

Guidance for Industry

INDs — Approaches to Complying with CGMP During Phase 1

Draft Guidance

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**January 2006
CGMP**

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**U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist persons producing drug and biological products (investigational drugs) for use during phase 1 development (21 CFR 312.21(a)) in complying with relevant current good manufacturing practice as required by § 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Controls for producing an investigational new drug for use in a phase 1 study are primarily aimed at ensuring subject safety. The Agency believes that applying quality control (QC) principles to the production of investigational products (i.e., interpreting and implementing CGMPs consistent with good scientific methodology) will facilitate the initiation of investigational studies in humans and protect study subjects. When finalized, this guidance will replace the *1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal)* for the production of IND products for phase 1 clinical trials described in the Scope section of this guidance.

This guidance is being issued concurrently with a direct final rule (and companion proposed rule), which specifies that the particular requirements in Part 211 (21 CFR 211) need not be met for most investigational drugs manufactured for use during phase 1 development. Instead, the Agency recommends the approaches outlined in this guidance for complying with § 501(a)(2)(B) of the FD&C Act.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by an Agency working group with representatives from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA), at the Food and Drug Administration.

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42 **II. BACKGROUND**

43

44 The FD&C Act specifies that drugs must be manufactured, processed, packed, and held in
45 accordance with current good manufacturing practice (CGMP), or they are deemed to be
46 adulterated. In September 1978, FDA implemented revised CGMP regulations for drug and
47 biological products (see 21 CFR Parts 210 and 211). These regulations were written primarily
48 with commercial manufacturing in mind. Although the Agency stated at the time that the
49 regulations applied to all types of pharmaceutical production,² we indicated in the preamble to
50 the regulations that we were considering proposing additional regulations governing drugs used
51 in investigational clinical studies.

52

53 In 1991, the Agency issued the *Guideline on the Preparation of Investigational New Drug*
54 *Products (Human and Animal)*. However, the 1991 document did not discuss all manufacturing
55 situations, including, for example, small- or laboratory-scale production of investigational new
56 drugs. In addition, the 1991 document did not address fully the Agency's expectation that an
57 **incremental approach** to manufacturing controls would be taken during investigational drug
58 development, which for most products includes a change in production scale.

59

60 This guidance (once finalized) and the regulation it complements, once finalized, will represent
61 the Agency's effort to proceed with its plans to formally describe an approach to aide
62 manufacturers in implementing manufacturing controls that are appropriate for the stage of
63 development. The use of this approach recognizes that some controls and the extent of controls
64 needed to achieve appropriate product quality differ not only between investigational and
65 commercial manufacture, but also among the various phases of clinical studies. Consistent with
66 the Agency's CGMP for the 21 Century initiative,³ where applicable, manufacturers are also
67 expected to implement controls that reflect product and production considerations, evolving
68 process and product knowledge, and manufacturing experience.⁴

69

70 This guidance describes FDA's current thinking regarding controls for special production
71 situations (e.g., a laboratory setting, exploratory studies, multi-product and multi-batch testing)
72 and specific types (e.g., biological/biotechnology products, aseptically processed products) of
73 investigational new drug (IND) products manufactured for use during phase 1 clinical trials as
74 described in the Scope section of this guidance. As the new rule specifies, the particular
75 requirements in Parts 211 (21 CFR 211) need not be met for certain exploratory products
76 manufactured for use during phase 1 clinical trials.

² Preamble to the CGMP 1978, comment #49. "The Commissioner finds that, as stated in 211.1, these CGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages. It is appropriate that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and for ultimate commercial production. The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stages."

³ See <http://www.fda.gov/cder/gmp/21stcenturysummary.htm>.

⁴ We are considering issuing additional guidance and/or regulations to clarify the Agency's expectations with regard to fulfilling the CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical studies.

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77
78 When finalized, this guidance will replace the *1991 Guideline on the Preparation of*
79 *Investigational New Drug Products (Human and Animal)* for the production of IND products for
80 phase 1 clinical trials described in the Scope section of this guidance. Phase 2 and 3 production
81 will continue to be subject to those portions of 210 and 211 that are applicable.

