Written procedures should be established and followed for the review and
620 approval of batch production and laboratory control records, including
621 packaging and labelling, to determine compliance of the intermediate or API
622 with established specifications before a batch is released or distributed.

623 6.71 Batch production and laboratory control records for critical process steps
624 should be reviewed and approved by the quality unit(s) before an API batch is
625 released or distributed. Production and laboratory control records for
626 earlier, non-critical process steps may be reviewed by qualified production
627 personnel or other units following procedures approved by the quality unit(s).

628 6.72 All deviation, investigation, and OOS reports should be reviewed as part of
629 the batch record review before the batch is released.

630 6.73 The quality unit(s) may delegate to the production unit the responsibility and
631 authority for release of intermediates.

632 **7. MATERIALS MANAGEMENT**

633 **7.1 General Controls**

634 7.10 There should be written procedures describing the receipt, identification,
635 quarantine, storage, handling, sampling, testing, and approval or rejection of
636 materials.

637 7.11 Manufacturers of intermediates and/or APIs should have a system for
638 evaluating the suppliers of critical materials.

639 7.12 Materials should be purchased against an agreed specification, from a
640 supplier or suppliers approved by the quality unit(s).

641 7.13 If the supplier of a critical material is not the manufacturer of that material,
642 the name and address of that manufacturer should be known by the
643 intermediate and/or API manufacturer.

644 7.14 Changing the source of supply of critical raw materials should be treated
645 according to Section 13, Change Control.

646 **7.2 Receipt and Quarantine**

647 7.20 Upon receipt and before acceptance, each container or grouping of containers
648 of materials should be examined visually for correct labelling, container
649 damage, broken seals and evidence of tampering or contamination. Materials
650 should be held under quarantine until they have been sampled, examined or
651 tested as appropriate, and released for use.

652 7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or
653 stocks in silos) they should be identified as correct and released. Procedures
654 should be available to prevent discharging into the wrong stock.

655 7.22 If bulk deliveries are made in non-dedicated tankers, there should be
656 assurance of no cross-contamination from the tanker. Means of providing this
657 assurance could include one or more of the following:

658 - certificate of cleaning

659 - testing for trace impurities

660 - audit of the supplier.

661 7.23 Large storage containers, and their attendant manifolds, filling and discharge
662 lines should be appropriately identified.

663 7.24 Each container or grouping of containers (batches) of materials should be
664 assigned and identified with a distinctive code, batch, or receipt number.
665 This number should be used in recording the disposition of each batch. A
666 system should be in place to identify the status of each batch.

667 **7.3 Sampling and Testing of Materials**

668 7.30 At least one test to verify the identity of each batch of material should be
669 conducted, with the exception of the materials described below in 7.32. A
670 supplier's Certificate of Analysis may be used in place of performing other

671 tests provided that the manufacturer has a system in place to evaluate
672 suppliers.

673 7.31 Supplier approval should require an evaluation including adequate evidence
674 (e.g., past quality history) that the supplier can consistently provide material
675 meeting specifications. Full analyses should be conducted on at least three
676 batches before reducing in-house testing. However, as a minimum, a full
677 analysis should be performed at appropriate intervals and compared with the
678 Certificates of Analysis. Reliability of Certificates of Analysis should be
679 checked at regular intervals.

680 7.32 Processing aids, hazardous or highly toxic raw materials, and other special
681 materials do not need to be tested, provided the manufacturer's Certificate of
682 Analysis is obtained showing that these raw materials conform to established
683 specifications. Visual examination of containers, labels, and recording of
684 batch numbers should help in establishing the identity of these materials.
685 The lack of on-site testing for these materials should be justified and
686 documented.

687 7.33 Samples should be representative of the batch of material from which they
688 are taken. Sampling methods should specify the number of containers to be
689 sampled, which part of the container to sample, and the amount of material to
690 be taken from each container. The number of containers to sample and the
691 sample size should be based upon a sampling plan which takes into
692 consideration criticality of the material, material variability, past quality
693 history of the supplier, and the quantity needed for analysis.

694 7.34 Sampling should be conducted at defined locations and by procedures
695 designed to prevent contamination of the material sampled and
696 contamination of other materials.

697 7.35 Containers from which samples are withdrawn should be opened carefully
698 and subsequently reclosed. They should be marked to indicate that a sample
699 has been taken.

700 **7.4 Storage**

701 7.40 Materials should be handled and stored in a manner to prevent degradation,
702 contamination, and cross-contamination.

703 7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor
704 and when necessary, suitably spaced to permit cleaning and inspection.

705 7.42 Materials should be stored under conditions and for a period that have no
706 adverse affect on their quality, and should normally be rotated so that the
707 oldest stock is used first.

708 7.43 Certain materials in suitable containers may be stored outdoors, provided
709 identifying labels remain legible and containers are appropriately cleaned
710 before opening and use.

711 7.44 Rejected materials should be identified and controlled under a quarantine
712 system designed to prevent their unauthorised use in manufacturing.

713 **7.5 Re-evaluation**

714 7.50 Materials should be re-evaluated as appropriate to determine their
715 suitability for use (e.g., after prolonged storage or exposure to heat or
716 humidity).

717 **8. PRODUCTION AND IN-PROCESS CONTROLS**

718 **8.1 Production Operations**

719 8.10 Raw materials for intermediate and API manufacturing should be weighed or
720 measured under appropriate conditions that do not affect their suitability for
721 use. Weighing and measuring devices should be of suitable accuracy for the
722 intended use.

723 8.11 If a material is subdivided for later use in production operations, the
724 container receiving the material should be suitable and should be so
725 identified that the following information is available:

726 - Material name and item code;

727 - Receiving or control number;

728 - Weight or measure of material in the new container; and

729 - Re-evaluation or retest date if appropriate.

730 8.12 Critical weighing, measuring, or subdividing operations should be supervised
731 or subjected to an equivalent control. Prior to use, production personnel
732 should verify that the materials are those specified in the batch record for the
733 intended intermediate or API.

734 8.13 Other critical activities should be supervised or subjected to an equivalent
735 control.

736 8.14 Actual yields should be compared with expected yields at designated steps in
737 the production process. Expected yields with appropriate ranges should be
738 established based on previous laboratory, pilot scale, or manufacturing data.
739 Deviations in yield associated with critical process steps should be
740 investigated to determine their impact or potential impact on the resulting
741 quality of affected batches.

742 8.15 Any deviation should be documented and explained. Any critical deviation
743 should be investigated.

744 8.16 The processing status of major units of equipment should be indicated either
745 on the individual units of equipment or by appropriate documentation,
746 computer control systems, or alternative means.

747 8.17 Materials to be reprocessed or reworked should be appropriately controlled
748 to prevent unauthorized use.

749 **8.2 Time Limits**

750 8.20 If time limits are specified in the master production instruction (see 6.41),
751 these time limits should be met to ensure the quality of intermediates and
752 APIs. Deviations should be documented and evaluated. Time limits may be
753 inappropriate when processing to a specification (e.g., pH adjustment,
754 hydrogenation, drying to predetermined specification) because completion of

755 reactions or processing steps are determined by in-process sampling and
756 testing.

757 8.21 Intermediates held for further processing should be stored under appropriate
758 conditions to assure their suitability for use.

759 **8.3 In-process Sampling and Controls**

760 8.30 Written procedures should be established to monitor the progress and control
761 the performance of processing steps that cause variability in the quality
762 characteristics of intermediates and APIs. In-process controls and their
763 acceptance criteria should be defined based on the information gained during
764 the development stage or historical data.

765 8.31 The acceptance criteria and type and extent of testing may depend on the
766 nature of the intermediate or API being manufactured, the reaction or
767 process step being conducted, and the degree to which the process introduces
768 variability in the product's quality. Less stringent in-process controls may be
769 appropriate in early processing steps, whereas tighter controls may be
770 appropriate for later processing steps (e.g., isolation and purification steps).

771 8.32 Critical in-process controls (and process monitoring), including the control
772 points and methods, should be stated in writing and approved by the quality
773 unit(s).

774 8.33 In-process controls may be performed by production department personnel
775 and the process adjusted without prior quality unit(s) approval, provided
776 adjustments are made within pre-established limits approved by the quality
777 unit(s). All tests and results should be fully documented as part of the batch
778 record.

779 8.34 Written procedures should describe the sampling methods for in-process
780 materials, intermediates, and APIs. Sampling plans and procedures should
781 be based on scientifically sound sampling practices.

782 8.35 In-process sampling should be conducted using procedures designed to
783 prevent contamination of the sampled material and other intermediates or
784 APIs. Procedures should be established to ensure the integrity of samples
785 after collection.

786 **8.4 Blending Batches of Intermediates or APIs**

787 8.40 For the purpose of this document, blending is defined as the process of
788 combining materials within the same specification to produce a homogeneous
789 intermediate or API. In-process mixing of fractions from single batches (e.g.,
790 collecting multiple fermentation batches in a single holding tank or collecting
791 several centrifuge loads from a single crystallization batch) is considered to
792 be part of the production process and is not considered to be blending.

793 8.41 Out-Of-Specification batches should not be blended with other batches for the
794 purpose of meeting specifications. Each batch incorporated into the blend
795 should have been manufactured using an established process and should have
796 been individually tested and found to meet appropriate specifications prior to
797 blending.

798 8.42 Acceptable blending operations include but are not limited to:

799 - Blending of small batches to increase batch size

- 800 - Blending of tailings (i.e., relatively small quantities of isolated material)
801 from batches of the same intermediate or API to form a single batch.
- 802 8.43 Blending processes should be adequately controlled and documented and the
803 blended batch should be tested for conformance to established specifications.
- 804 8.44 The batch record of the blending process should allow traceability back to the
805 individual batches that make up the blend.
- 806 8.45 Where physical attributes of the API are critical (e.g., APIs intended for use
807 in solid oral dosage forms or suspensions) blending operations should be
808 validated to show homogeneity of the combined batch. Validation should
809 include testing of critical attributes (e.g., particle size distribution, bulk
810 density, and tap density) that may be affected by the blending process.
- 811 8.46 Stability testing of the final blended batches is necessary if the blending could
812 cause a change in the already established stability data.
- 813 8.47 The expiry or retest date of the blended batch should be based on the
814 manufacturing date of the oldest tailings or batch in the blend.
- 815 **8.5 Contamination Control**
- 816 8.50 Carryover of leftover materials from successive batches of the same
817 intermediate or API (e.g., residue adhering to the wall of a micronizer,
818 residual layer of damp crystals remaining in a centrifuge bowl after
819 discharge, and incomplete discharge of fluids or crystals from a processing
820 vessel upon transfer of the material to the next step in the process) is
821 acceptable provided it is adequately controlled. Such carryover should not
822 result in the carryover of degradants or microbial contamination that may
823 adversely alter the established API impurity profile.
- 824 8.51 Production operations should be conducted in a manner that will prevent
825 contamination of intermediates or APIs by other materials.
- 826 8.52 Special attention should be taken when APIs are handled after purification to
827 avoid contamination.
- 828 **9. PACKAGING AND LABELLING OF APIS AND INTERMEDIATES**
829 **FOR TRANSPORT**
- 830 **9.1 General**
- 831 9.10 There should be written procedures describing the receipt, identification,
832 quarantine, sampling, examination and/or testing and release, and handling of
833 packaging and labelling materials.
- 834 9.11 Packaging and labelling materials should conform to established
835 specifications. Those that do not comply with such specifications should be
836 rejected to prevent their use in operations for which they are unsuitable.
- 837 9.12 Records should be maintained for each shipment of labels and packaging
838 materials showing receipt, examination, or testing, and whether accepted or
839 rejected.

840 **9.2 Packaging Materials**

841 9.20 Containers should provide adequate protection against deterioration or
842 contamination of the intermediate or API that may occur during
843 transportation and recommended storage.

844 9.21 Containers should be clean, and where indicated by the nature of the
845 intermediate or API, sanitized to ensure that they are suitable for their
846 intended use. These containers should not be reactive, additive, or
847 absorptive so as to alter the quality of the intermediate or API beyond the
848 specified limits.

849 9.22 If containers are re-used, they should be cleaned in accordance with
850 documented procedures and all previous labels should be removed or defaced.

851 **9.3 Label Issuance and Control**

852 9.30 Access to the label storage areas should be limited to authorised personnel.

853 9.31 Procedures should be used to reconcile the quantities of labels issued, used,
854 and returned and to evaluate discrepancies found between the number of
855 containers labelled and the number of labels issued. Such discrepancies
856 should be investigated, and the investigation should be approved by the
857 quality unit(s).

858 9.32 All excess labels bearing batch numbers or other batch related printing
859 should be destroyed. Returned labels should be maintained and stored in a
860 manner that prevents mix-ups and provides proper identification.

861 9.33 Obsolete and out-dated labels should be destroyed.

862 9.34 Printing devices used to print labels for packaging operations should be
863 controlled to ensure that all imprinting conforms to the print specified in the
864 batch production record.

865 9.35 Printed labels issued for a batch should be carefully examined for proper
866 identity and conformity to specifications in the master production record.
867 The results of this examination should be documented in the batch production
868 record.

869 9.36 A printed label representative of those used should be included in the batch
870 production record.

871 **9.4 Packaging and Labelling Operations**

872 9.40 There should be documented procedures designed to ensure that correct
873 packaging materials and labels are used.

874 9.41 Labelling operations should be designed to prevent mix-ups. There should be
875 physical or spatial separation from operations involving other intermediates
876 or APIs.

877 9.42 Labels used on containers of intermediates or APIs should indicate the name
878 or identifying code, the batch number of the product and storage conditions
879 when such information is critical to assure the quality of intermediate or API.
880 If the intermediate or API is intended to be transferred outside the control of
881 the manufacturer's material management system, the name and address of
882 the manufacturer, quantity of contents, and special transport conditions and
883 any special legal requirements should also be included on the label. For

884 intermediates or APIs with an expiry date, the expiry date should be
885 indicated on the label and Certificate of Analysis. For intermediates or APIs
886 with a retest date, the retest date should be indicated on the label and/or
887 Certificate of Analysis.

888 9.43 Packaging and labelling facilities should be inspected immediately before use
889 to ensure that all materials not needed for the next packaging operation have
890 been removed. This examination should be documented in the batch
891 production records, the facility log, or other documentation system.

892 9.44 Packaged and labelled intermediates or APIs should be examined to ensure
893 that containers and packages in the batch have the correct label. This
894 examination may be part of the packaging operation. Results of these
895 examinations should be recorded in the batch production or control records.

896 9.45 Intermediate or API containers that are transported outside of the
897 manufacturer's control should be sealed in a manner such that, if the seal is
898 breached or missing, the recipient will be alerted to the possibility that the
899 contents may have been altered.

900 **10. STORAGE AND DISTRIBUTION**

901 **10.1 Warehousing Procedures**

902 10.10 Facilities should be available for the storage of all materials under
903 appropriate conditions (e.g. controlled temperature and humidity when
904 necessary). Records should be maintained of these conditions if they are
905 critical for the maintenance of material characteristics.

906 10.11 Unless there is an alternative system to prevent the unintentional or
907 unauthorised use of quarantined, rejected, returned, or recalled materials,
908 separate storage areas should be assigned for their temporary storage until
909 the decision as to their future use has been taken.

910 **10.2 Distribution Procedures**

911 10.20 APIs should only be released for distribution to third parties after they have
912 been released by the quality unit(s). API's may be transferred under
913 quarantine to another unit under the company's control when authorized by
914 the quality unit(s) and providing appropriate controls and documentation are
915 in place.

916 10.21 APIs should be transported in a manner that does not adversely affect their
917 quality.

918 10.22 Special transport or storage conditions for an API should be stated on the
919 label.

920 10.23 The API manufacturer should ensure that the contract acceptor (contractor)
921 for transportation of the API knows and follows the appropriate transport
922 and storage conditions.

923 10.24 A system should be in place by which the distribution of each batch of
924 intermediate and/or API can be readily determined to permit its recall if
925 necessary.

926 **11. LABORATORY CONTROLS**

927 **11.1 General Controls**

928 11.10 The independent quality unit(s) must have at its disposal adequate laboratory
929 facilities.

930 11.11 There should be documented procedures describing sampling, testing,
931 approval or rejection of materials, and recording and storage of laboratory
932 data.

933 11.12 Laboratory records should be maintained in accordance with Section 6.6.