82
83

84 III. SCOPE

85

86 This guidance applies to the following:

Investigational new human drug and biological products (including finished dosage forms used as placebos) intended for human use during phase 1 development, including, for example, investigational recombinant and nonrecombinant therapeutic products, vaccine products, allergenic products, in vivo diagnostics, plasma derivative products, blood and blood components, gene therapy products, and somatic cellular therapy products (including xenotransplantation products) that are subject to CGMP requirements of § 501(a)(2)(B) of the FD&C Act.

87
88

89 The guidance applies to investigational products whether they are produced in small- or large-scale
90 environments because such studies are typically designed to assess tolerability or feasibility for
91 further development of a specific drug or biological product. However, if an investigational drug
92 has already been manufactured by an IND sponsor for use during phase 2 or phase 3 studies or has
93 been lawfully marketed, manufacture of such a drug must comply with the appropriate sections of
94 21 CFR Part 211 for the drug to be used in any subsequent phase 1 investigational studies,
95 irrespective of the trial size or duration of dosing.

96

97 This guidance does *not* apply to the following:

98

- 99
- Human cell or tissue products regulated solely under Section 361 of the PHS Act
 - 100 • Clinical trials for products subject to the device approval or clearance provisions of the
101 Food, Drug, and cosmetic Act
 - 102 • Investigational new drugs manufactured for phase 2 and 3 studies
 - 103 • Already approved products that are being used during phase 1 studies (e.g., for a new
104 indication)

105 If clarification on applicability of this guidance to a specific clinical study is needed, please
106 contact the appropriate center with responsibility for review of the IND.

107

108 We recommend that this guidance be used as a companion to other guidances describing the
109 chemistry, manufacturing, and control (CMC) information submitted and reviewed in an IND
110 application for phase 1 studies (References 1, 2, 3). At this stage of development, in many cases,
111 manufacture of the active ingredient and the final investigational product will be accomplished
112 through a series of steps within a single facility. Producers of new active pharmaceutical

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113 ingredients (also referred to as an *API* or *drug substance*) must also conform with CGMP as
114 required in § 501(a)(2)(B) of the FD&C Act. Guidance on CGMP for the manufacture of new
115 API for some products used in clinical studies is also available (Reference 4). Such producers
116 should implement controls appropriate to the stage of development and, thus, may want to
117 consider the recommendations described in this guidance.
118
119

118
119

IV. STATUTORY AND REGULATORY REQUIREMENTS

120

122 Section 501(a)(2)(B) of the FD&C Act requires drugs, which include investigational new drugs,
123 to comply with current good manufacturing practice:
124

124

125 A drug...shall be deemed adulterated...if...the methods used in, or the facilities or
126 controls used for, its manufacture, processing, packing, or holding do not conform to or
127 are not operated or administered in conformity with current good manufacturing
128 practice to assure that such drug meets the requirements of this chapter as to safety and
129 has the identity and strength, and meets the quality and purity characteristics, which it
130 purports or is represented to possess
131

130

132 Certain of the requirements of 21 CFR Parts 211, which implement section § 501(a)(2)(B) of the
133 FD&C Act, were directed at commercial manufacture of products, typically characterized by
134 large, repetitive, commercial batch production (e.g., those that address expiration dating
135 (§ 211.137(g)), and warehousing (§ 211.142) and are not relevant to the manufacture of most
136 drugs for investigational use for phase 1 studies.
137

136

138 In addition, section 505(i) of the FD&C Act (21 U.S.C. 355(i)) directs FDA to promulgate
139 regulations governing investigational drugs to protect human subjects enrolled in investigations.
140 Under these regulations (21 CFR 312), sponsors must submit information — for example CMC
141 information (§ 312.23(a)(7)) — about a drug or biological product when submitting an IND
142 application (References 1, 2, 3). FDA reviews the submitted information to determine whether
143 the drug to be used in the investigation has the identity, quality, purity, strength, and potency
144 necessary to ensure the safety of the subjects in the proposed phase 1 study. In certain
145 circumstances, the Agency may choose to conduct an inspection (e.g., if there is insufficient
146 information to assess the risks to subjects or if the subjects would be exposed to unreasonable
147 and significant risk). Alternatively, the Agency could decide to place a proposed or ongoing
148 phase 1 investigation on clinical hold or terminate the IND. Such actions can also be taken if
149 there is evidence of inadequate quality control procedures that would compromise the safety of
150 an investigational product.
151