934 11.13 All specifications, sampling plans, and test procedures should be scientifically
935 sound and appropriate to ensure that raw materials, intermediates, APIs, and
936 labels and packaging materials conform to established standards of quality
937 and/or purity. Specifications and test procedures should be consistent with
938 those included in the registration/filing. There may be specifications in
939 addition to those in the registration/filing. All specifications, sampling plans,
940 and test procedures, including changes to them, should be drafted by the
941 appropriate organizational unit and reviewed and approved by the quality
942 unit(s).

943 11.14 Appropriate specifications should be established for APIs in accordance with
944 accepted standards and consistent with the manufacturing process. The
945 specifications should include a control of the impurities (e.g. organic
946 impurities, inorganic impurities, and residual solvents). If the API needs to
947 be of a specified microbiological purity, appropriate action limits for total
948 microbial counts, objectionable organisms, and endotoxins may need to be
949 established and met.

950 11.15 Laboratory controls should be followed and documented at the time of
951 performance. Any deviation from the above described procedures should be
952 documented and justified.

953 11.16 Any out-of-specification result obtained should be investigated and
954 documented according to a procedure. This procedure should require analysis
955 of the data, assessment of whether a significant problem exists, allocation of
956 the tasks for corrective actions and conclusions. Any resampling and/or
957 retesting after OOS results should be performed according to a documented
958 procedure.

959 11.17 Primary standards should be obtained as appropriate for the manufacture of
960 APIs. The source of each primary standard should be documented. Records
961 should be maintained of each primary standards storage and use in
962 accordance with the supplier's recommendations. Primary reference
963 standards obtained from an officially recognized source need not be tested if
964 stored under conditions consistent with the supplier's recommendations.

965 11.18 In cases where a primary standard is necessary and one is not available from
966 an officially recognized source, an "in-house primary standard" should be
967 established. This standard may be prepared by independent synthesis or by
968 further purification of existing production material. Appropriate testing
969 should be performed to establish fully the identity and purity. Appropriate
970 documentation of this testing should be maintained.

971 11.19 Secondary laboratory reference standards should be appropriately prepared,
972 identified, tested, approved, and stored. The suitability of each batch of
973 secondary reference standard should be determined prior to first use by

974 comparing against a primary reference standard. Each batch of secondary
975 reference standard should be periodically requalified in accordance with a
976 written protocol.

977 **11.2 Testing of Intermediates and APIs**

978 11.20 For each batch of intermediate and API, appropriate laboratory tests should
979 be conducted to determine conformance to specifications.

980 11.21 An impurity profile describing the identified and unidentified impurities
981 present in a typical batch produced by a specific controlled production
982 process should normally be established for each API. The impurity profile
983 includes the identity or some qualitative analytical designation (e.g. retention
984 time), the range of each impurity observed, and classification of each
985 identified impurity (e.g. inorganic, organic, solvent). The impurity profile is
986 normally dependent upon the process and origin of the API. Impurity
987 profiles are normally not necessary for APIs from herbal or animal tissue
988 origin. Biotech considerations are covered in ICH Guideline Q6B.

989 11.22 The impurity profile should be compared at appropriate intervals against the
990 impurity profile in the regulatory submission or compared against historical
991 data in order to detect changes to the API resulting from modifications in raw
992 materials, equipment operating parameters, or the production process.

993 11.23 Appropriate microbiological tests should be conducted on each batch of
994 intermediate and API where a defined microbial quality is necessary.

995 **11.3 Validation of Analytical Procedures - see Section 12.**

996 **11.4 Certificates of Analysis**

997 11.40 Authentic Certificates of Analysis should be issued for each batch of
998 intermediate or API on request.

999 11.41 Information on the name of the intermediate or API including its grade,
1000 where appropriate, the batch number, the date of release, and the expiry date
1001 should be provided on the label and Certificate of Analysis. For intermediates
1002 or APIs with a retest date, the retest date should be indicated on the label
1003 and/or Certificate of Analysis.

1004 11.42 The Certificate should list each test performed in accordance with
1005 compendial or customer requirements, including the acceptance limits, and
1006 the numerical results obtained (if test results are numerical).

1007 11.43 Certificates should be dated and signed by authorised personnel of the
1008 quality unit(s) and should show the name, address and telephone number of
1009 the original manufacturer. In case the analysis has been carried out by a
1010 repacker or reprocessor, the Certificate of Analysis should show the name,
1011 address and telephone number of the repacker/reprocessor and a reference to
1012 the name of the original manufacturer.

1013 11.44 If new Certificates are issued by or on behalf of repackers/reprocessors,
1014 agents or brokers, these Certificates should show the name, address and
1015 telephone number of the laboratory that performed the analysis. They should
1016 also contain a reference to the name and address of the original manufacturer
1017 and to the original batch Certificate, a copy of which should be attached.

1018 **11.5 Stability Monitoring of APIs**

1019 11.50A documented, on-going, testing program should be designed to monitor the
1020 stability characteristics of APIs, and the results should be used to confirm
1021 appropriate storage conditions and retest or expiry dates. Where
1022 appropriate, these programs should be consistent with the ICH guidelines on
1023 stability.

1024 11.51 The test procedures used in stability testing should be validated and be
1025 stability indicating.

1026 11.52 Stability samples should be stored in containers that simulate the market
1027 container. For example, if the API is marketed in bags within fiber drums,
1028 stability samples may be packaged in bags of the same material and in
1029 smaller-scale drums of similar or identical material composition to the
1030 market drums.

1031 11.53 Normally the first three commercial production batches should be placed on
1032 the stability monitoring program to confirm the retest or expiry date.
1033 However, where data from previous studies shows that the API is expected to
1034 remain stable for at least two years, fewer than three batches may be used.

1035 11.54 Thereafter, at least one batch per year of API manufactured (unless none is
1036 produced that year) should be added to the stability monitoring program and
1037 tested at least annually to confirm the stability.

1038 11.55 For APIs with short shelf-lives, testing should be done more frequently. For
1039 example, for those biotechnological/biologic and other APIs with shelf-lives of
1040 one year or less, stability samples should be obtained and should be tested
1041 monthly for the first three months, and at three month intervals after that.
1042 When data exist that confirm that the stability of the API is not compromised,
1043 elimination of specific test intervals (e.g. 9 month testing) may be considered.

1044 **11.6 Expiry and Retest Dating**

1045 11.60 When an intermediate is intended to be transferred outside the control of the
1046 manufacturer's material management system and an expiry or retest date is
1047 assigned, supporting stability information should be available (e.g. published
1048 data, test results).

1049 11.61 An API expiry or retest date should be based on an evaluation of data derived
1050 from stability studies. Common practice is to use a retest date, not an
1051 expiration date.

1052 11.62 Preliminary API expiry or retest dates may be based on pilot scale batches if
1053 (1) the pilot batches employ a method of manufacture and procedure that
1054 simulates the final process to be used on a commercial manufacturing scale;
1055 and (2) the quality of the API represents the material to be made on a
1056 commercial scale.

1057 11.63 A representative sample should be taken for the purpose of performing a
1058 retest.

1059 **11.7 Reserve/Retention Samples**

1060 11.70 Reserve samples are maintained for the purpose of evaluating the quality of
1061 batches of API at a later date, if necessary. The packaging and holding of
1062 these samples is for the purpose of potential future evaluation and not for
1063 future stability testing purposes.

1064 11.71 Appropriately identified reserve samples of each API batch should be
1065 retained for one year after the expiry date of the batch assigned by the
1066 manufacturer, or for three years after distribution of the batch, whichever is
1067 the longer. For APIs with retest dates, similar reserve samples should be
1068 retained for three years after the batch is completely distributed from the
1069 manufacturer.

1070 11.72 The reserve sample should be stored under conditions consistent with
1071 product labels, in the same packaging system in which the API is stored or in
1072 one that is equivalent to or more protective than the marketed packaging
1073 system. Sufficient quantities should be retained to conduct at least two full
1074 compendial analyses or, when there is no pharmacopeial monograph, two full
1075 specification analyses.

1076 **12. VALIDATION**

1077 **12.1 Validation Policy**

1078 12.10 The company's overall policy, intentions, and approach to validation,
1079 including the validation of production processes, cleaning procedures,
1080 analytical methods, in-process control test procedures, computerized
1081 systems, and persons responsible for design, review, approval and
1082 documentation of each validation phase, should be documented.

1083 12.11 The critical parameters/attributes should normally be identified during the
1084 development stage or from historical data, and the ranges necessary for the
1085 reproducible operation should be defined. This should include:

- 1086 - Defining the API in terms of its critical product attributes;
- 1087 - Identifying process parameters that may affect the critical quality
1088 attributes of the API;
- 1089 - Determining the range for each critical process parameter expected to be
1090 used during routine manufacturing and process control.

1091 12.12 Validation should extend to those operations determined to be critical to the
1092 quality and purity of the API.

1093 **12.2 Validation Documentation**

1094 12.20 A written validation protocol should be established that specifies how
1095 validation of a particular process will be conducted. The protocol should be
1096 reviewed and approved by the quality unit(s) and other designated units.

1097 12.21 The validation protocol should specify critical process steps and acceptance
1098 criteria as well as the type of validation to be conducted (e.g. retrospective,
1099 prospective, concurrent) and the number of process runs.

1100 12.22 A validation report that cross-references the validation protocol should be
1101 prepared, summarising the results obtained, commenting on any deviations

1102 observed, and drawing the necessary conclusions, including recommending
1103 changes necessary to correct deficiencies.

1104 12.23 Any changes to the plan as defined in the validation protocol should be
1105 documented with appropriate justification.

1106 **12.3 Qualification**

1107 12.30 Before starting process validation activities, appropriate qualification of
1108 equipment and ancillary systems should be completed. Qualification is
1109 usually carried out by conducting the following activities, individually or
1110 combined:

1111 - Design Qualification (DQ) is documented verification that the proposed
1112 design of the facilities, equipment, or systems is suitable for the intended
1113 purpose.

1114 - Installation Qualification (IQ) is documented verification that the
1115 equipment or systems, as installed or modified, comply with the approved
1116 design and the manufacturer's recommendations.

1117 - Operational Qualification (OQ) is documented verification that the
1118 equipment or systems, as installed or modified, perform as intended
1119 throughout the anticipated operating ranges.

1120 - Performance Qualification (PQ) is documented verification that the
1121 equipment and ancillary systems, as connected together, can perform
1122 effectively and reproducibly based on the approved process method and
1123 specifications.

1124 **12.4 Approaches to Process Validation**

1125 12.40 Process Validation (PV) is the documented evidence that the process,
1126 operated within established parameters, can perform effectively and
1127 reproducibly to produce an intermediate or API meeting its predetermined
1128 specifications and quality attributes.

1129 12.41 There are three approaches to validation. Prospective validation is the
1130 preferred approach, but there are exceptions where the other approaches
1131 may be used. These approaches and their applicability are listed below.

1132 12.42 Prospective validation should normally be performed for all API processes as
1133 defined in 12.12. Results of prospective validation when performed on an API
1134 process must be completed at the latest before the commercial distribution of
1135 the final drug product manufactured from that API.

1136 12.43 Concurrent validation may be conducted when data from replicate production
1137 runs are unavailable because only a limited number of API batches have been
1138 produced, API batches are produced infrequently, or API batches are
1139 produced by a validated process that has been modified. Prior to the
1140 completion of concurrent validation, batches may be released and used in
1141 final drug product for commercial distribution based on thorough monitoring
1142 and testing of the API batches.

1143 12.44 An exception may be made for retrospective validation for well established
1144 processes that have been used without significant changes to API quality due
1145 to changes in raw materials, equipment, systems, facilities, or the production
1146 process. This validation approach may be used where:

- 1147 (1) Critical quality attributes and critical process parameters have been
1148 identified;
- 1149 (2) Appropriate in-process acceptance criteria and controls have been
1150 established;
- 1151 (3) There have not been significant process/product failures attributable to
1152 causes other than operator error or equipment failures unrelated to
1153 equipment suitability; and
- 1154 (4) Impurity profiles have been established for the existing API.

1155 12.45 Batches selected for retrospective validation should be representative of all
1156 batches made during the review period, including any batches that failed to
1157 meet specifications, and should be sufficient in number to demonstrate
1158 process consistency. Additional testing of retained samples may be needed to
1159 obtain the necessary amount or type of data to retrospectively validate the
1160 process.

1161 **12.5 Process Validation Program**

1162 12.50 The number of process runs needed for validation should depend on the
1163 complexity of the process or the magnitude of the process change being
1164 considered. For prospective and concurrent validation, three consecutive
1165 successful production batches should be used as a guide, but there may be
1166 situations where additional process runs are warranted to prove consistency
1167 of the process (e.g., complex API processes or API processes with prolonged
1168 completion times). For retrospective validation, generally data from ten to
1169 thirty consecutive batches should be examined to assess process consistency,
1170 but fewer batches may be examined if justified.

1171 12.51 Critical process parameters should be controlled and monitored during
1172 process validation studies. Process parameters unrelated to quality, such as
1173 variables controlled to minimize energy consumption or equipment use, need
1174 not be included in the process validation.

1175 12.52 Process validation should confirm that the impurity profile for each API is
1176 within the limits specified. The impurity profile should be comparable to or
1177 better than historical data and, where applicable, the profile determined
1178 during process development or for batches used for pivotal clinical and
1179 toxicological studies.

1180 **12.6 Periodic Review of Validated Systems**

1181 12.60 Systems and processes should be periodically evaluated to verify that they
1182 are still operating in a valid manner. Where no significant changes have been
1183 made to the system or process, a quality review with evidence that the system
1184 or process is consistently producing product meeting its specifications fulfils
1185 the need for revalidation.

1186 **12.7 Cleaning Validation**

1187 12.70 Cleaning procedures should normally be validated. In general, cleaning
1188 validation should be directed to situations or process steps where
1189 contamination or incidental carryover of materials pose the greatest risk to
1190 API quality. For example, in early production it may be unnecessary to

1191 validate equipment cleaning procedures where residues are removed by
1192 subsequent purification steps.

1193 12.71 Validation of cleaning procedures should reflect actual equipment usage
1194 patterns. If various APIs or intermediates are manufactured in the same
1195 equipment and the equipment is cleaned by the same process, a
1196 representative intermediate or API may be selected for cleaning validation.
1197 This selection may be based on the solubility and difficulty of cleaning and the
1198 calculation of residue limits based on potency, toxicity, and stability.

1199 12.72 The cleaning validation protocol should describe the equipment to be cleaned,
1200 procedures, materials, acceptable cleaning levels, parameters to be monitored
1201 and controlled, and analytical methods. The protocol should also indicate the
1202 type of samples to be obtained and how they are collected and labelled.

1203 12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g.,
1204 direct extraction), as appropriate, to detect both insoluble and soluble
1205 residues. The sampling methods used should be capable of quantitatively
1206 measuring levels of residues remaining on the equipment surfaces after
1207 cleaning. Swab sampling may be impractical when product contact surfaces
1208 are not easily accessible due to equipment design and/or process limitations
1209 (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or
1210 handling toxic materials, and small intricate equipment such as micronizers
1211 and microfluidizers).

1212 12.74 Validated analytical methods having sensitivity to detect residues or
1213 contaminants should be used. The detection limit for each analytical method
1214 should be sufficiently sensitive to detect the established acceptable level of
1215 the residue or contaminant. The method's attainable recovery level should be
1216 established. Residue limits should be practical, achievable, verifiable and
1217 based on the most deleterious residue. Limits may be established based on
1218 the minimum known pharmacological, toxicological, or physiological activity
1219 of the API or its most deleterious component.

1220 12.75 Equipment cleaning/sanitization studies should address microbiological and
1221 endotoxin contamination for those processes where there is a need to reduce
1222 total microbiological count or endotoxins in the API, or other processes where
1223 such contamination may be of concern (e.g., non-sterile APIs used to
1224 manufacture sterile products).

1225 12.76 Cleaning procedures should be monitored at appropriate intervals after
1226 validation to ensure that these procedures are effective when used during
1227 routine production. Equipment cleanliness may be monitored by analytical
1228 testing and visual examination, where feasible. Visual inspection may allow
1229 detection of gross contamination concentrated in small areas that could go
1230 undetected by sampling and/or analysis.

1231 **12.8 Validation of Analytical Methods**

1232 12.80 Analytical methods should be validated unless the method employed is
1233 included in the current edition of an official pharmacopoeia or other
1234 recognised standard references. The suitability of all testing methods used
1235 should nonetheless be verified under actual conditions of use and
1236 documented.