150

151

V. RECOMMENDATIONS FOR COMPLYING WITH THE STATUTE

153

154
155 This guidance outlines approaches that sponsors and producers of phase 1 investigational new
156 drugs can use to comply with the requirements of CGMP under section 501(a)(2)(B) of the
157 FD&C Act. These recommendations are designed to provide approaches to CGMP that
158 appropriately address factors associated with the production of clinical supplies for use in most

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159 phase 1 studies. The recommendations will also help provide an appropriate quality framework
160 for a variety of investigational new drugs manufactured in various situations.

161
162 During product development, the quality and safety of investigational drug products are
163 maintained, in part, by having appropriate quality control (QC) procedures in effect. Using
164 established or standardized procedures will also facilitate the production of equivalent or
165 comparable investigational product for further clinical study as needed.

166
167 Adherence to QC procedures during phase 1 development occurs largely through having:

- 168
- 169 • Written procedures that are well defined
 - 170 • Equipment that is adequately controlled
 - 171 • Data from production, including testing, that are accurately and consistently recorded
- 172

173 Producers may have acceptable alternative ways of meeting the objectives described in this
174 guidance. It is the responsibility of the sponsors/producers to provide and use such methods,
175 facilities, and controls to ensure that the investigational drug meets appropriate standards of
176 safety, identity, strength, quality, and purity. Producers of investigational products should
177 consider carefully how to best ensure the implementation of standards, practices and procedures
178 that conform to CGMP for their specific product and production operation.

179
180 A number of technologies and resources are available for use that can facilitate conformance
181 with CGMP and help streamline product development. Some examples include:

- 182
- 183 • Use of disposable equipment and process aids, which can reduce cleaning burden
 - 184 • Use of prepackaged Water For Injection (WFI) and presterilized containers, which can
185 eliminate the need for additional equipment or qualifying existing equipment
 - 186 • Use of process equipment that is closed (i.e., product not exposed to the environment
187 during processing), which can alleviate the need for stricter room classification for air
188 quality
 - 189 • Use of contract or shared production facilities and testing laboratories, for production and
190 testing (including specialized services) of investigational product. Some academic
191 institutions have developed shared production and testing facilities that can be used by
192 institutional sponsors.

193
194 Because the sponsor is responsible for important aspects of the clinical investigation, we
195 recommend that sponsors and producers consider carefully the risks from the production
196 environment that might adversely affect the resulting quality of an investigational product,
197 especially when the investigational product is produced in laboratory facilities that are not
198 expressly or solely designed for their production. For example, of particular importance is the
199 susceptibility of a product to contamination or cross contamination with other substances (e.g.
200 chemicals, biological substances, adventitious agents) that may be present from previous or
201 concurrent research or production activities.

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203 We recommend the following:

204

- 205 • A formal evaluation of the production environment to identify potential hazards
- 206 • Taking of appropriate actions prior to and during production to minimize risks and
207 safeguard the quality of the investigational product

208 Some recommendations pertaining to specific areas of CGMP follow. Consistent with the statute
209 (§ 501(a) (2) (b)), CGMP must be in effect for the production of each investigational drug batch
210 used in clinical trials. The following recommendations provide for flexibility to allow producers
211 to implement controls appropriate for their specific situation and application. Producers should
212 establish production controls based on a risk assessment for the product and manufacturing
213 process and follow good scientific and quality control principles when implementing specific
214 practices and procedures for CGMP.

215

A. Personnel

217

218 All personnel should have the education, experience and training or any combination thereof to
219 enable that person to perform the assigned function. In particular, personnel should have the
220 appropriate experience to prepare the investigational product and be familiar with QC principles
221 and acceptable methods for complying with the statutory requirement of CGMP, such as the
222 recommendations outlined in this guidance.