- 1237 12.81 Methods should be validated to include consideration of characteristics
1238 included within the ICH guidelines on validation of analytical methods. The
1239 degree of analytical validation performed should reflect the purpose of the
1240 analysis and the stage of the API process.
- 1241 12.82 Appropriate qualification of analytical equipment should be considered before
1242 starting validation of analytical methods.
- 1243 12.83 Complete records should be maintained of any modification of a validated
1244 analytical method. Such records should include the reason for the
1245 modification and appropriate data to verify that the modification produces
1246 results that are as accurate and reliable as the established method.
- 1247 **13. CHANGE CONTROL**
- 1248 13.10 A formal change control system should be established to evaluate all changes
1249 that may affect the production and control of the intermediate or API .
- 1250 13.11 Written procedures should provide for the identification, documentation,
1251 appropriate review, and approval of changes in raw materials, specifications,
1252 analytical methods, facilities, support systems, equipment (including
1253 computer hardware), processing steps, labelling and packaging materials, and
1254 computer software.
- 1255 13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and
1256 approved by the appropriate organisational units, and reviewed and
1257 approved by the quality unit(s).
- 1258 13.13 The potential impact of the proposed change on the quality of the
1259 intermediate or API should be evaluated. A classification procedure may
1260 help in determining the level of testing, validation, and documentation
1261 needed to justify changes to a validated process. Changes may be classified
1262 (e.g. as minor or major) depending on the nature and extent of the changes,
1263 and the effects these changes may impart to the process. Scientific judgement
1264 should determine what additional testing and validation studies are needed
1265 to justify a change in a validated process.
- 1266 13.14 When implementing approved changes, measures should be taken to ensure
1267 that all documents affected by the changes are revised.
- 1268 13.15 After the change has been implemented, there should be an evaluation of the
1269 first batches produced or tested under the change.
- 1270 13.16 The potential effects of critical process changes upon established retest or
1271 expiry dates should be evaluated. If necessary, samples of the intermediate
1272 or API produced by the modified process may be placed on an accelerated
1273 stability program and/or may be added to the stability monitoring program.
- 1274 13.17 Current dosage form manufacturers should be notified of changes from
1275 established production and process control procedures which can impact the
1276 quality of the API.

1277 **14. REJECTION AND RE-USE OF MATERIALS**

1278 **14.1 Rejection**

1279 14.10 Intermediates and APIs failing to meet established specifications should be
1280 identified as such and quarantined. These intermediates or APIs can be
1281 reprocessed or reworked as described below. The final disposition of rejected
1282 materials should be recorded.

1283 **14.2 Reprocessing**

1284 14.20 Introducing an intermediate or API, including one which does not conform to
1285 standards or specifications, back into the process and reprocessing by
1286 repeating a crystallization step or other appropriate chemical or physical
1287 manipulation steps (e.g., distillation, filtration, chromatography, milling) that
1288 are part of the established manufacturing process is generally acceptable.
1289 However, if such reprocessing is used for a majority of batches, such
1290 reprocessing should be included as part of the standard manufacturing
1291 process.

1292 14.21 Continuation of a chemical reaction after an in-process control test shows the
1293 reaction to be incomplete is considered to be part of the normal process. This
1294 is not considered to be reprocessing.

1295 14.22 Introducing unreacted material back into a process and repeating a chemical
1296 reaction is considered to be reprocessing unless it is part of the established
1297 process. Such reprocessing should be preceded by careful evaluation to
1298 ensure that the quality of the intermediate or API is not adversely impacted
1299 due to the potential formation of by-products and over reacted materials.

1300 **14.3 Reworking**

1301 14.30 Before a decision is taken to rework batches that do not conform to
1302 established standards or specifications, an investigation into the reason for
1303 non-conformance should be performed.

1304 14.31 Batches that have been reworked should be subjected to appropriate
1305 evaluation, testing, stability testing if warranted, and documentation to show
1306 that the reworked product is of equivalent quality to that produced by the
1307 original process. Concurrent validation is often the appropriate validation
1308 approach for rework procedures. This allows a protocol to define the rework
1309 procedure, how it will be carried out, and the expected results. If there is
1310 only one batch to be reworked, then an interim report can be written and the
1311 batch released once it is found to be acceptable.

1312 14.32 Procedures should provide for comparing the impurity profile of each
1313 reworked batch against batches manufactured by the established process.
1314 Where routine analytical methods are inadequate to characterize the
1315 reworked batch, additional methods should be used.

1316 **14.4 Recovery of Materials and Solvents**

1317 14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or
1318 the API is acceptable, provided that approved procedures exist for the
1319 recovery and that the recovered materials meet specifications suitable for
1320 their intended use.

1321 14.41 Solvents may be recovered and reused in the same processes or in different
1322 processes, provided that the recovery procedures are controlled and
1323 monitored to ensure that solvents meet appropriate standards before reuse
1324 or co-mingling with other approved materials.

1325 14.42 Fresh and recovered solvents and reagents may be combined if adequate
1326 testing has shown their suitability for all manufacturing processes in which
1327 they may be used.

1328 14.43 The use of recovered solvents, mother liquors, and other recovered materials
1329 should be adequately documented.

1330 **14.5 Returns**

1331 14.50 Returned intermediates or APIs should be identified as such and
1332 quarantined.

1333 14.51 If the conditions under which returned intermediates or APIs have been
1334 stored or shipped before or during their return or the condition of their
1335 containers casts doubt on their quality, the returned intermediates or APIs
1336 should be reprocessed, reworked, or destroyed, as appropriate.

1337 14.52 Records of returned intermediates or APIs should be maintained. For each
1338 return, documentation should include:

- 1339 - Name and address of the consignee
- 1340 - Intermediate or API, batch number, and quantity returned
- 1341 - Reason for return
- 1342 - Use or disposal of the returned intermediate or API

1343 **15. COMPLAINTS AND RECALLS**

1344 15.10 All quality related complaints, whether received orally or in writing, should
1345 be recorded and investigated according to a written procedure.

1346 15.11 Complaint records should include:

- 1347 - Name and address of complainant;
- 1348 - Name (and, where appropriate, title) and phone number of person
1349 submitting the complaint;
- 1350 - Complaint nature (including name and batch number of the API);
- 1351 - Date complaint is received;
- 1352 - Action initially taken (including dates and identity of person taking the
1353 action);
- 1354 - Follow-up action taken (if necessary);
- 1355 - Response provided to the originator of complaint (including date response
1356 sent); and
- 1357 - Final decision on intermediate or API batch or lot.

1358 15.12 Records of complaints should be retained in order to evaluate trends,
1359 product-related frequencies, and severity with a view to taking additional,
1360 and if necessary, immediate corrective action.

1361 15.13 There should be a written procedure that defines the circumstances under
1362 which a recall of an intermediate or API should be considered.

1363 15.14 The recall procedure should designate who should be involved in evaluating
1364 the information, how a recall should be initiated, who should be informed
1365 about the recall, and how the recalled material should be treated.

1366 15.15 In the event of a serious or potentially life-threatening situation, local,
1367 national, and/or international authorities should be informed and their advice
1368 sought.

1369 **16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

1370 16.10 All contract manufacturers (including laboratories) should comply with the
1371 GMP defined in this Guide. Special consideration should be given to the
1372 prevention of cross-contamination and to maintaining traceability.

1373 16.11 Contract manufacturers (including laboratories) should be evaluated by the
1374 contract giver to ensure GMP compliance of the specific operations occurring
1375 at the contract sites.

1376 16.12 There should be a written and approved contract or formal agreement
1377 between the contract giver and the contract acceptor that defines in detail
1378 the GMP responsibilities, including the quality measures, of each party.

1379 16.13 The contract should permit the contract giver to audit the contract acceptor's
1380 facilities for compliance with GMP.

1381 16.14 Where subcontracting is allowed, the contract acceptor should not pass to a
1382 third party any of the work entrusted to him under the contract without the
1383 contract giver's prior evaluation and approval of the arrangements.

1384 16.15 Manufacturing and analytical records should be kept at the site where the
1385 activity occurs and be readily available.

1386 16.16 Changes in the process, equipment, test methods, specifications, or other
1387 contractual requirements should not be made unless the contract giver is
1388 informed and approves the changes.

1389 **17. AGENTS, BROKERS, DISTRIBUTORS, REPACKERS, AND** 1390 **RELABELLERS**

1391 **17.1 Applicability**

1392 17.10 Throughout Section 17 the term API refers to both API and intermediate.

1393 17.11 This section applies to any party other than the original manufacturer who
1394 may trade and/or take possession, handle, repack, relabel, manipulate, or
1395 store an API.

1396 17.12 All agents, brokers, distributors, repackers, and relabellers should comply
1397 with GMP as defined in this Guide.

1398 **17.2 Traceability of Distributed APIs**

1399 17.20 Agents, brokers, distributors, repackers, or relabellers should maintain
1400 complete traceability of APIs that they distribute. Documents that should be
1401 retained and available include:

- 1402 - Identity of original manufacturer
- 1403 - Address of original manufacturer
- 1404 - Purchase orders
- 1405 - Bills of lading (transportation documentation)
- 1406 - Receipt documents
- 1407 - Name or designation of API
- 1408 - Manufacturer's batch number
- 1409 - Transportation and distribution records
- 1410 - All authentic Certificates of Analysis including those of the original
- 1411 manufacturer
- 1412 - Retest or expiry date

1413 **17.3 Quality Management**

- 1414 17.30 Agents, brokers, distributors, repackers, or relabellers should establish,
1415 document and implement an effective system of managing quality as specified
1416 in Section 2.

1417 **17.4 Repackaging, Relabelling and Holding of APIs**

- 1418 17.40 Repackaging, relabelling and holding of APIs should be performed under
1419 appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and
1420 loss of API identity or purity.
- 1421 17.41 Repackaging should be conducted under appropriate environmental
1422 conditions to avoid contamination and cross-contamination.

1423 **17.5 Stability**

- 1424 17.50 Stability studies to justify assigned expiration or retest dates should be
1425 conducted if the API is repackaged in a different type of container than that
1426 used by the API manufacturer.

1427 **17.6 Transfer of Information**

- 1428 17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all
1429 quality or regulatory information received from an API manufacturer to the
1430 customer, and from the customer to the API manufacturer.
- 1431 17.61 The agent, broker, distributor, repacker, or relabeller who supplies the API
1432 to the customer should provide the name of the original API manufacturer
1433 and the batch number(s) supplied.
- 1434 17.62 The agent should also provide the identity of the original API manufacturer
1435 to regulatory authorities upon request. The original manufacturer may
1436 respond to the regulatory authority directly or through its authorized agents
1437 depending on the legal relationship between the authorized agents and the
1438 original API manufacturer. (In this context "authorized" refers to authorized
1439 by the manufacturer.)
- 1440 17.63 The specific guidance for Certificates of Analysis included in Section 11.4
1441 should be met.

1442 **17.7 Handling of Complaints and Recalls**

1443 17.70 Agents, brokers, distributors, repackers, or relabellers should maintain
1444 records of complaints and recalls, as specified in Section 15, for all
1445 complaints and recalls that come to their attention.

1446 17.71 If the situation warrants, the agents, brokers, distributors, repackers, or
1447 relabellers should review the complaint with the original API manufacturer
1448 in order to determine whether any further action, either with other
1449 customers who may have received this API or with the regulatory authority,
1450 or both, should be initiated. The investigation into the cause for the complaint
1451 or recall should be conducted and documented by the appropriate party.

1452 17.72 Where a complaint is referred to the original API manufacturer, the record
1453 maintained by the agents, brokers, distributors, repackers, or relabellers
1454 should include any response received from the original API manufacturer
1455 (including date and information provided).

1456 **17.8 Handling of Returns**

1457 17.80 Returns should be handled as specified in Section 14.52. The agents, brokers,
1458 distributors, repackers, or relabellers should maintain documentation for
1459 returned APIs.

1460 **18. SPECIFIC GUIDANCE FOR APIS MANUFACTURED BY CELL**
1461 **CULTURE/FERMENTATION**

1462 **18.1 General**

1463 18.10 Section 18 is intended to address specific controls for APIs or intermediates
1464 manufactured by cell culture or fermentation using natural or recombinant
1465 organisms which have not been covered adequately in the previous sections.
1466 It is not intended to be a stand alone Section. In general, the GMP principles
1467 in the other sections of this document apply. Note that the principles of
1468 fermentation for “classical” processes for production of small molecules and
1469 for processes using recombinant and non-recombinant organisms for
1470 production of proteins and/or polypeptides are the same, although the degree
1471 of control will vary. Where practical this section will address these
1472 differences. In general, the degree of control for biotech processes is greater
1473 than that for classical fermentation processes.

1474 18.11 Production of APIs or intermediates from cell culture or fermentation
1475 involves biological processes such as cultivation of cells or extraction and
1476 purification of material from living organisms. Note that there may be
1477 additional process steps, such as physicochemical modification, that are part
1478 of the manufacturing process. The raw materials (media, buffer components)
1479 used may provide good substrates for microbiological contaminants.
1480 Depending on the source, method of preparation, and the intended use of the
1481 API or intermediate, control of bioburden, viral contamination, and/or
1482 endotoxins during manufacturing and monitoring of the process at
1483 appropriate stages may be necessary.

1484 18.12 Appropriate controls need to be in place at all stages of manufacturing to
1485 preserve intermediate and/or API quality. While this Guide starts at the cell
1486 culture/fermentation step, prior steps (e.g. cell banking) should be performed

1487 under appropriate process controls. This Guide covers cell
1488 culture/fermentation from the point at which a vial of the cell bank is
1489 retrieved for use in manufacturing.

1490 18.13 Appropriate equipment and environmental controls should be used to
1491 minimize contamination. The acceptance criteria for quality of the
1492 environment and the frequency of monitoring depend on the step in
1493 production and the production conditions (open, closed, or contained
1494 systems).

1495 18.14 In general, process controls should take into account:

- 1496 - Maintenance of the Working Cell Bank;
- 1497 - Proper inoculation and expansion of the culture;
- 1498 - Control of the critical operating parameters during fermentation/cell
1499 culture;
- 1500 - Monitoring of the process for cell growth, viability (for biotech processes)
1501 and productivity;
- 1502 - Harvest and purification procedures that remove cells, cellular debris and
1503 media components while protecting the intermediate or API from
1504 contamination, particularly of a microbiological nature and loss of
1505 intermediate or API quality;
- 1506 - Bioburden and endotoxin levels should be monitored at appropriate stages
1507 of production; and
- 1508 - For biotech products, viral safety concerns should be as described in ICH
1509 Guideline Q5A Quality of Biotechnological Products: Viral Safety
1510 Evaluation of Biotechnology Products Derived from Cell Lines of Human
1511 or Animal Origin.

1512 18.15 For biotech products, validation of the removal of media components, host
1513 cell proteins, other process-related impurities, product related impurities
1514 and contaminants may be necessary.

1515 **18.2 Cell Bank Maintenance and Record Keeping**

1516 18.20 Access to cell banks should be limited to authorized personnel.

1517 18.21 Cell banks should be maintained under storage conditions designed to
1518 maintain viability and prevent contamination

1519 18.22 Records of the use of the vials from the cell banks and storage conditions
1520 should be maintained

1521 18.23 Cell banks should be periodically monitored to determine suitability for use.
1522 For classical fermentation the usage period of the cell strain is usually
1523 defined.

1524 18.24 See ICH Guideline Q5D Quality of Biotechnological Products: Derivation and
1525 Characterization of Cell Substrates Used for Production of
1526 Biotechnological/Biological Products for a more complete discussion of cell
1527 banking.

1528 **18.3 Cell Culture/Fermentation**

1529 18.30 Where possible, closed or contained systems should be used to permit the
1530 aseptic addition of cell substrates, media, buffers and gases. If the inoculation
1531 of the initial vessel or subsequent transfers or additions (media, buffers) are
1532 performed in open vessels, there should be controls and procedures in place
1533 to minimize contamination.

1534 18.31 For biotech processes, manipulations using open vessels should be performed
1535 in a biosafety cabinet or similarly controlled environment to prevent
1536 contamination.

1537 18.32 Personnel should be appropriately gowned and take special precautions
1538 handling the cultures.

1539 18.33 Critical operating parameters, for example temperature, pH, agitation rates,
1540 addition of gases, pressure, should be monitored to ensure consistency with
1541 the established process. Cell growth, viability (for biotech processes), and
1542 productivity should also be monitored. Critical parameters will vary from
1543 one process to another, and for classical fermentation certain parameters
1544 (cell viability, for example) may not need to be monitored.