223

B. Quality Control Function

224

225 We recommend that every producer establish a QC plan and document that plan in writing. For
226 example, a sound QC plan should provide for the following functions:

227

- 228 • Responsibility for examining the various components used in the production of a product
229 (e.g., containers, closures, in-process materials, packaging materials, and labeling) to
230 ensure that they are appropriate and meet defined, relevant quality standards
- 231 • Responsibility for review and approval of production procedures, testing procedures, and
232 acceptance criteria
- 233 • Responsibility for releasing or rejecting each clinical batch based upon a cumulative
234 review of completed production records and other relevant information (e.g., procedures
235 were followed, product tests performed appropriately, acceptance criteria met)
- 236 • Responsibility for investigating and initiating corrective action if unexpected results or
237 errors occur during production

238

239 We also recommend that QC responsibilities be performed independently from production
240 responsibilities. When activities such as testing, commonly performed by dedicated QC
241 personnel in commercial manufacture, are performed by production personnel, adequate controls
242 should be in place (e.g., segregation of testing from production so as to not contaminate testing
243 or negatively affect test results).

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245 However, in limited circumstances, depending on the size and structure of an organization, all
246 QC functions could be performed by the same individual. For example, in some small
247 operations, it may be justified to have the same individual perform both production and QC
248 functions, including release or rejection of each batch. Under such circumstances, we
249 recommend that another qualified individual not involved in the production operation carry out
250 an additional, periodic review of production records. It is important to note that quality should
251 be the responsibility of all personnel involved in manufacturing

C. Facility and Equipment

253 Any facility, including a laboratory, used for production of investigational drugs for use in phase
254 I studies should have adequate work areas and equipment for the intended task:

- 258 • Sufficient space, clean environment, appropriate construction
- 259 • Appropriate lighting, ventilation, and heating
- 260 • Appropriate cooling, plumbing, washing, and sanitation
- 261 • Appropriate air handling systems (e.g., laminar flow hoods) to aid in preventing
262 contamination and cross-contamination of product
- 263 • Appropriate equipment that will not contaminate the product or otherwise be reactive,
264 additive, or absorptive with the product and that is properly maintained, calibrated,
265 cleaned, and sanitized at appropriate intervals following written procedures

266 We recommend that all equipment used for a particular process be identified and documented in
267 the production record. We also recommend that the provisions in section VI.D, Sterile
268 Products/Aseptically Processed Products, be followed for investigational products prepared using
269 aseptic processing.

270 Use of procedural controls in an appropriate facility promotes orderly production and aids in
271 preventing contamination, cross contamination and mix-ups (see Section VI.B).

D. Control of Components

274 We recommend there be written procedures describing the handling, review, and acceptance and
275 control of components used in the production of an investigational product. Components should
276 be controlled (e.g., segregated, labeled) until they have been examined or tested, as appropriate,
277 and released for use in production. It is important to handle and store components in a manner
278 that prevents degradation or contamination. We recommend keeping a record (e.g., log book)
279 containing relevant information on all components. Information to record would include receipt
280 date, quantity of the shipment, supplier's name, component lot number, investigational product
281 batch number, storage conditions, and corresponding expiration date.

282 We recommend establishing acceptance criteria for specified attributes on each component. For
283 some components, all relevant attributes or acceptance criteria may not be known at this stage of
284 product development. However, attributes and acceptance criteria selected for assessment
285 should be based on scientific knowledge and experience for use in the specific investigational
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288 drug. The component attributes and acceptance criteria will be reviewed in the IND application
289 (Ref 1-3).

290
291 We recommend that the certificate of analysis (COA) and/or other documentation on each lot of
292 component be examined to ensure that it meets established acceptance criteria for specified
293 attributes. For some materials (e.g., human and animal derived), documentation should include
294 information on sourcing and/or test results for adventitious agents, as appropriate. If
295 documentation for a component is incomplete, testing for the incomplete attribute of the
296 component is recommended. For each batch of the drug substance (or API), we strongly
297 recommend performing confirmatory identity testing, regardless of whether documentation has
298 been provided.

299

E. Production and Documentation

301

302 We recommend that production of investigational products follow written production procedures
303 that provide the following:

304

305 • A record of laboratory testing and production data that details the components,
306 equipment, and procedures used. We recommend that sponsors retain documentation
307 sufficient to replicate the production process. Similarly, if production of a clinical batch
308 is initiated but not completed, we recommend that the record include an explanation of
309 why production was terminated.