1545 18.34 Cell culture and fermentation equipment should be cleaned and sterilized
1546 after use when used in the manufacture of biotech products. Fermentation
1547 equipment for the “classical fermentation” processes should be cleaned and
1548 sanitized as appropriate.

1549 18.35 Culture media should be sterilized before use when necessary to protect the
1550 quality of the API.

1551 18.36 There should be appropriate procedures in place to detect contamination and
1552 determine the course of action to be taken. This should include procedures to
1553 determine the impact of the contamination on the product and those to
1554 decontaminate the equipment and return them to a condition to be used in
1555 subsequent batches. Foreign organisms observed during fermentation
1556 processes should be identified as appropriate and the effect of their presence
1557 on product quality should be assessed if necessary. The results of such
1558 assessments should be taken into consideration in the disposition of the
1559 material produced.

1560 18.37 Records of contamination events should be maintained.

1561 18.38 Shared equipment (multi-product) may require additional cleaning or testing
1562 between product campaigns, as appropriate, to minimize cross-contamination
1563 of previous activities into subsequent activities.

1564 **18.4 Harvesting, Isolation and Purification**

1565 18.40 Harvesting steps, whether to remove cells from the supernatant (media) or
1566 the collection of cellular components after disruption, should be done in
1567 equipment and areas designed to minimize contamination, particularly of a
1568 microbiological nature.

1569 18.41 Harvest and purification procedures that remove or inactivate the producing
1570 organism, cellular debris and media components while minimizing
1571 degradation, contamination, and loss of quality, should be adequate to ensure
1572 that the intermediate or API is recovered with consistent quality.

1573 18.42 All equipment should be properly cleaned/sanitized after use. Multiple
1574 successive batching without cleaning may be utilized if intermediate or API
1575 quality is not compromised.

1576 18.43 If open systems are used, purification may need to be done under controlled
1577 environmental conditions appropriate for the preservation of product quality.
1578 For biotech products this is normally achieved in areas using HEPA filtered
1579 air.

1580 18.44 Additional purification controls, such as dedicated chromatography resins or
1581 additional testing, may be necessary if equipment is to be used for multiple
1582 products.

1583 **18.5 Viral removal /inactivation steps (biotech products only)**

1584 18.50 See the ICH Guideline ICH Guideline Q5A Quality of Biotechnological
1585 Products: Viral Safety Evaluation of Biotechnology Products Derived from
1586 Cell Lines of Human or Animal Origin for more specific information.

1587 18.51 Viral removal and viral inactivation steps are critical processing steps for
1588 some biotech processes and should be performed within their validated
1589 parameters.

1590 18.52 Appropriate precautions should be taken to prevent potential viral
1591 contamination from pre- to post-viral removal/inactivation steps. Therefore,
1592 open processing should be performed in separate areas with separate air
1593 handling units.

1594 18.53 Separate equipment is normally used for different purification steps.
1595 However, if the same equipment is to be used, the respective equipment
1596 should be appropriately cleaned and sanitized before reuse. Appropriate
1597 precautions should be taken to prevent potential virus carry-over (e.g.
1598 through equipment or environment) from previous steps.

1599 **19. APIS FOR USE IN CLINICAL TRIALS**

1600 **19.1 General**

1601 19.10 Not all the controls in the previous sections of this Guide are appropriate for
1602 the manufacture of a new API for investigational use during its development.
1603 Section 19 provides specific guidance unique to these circumstances.

1604 19.11 The controls used in the manufacture of APIs for use in clinical trials should
1605 be consistent with the stage of development of the drug product incorporating
1606 the API. Process and test procedures should be flexible to provide for
1607 changes as knowledge of the process increases and clinical testing of a drug
1608 product progresses from pre-clinical stages through clinical stages. Once
1609 drug development reaches the stage where the API is produced for use in
1610 drug products intended for clinical trials, manufacturers should ensure that
1611 APIs are manufactured in suitable facilities using appropriate production and
1612 control procedures to ensure the quality of the API.

1613 **19.2 Quality**

1614 19.20 Appropriate GMP concepts should be applied in the production of APIs for
1615 use in clinical trials with a suitable mechanism of approval of each batch.

1616 19.21 A quality unit(s) independent from production should be established for the
1617 approval or rejection of each batch of API for use in clinical trials.

1618 19.22 Some of the testing functions commonly performed by the quality unit(s) may
1619 be performed within other areas.

1620 19.23 Quality measures should include a system for testing of raw materials,
1621 packaging materials, intermediates, and APIs.

1622 19.24 Process and quality problems should be evaluated.

1623 19.25 Labelling for APIs intended for use in clinical trials should be appropriately
1624 controlled and identified as being for investigational use.

1625 **19.3 Equipment and Facilities**

1626 19.30 During all phases of clinical development, including the use of small scale
1627 facilities or laboratories to manufacture batches of APIs for use in clinical
1628 trials, procedures should be in place to ensure that equipment is calibrated,
1629 clean and suitable for its intended use.

1630 19.31 Procedures for the use of facilities should ensure that materials are handled
1631 in a manner that minimizes the risk of contamination and cross-
1632 contamination.

1633 **19.4 Control of Raw Materials**

1634 19.40 Raw materials used in production of APIs for use in clinical trials should be
1635 evaluated by testing, or received with a supplier's analysis and subjected to
1636 identity testing. When a material is considered hazardous, a supplier's
1637 analysis should suffice.

1638 19.41 In some instances, the suitability of a raw material may be determined before
1639 use based on acceptability in small-scale reactions (i.e., use testing) rather
1640 than on analytical testing alone.

1641 **19.5 Production**

1642 19.50 The production of APIs for use in clinical trials should be documented in
1643 laboratory notebooks, batch records, or other appropriate means. These
1644 documents should include information on the use of production materials,
1645 equipment, processing, and scientific observations.

1646 19.51 Expected yields may be more variable and less defined than the expected
1647 yields used in commercial processes. Investigations into yield variations are
1648 not expected.

1649 **19.6 Validation**

1650 19.60 Process validation may be inappropriate during clinical API production
1651 where a single API batch may be produced or where process changes during
1652 development make batch replication difficult or inexact. The combination of
1653 controls, calibration, and, where appropriate, equipment qualification
1654 provides the assurance during this development phase.

1655 19.61 Process validation should be conducted in accordance with Section 12 when
1656 batches are produced for commercial use, even when such batches are
1657 produced on a pilot or small scale.

1658 **19.7 Changes**

1659 19.70 Although changes are expected during clinical development, as knowledge is
1660 gained and the production is scaled up, every change in the production,
1661 specifications, or test procedures should be adequately recorded.

1662 **19.8 Laboratory Controls**

1663 19.80 All analyses performed to evaluate a batch of API for clinical trials should be
1664 scientifically sound; these methods may not yet be fully validated.

1665 19.81 A system for retaining reserve samples of all batches should be in place. This
1666 system should ensure that a sufficient quantity of each reserve sample is
1667 retained for an appropriate length of time after approval, termination, or
1668 discontinuation of an application.

1669 19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs
1670 used in clinical trials. For new APIs, Section 11.6 does not normally apply in
1671 early stages of clinical trials.

1672 **19.9 Documentation**

1673 19.90 A system should be in place to ensure that information gained during the
1674 development and the manufacture of APIs for use in clinical trials is
1675 documented and available.

1676 19.91 The development and implementation of the analytical methods used to
1677 support the release of a batch of API for use in clinical trials should be
1678 appropriately documented.

1679 19.92 A system for retaining production and control records should be used. This
1680 system should ensure that records are retained for an appropriate length of
1681 time after the approval, termination, or discontinuation of an application.

1682 **20. GLOSSARY**

1683 ***Active Pharmaceutical Ingredient (API) (or Drug Substance)***

1684 Any substance or mixture of substances intended to be used in the manufacture of a
1685 drug (medicinal) product and that, when used in the production of a drug, becomes
1686 an active ingredient of the drug product. Such substances are intended to furnish
1687 pharmacological activity or other direct effect in the diagnosis, cure, mitigation,
1688 treatment, or prevention of disease or to affect the structure and function of the
1689 body.

1690 ***API Starting Material***

1691 A material used in the production of an API which is incorporated as a significant
1692 structural fragment into the structure of the API. An API Starting Material may be
1693 an article of commerce, a material purchased from one or more suppliers under
1694 contract or commercial agreement, or it may be produced in-house. API Starting
1695 Materials are normally of defined chemical properties and structure.