310 • A record of changes in procedures and processes used for subsequent batches along with
311 the rationale for any changes

312 • A record of the microbiological controls that have been implemented (including written
313 procedures) for the production of sterile processed investigational new drugs that are
314 covered by this guidance. We also recommend the use of aseptic techniques and the
315 control of in-process components designed to prevent microbial and endotoxin
316 contamination (see Section VI.D, Sterile Products/Aseptically Processed Products).

317

F. Laboratory Controls

318

319

1. Testing

320

321
322 Analytical tests used in production (e.g., testing of components, in-process material, packaging,
323 drug product) should be scientifically sound (e.g., specific, sensitive, and accurate) and
324 reproducible for the specified purpose. We recommend that tests be performed under controlled
325 conditions and follow written procedures describing the testing methodology.

326

327 Laboratory testing of the investigational product to evaluate identity, strength, potency, purity,
328 and quality attributes should be performed, as appropriate. Specified attributes should be
329 monitored, and acceptance criteria applied appropriately. For known safety-related concerns,
330 specifications should be established and met. For some product attributes, all relevant
331 acceptance criteria may not be known at this stage of product development. This information
332 will be reviewed in the IND submission (References 1, 2, 3).

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333
334 We recommend that laboratory equipment be calibrated at appropriate intervals and be
335 maintained according to established written procedures to ensure reliability of test results. We
336 recommend that personnel verify that the equipment is in good working condition when samples
337 are analyzed (e.g., systems suitability).
338

339 We further recommend that a representative sample from each product batch be retained. When
340 feasible, we recommend that the sample consist of twice the quantity necessary to conduct release
341 testing (excluding any testing for pyrogenicity and sterility). We recommend that the samples be
342 appropriately stored and retained for at least 2 years following study termination, or withdrawal of
343 the IND application.
344

2. *Stability*

345
346 We recommend that sponsors initiate a stability study using representative samples of the
347 investigational new drug to monitor the stability and quality of the product during the clinical
348 investigation (i.e., date of manufacture through date of last administration).
349

G. Container Closure and Labeling

350
351
352 When an investigational new drug covered by this guidance will be stored or shipped, the
353 product should be suitably packaged to protect it from alteration, contamination, and damage
354 during conditions of storage, handling, and shipping. We recommend that labeling and storage
355 operations be controlled to prevent the possibility of mix-ups.
356

H. Distribution

357
358
359 As it relates to phase 1 trials, the term *distribution* includes the transport of an investigational
360 new product covered by this guidance to clinical investigators and, ultimately, to the subjects
361 enrolled in the study. Products should be handled in accordance with labeled conditions (e.g.,
362 temperature) to ensure retention of the quality of the product. A distribution record of each batch
363 of investigational new drug covered by this guidance must be sufficiently detailed to allow
364 traceability and facilitate recall of the product if necessary (§ 312.57).⁵
365
366

I. Recordkeeping

367
368 As indicated in previous sections, we recommend that sponsors keep complete records relating to
369 the quality and operation of the production processes, including:
370

- 371 • Equipment maintenance and calibration
- 372 • Production records and related analytical test records
- 373 • Distribution records
- 374 • All quality control functions
- 375 • Component records

⁵ IND regulation 21 CFR 312.57 governs the retention of all records required by Part 312 (see 21 CFR 312.57(C)).

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376
377 Under the applicable IND regulations, sponsors must retain records for at least 2 years after a
378 marketing application is approved for the drug, or if an application is not approved for the drug,
379 until 2 years after shipment and delivery of the drug for investigational use is discontinued and
380 the FDA is notified.⁶

381

382

383 **VI. SPECIAL PRODUCTION SITUATIONS**

384

385 **A. Screening Studies/Microdose Producers**

386

387 A *screening study*, which is performed under an exploratory IND application, is intended to
388 compare the properties of related active moieties to screen for the preferred compound or
389 formulations for additional clinical development under a traditional IND application (Reference
390 5). Screening studies involve single-dose or short-term (e.g., ≤ 7 days of dosing) studies in
391 humans of up to 5 chemically or pharmacologically related new chemical entities.