1696 ***Batch (or Lot)***

1697 A specific quantity of material produced in a process or series of processes so that
1698 it is expected to be homogeneous within specified limits. In the case of continuous
1699 production, a batch may correspond to a defined fraction of the production. The

1700 batch size may be defined either by a fixed quantity or the amount produced in a
1701 fixed time interval.

1702 ***Batch Number (or Lot Number)***

1703 A unique combination of numbers, letters, and/or symbols which identifies a batch
1704 (or lot) and from which the production and distribution history can be determined.

1705 ***Bioburden***

1706 The level and type (e.g. objectionable or not) of micro-organisms which may be
1707 present in raw materials, API starting materials, intermediates or APIs. Bioburden
1708 should not be considered contamination unless the levels have been exceeded or
1709 defined objectionable organisms have been detected.

1710 ***Calibration***

1711 The demonstration that a particular instrument or device produces results within
1712 specified limits by comparison with those produced by a reference or traceable
1713 standard over an appropriate range of measurements.

1714 ***Computer System***

1715 A group of hardware components and associated software, designed and assembled
1716 to perform a specific function or group of functions.

1717 ***Computerized System***

1718 A process or operation integrated with a computer system.

1719 ***Contamination***

1720 The undesired introduction of impurities of a chemical or microbiological nature,
1721 or of foreign matter, into or onto a raw material, intermediate, or API during
1722 production, sampling, packaging or repackaging, storage or transport.

1723 ***Contract Manufacturer***

1724 A company holding an agreement requiring the performance of some aspect of API
1725 manufacturing.

1726 ***Critical***

1727 A process step, process condition, test requirement, or other relevant parameter or
1728 item that must be controlled within predetermined criteria to ensure that the API
1729 meets its specification.

1730 ***Cross-Contamination***

1731 Contamination of a material or product with another material or product.

1732 ***Drug (Medicinal) Product***

1733 The dosage form in the final immediate packaging intended for marketing.
1734 (Reference Q1A)

1735 ***Drug Substance***

1736 See Active Pharmaceutical Ingredient Expiration Date:

1737 ***Expiration Date*** : See Expiry Date

1738 **Expiry Date (or Expiration Date)**

1739 The date placed on the container/labels of an API designating the time during
1740 which the API is expected to remain within established shelf life specifications if
1741 stored under defined conditions, and after which it should not be used.

1742 **Impurity**

1743 Any component present in the intermediate or API that is not the desired entity.

1744 **Impurity Profile**

1745 A description of the identified and unidentified impurities present in an API.

1746 **In-Process Control (or Process Control)**

1747 Checks performed during production in order to monitor and, if necessary, to
1748 adjust the process and/or to ensure that the intermediate or API conforms to its
1749 specifications.

1750 **Intermediate**

1751 A material produced during steps of the processing of an API that must undergo
1752 further molecular change or purification before it becomes an API. Intermediates
1753 may or may not be isolated.

1754 **Lot**

1755 See Batch

1756 **Lot Number** see Batch Number

1757 **Manufacture**

1758 All operations of receipt of materials, production, packaging, repackaging,
1759 labelling, relabelling, quality control, release, storage, and distribution of APIs and
1760 the related controls.

1761 **Material**

1762 A general term used to denote raw materials (starting materials, reagents,
1763 solvents), process aids, intermediates, APIs and packaging and labelling materials.

1764 **Mother Liquor**

1765 The residual liquid which remains after the crystallization or isolation processes. A
1766 mother liquor may contain unreacted materials, intermediates, levels of the API
1767 and/or impurities. It may be used for further processing.

1768 **Packaging Material**

1769 Any material intended to protect an intermediate or API during storage and
1770 transport.

1771 **Procedure**

1772 A documented description of the operations to be performed, the precautions to be
1773 taken and measures to be applied directly or indirectly related to the manufacture
1774 of an intermediate or API.

1775 **Process Aids**

1776 Materials, excluding solvents, used as an aid in the manufacture of an intermediate
1777 or API that do not themselves participate in a chemical or biological reaction (e.g.
1778 filter aid, activated carbon, etc).

1779 **Process Control**

1780 See In-Process Control

1781 **Production**

1782 All operations involved in the preparation of an API, from receipt of materials,
1783 through processing and packaging, to its completion as a finished API.

1784 **Qualification**

1785 Action of proving and documenting that equipment or ancillary systems are
1786 properly installed, work correctly, and actually lead to the expected results.
1787 Qualification is part of validation, but the individual qualification steps alone do
1788 not constitute process validation.

1789 **Quality Assurance (QA)**

1790 The sum total of the organised arrangements made with the object of ensuring that
1791 all APIs are of the quality required for their intended use and that quality systems
1792 are maintained.

1793 **Quality Control (QC)**

1794 Checking or testing that specifications are met.

1795 **Quality Unit(s)**

1796 An organizational unit independent of production which fulfills both Quality
1797 Assurance and Quality Control responsibilities. This may be in the form of
1798 separate QA and QC units or a single individual (or group), depending upon the
1799 size and structure of the organization.

1800 **Quarantine**

1801 The status of materials isolated physically or by other effective means pending a
1802 decision on their subsequent approval or rejection.

1803 **Raw Material**

1804 A general term used to denote starting materials, reagents, and solvents intended
1805 for use in the production of intermediates or APIs.

1806 **Reference Standard, Primary**

1807 A substance that has been shown by an extensive set of analytical tests to be
1808 authentic material that should be of high purity. This standard may be obtained
1809 from an officially recognised source or may be prepared by independent synthesis
1810 or by further purification of existing production material.

1811 **Reference Standard, Secondary**

1812 A substance of established quality and purity, as shown by comparison to a primary
1813 reference standard, used as a reference standard for routine laboratory analysis.

1814 **Reprocessing**

1815 Introducing an intermediate or API, including one that does not conform to
1816 standards or specifications, back into the process and repeating a crystallization
1817 step or other appropriate chemical or physical manipulation steps (e.g.,
1818 distillation, filtration, chromatography, milling) that are part of the established
1819 manufacturing process. Continuation of a chemical reaction after an in-process
1820 control test shows the reaction to be incomplete is considered to be part of the
1821 normal process, and not reprocessing.

1822 **Retest Date**

1823 The date when a material should be re-examined to ensure that it is still suitable
1824 for use.

1825 **Reworking**

1826 Subjecting an intermediate or API that does not conform to standards or
1827 specifications to one or more processing steps that are different from the
1828 established manufacturing process so that its quality may be made acceptable (e.g.,
1829 recrystallizing with a different solvent).

1830 **Signature (signed)**

1831 See definition for signed

1832 **Signed (signature)**

1833 The record of the individual who performed a particular action or review. This
1834 record may be initials, full handwritten signature, personal seal, or authenticated
1835 and secure electronic signature.

1836 **Solvent**

1837 An inorganic or organic liquid used as a vehicle for the preparation of solutions or
1838 suspensions in the manufacture of an intermediate or API .

1839 **Specification**

1840 A list of tests, references to analytical procedures, and appropriate acceptance
1841 criteria that are numerical limits, ranges, or other criteria for the test described.
1842 It establishes the set of criteria to which a material should conform to be
1843 considered acceptable for its intended use. "Conformance to specification" means
1844 that the material, when tested according to the listed analytical procedures, will
1845 meet the listed acceptance criteria.

1846 **Validation**

1847 A documented program that provides a high degree of assurance that a specific
1848 process, method, or system will consistently produce a result meeting pre-
1849 determined acceptance criteria.

1850 **Validation Protocol**

1851 A written plan stating how validation will be conducted and defining acceptance
1852 criteria. For example, the protocol for a manufacturing process identifies
1853 processing equipment, critical process parameters/operating ranges, product

1854 characteristics, sampling, test data to be collected, number of validation runs, and
1855 acceptable test results.

1856 ***Yield, Expected***

1857 The quantity of material or the percentage of theoretical yield anticipated at any
1858 appropriate phase of production based on previous laboratory, pilot scale, or
1859 manufacturing data.

1860 ***Yield, Theoretical***

1861 The quantity that would be produced at any appropriate phase of production, based
1862 upon the quantity of material to be used, in the absence of any loss or error in
1863 actual production.

1864