392

393 *Microdose studies* are defined as studies in which participants are administered a single dose of
394 less than $1/100^{\text{th}}$ of the dose calculated to yield a pharmacological effect of the test substance
395 based on primary pharmacodynamic data obtained in vitro and in vivo (typically doses in, or
396 below the low microgram range) and at a maximum dose of ≤ 100 micrograms.

397

398 These types of investigational studies are often performed in small-scale laboratories or research
399 organizations.⁷ In such cases, special considerations are warranted. For example, when the
400 same area or room is used for both the production of investigational products and research, we
401 recommend that the sponsor segregate the operations sufficiently to

402

- 403 • Promote the orderly handling of materials and equipment
- 404 • Avoid contamination of equipment and product by other substances, personnel, or
405 environmental conditions
- 406 • Prevent mix-ups

407

408 Reagents and components used for investigational product production may be stored safely in the
409 same area as those used for research as long as they are properly labeled and organized in a
410 manner that avoids mix-ups or unintended use.

411

412 Finally, we recommend that equipment be used for a single purpose (i.e., research only or
413 production only) at any given time.

414

415 **B. Multi-Product Facilities**

416

⁶ Ibid.

⁷ A draft guidance entitled *Exploratory IND Studies* issued in April 2005. The guidance clarifies what preclinical and clinical issues (including chemistry, manufacturing, and controls issues) should be considered when planning exploratory studies. Once finalized, it will represent the Agency's thinking on this topic.

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417 Ideally, we recommend that one product be produced in an area or room at any given time
418 separate from unrelated activities. However, the same area or room could be used for multiple
419 purposes, including production of other investigational products or laboratory research, provided
420 that appropriate cleaning and control procedures are in place to ensure that there is no carry-over
421 of materials or products or mix-ups. We recommend that in such cases, the design or layout of
422 an area promote the orderly handling of materials and equipment, the prevention of mix-ups, and
423 the prevention of contamination of equipment or product by substances, previously produced
424 products, personnel, or environmental conditions.

425
426 Additional controls could include procedures for clearing the room of previous product
427 materials, product segregation, component segregation, and use of unique identifiers. We
428 recommend that the implemented controls be assessed periodically to evaluate their
429 effectiveness. Appropriate corrective action should be taken as a result of this assessment, or
430 when other events warrant.

C. Biological and Biotechnological Products

1. General Considerations

431
432
433
434
435
436 Some biological and biotechnology investigational products, including those made from
437 pathogenic microorganisms, spore-forming microorganisms, transgenic animals and plants, live
438 viral vaccines, and gene therapy vectors, warrant additional containment considerations. We
439 encourage early discussions with the applicable Agency center (i.e., product and facility group
440 with responsibility for the product) prior to engaging in the production of such IND products.

441
442 The production process is critical to ensuring the correct composition and safety of biological
443 and biotechnology products. For these products, it can be difficult to distinguish changes in
444 quality attributes, or predict the impact of observed changes in quality attributes on safety. This
445 is especially true for phase 1 studies where knowledge and understanding of an investigational
446 new drug is limited and where comprehensive product characterization is often unavailable,
447 especially for products that are difficult to characterize. Therefore, it is critical, beginning with
448 phase 1 studies, to adequately control and document the production process in conjunction with
449 appropriate testing to reproduce comparable IND product as necessary. Retained samples (e.g.,
450 drug substance, drug product, intermediate, in-process material) that can be subsequently
451 analyzed for comparison, can provide important links in reproducing comparable biological and
452 biotechnological products.

453
454 We recommend that appropriate equipment qualification and controls in production be in place
455 to ensure that units with safety-related functions (e.g., viral clearance, virus/toxin attenuation,
456 pasteurization) will perform as intended. Specific testing may also serve to complement these
457 functions. We recommend that testing for safety-related purposes such as viral loads, bioburden,
458 detoxification of bacterial toxins, virus clearance or inactivation, and clearance of substances
459 (e.g., antibiotics, chemicals) be used in production and that adventitious agent testing be
460 established as appropriate.

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462 Of particular importance in evaluating the environment to be used for production (see section V)
463 is the susceptibility of biotechnology and biological products to contamination with biological
464 substances including microbial adventitious agents (e.g., bacterial, viral, mycoplasma) that may
465 remain from previous research or production activities.

2. Multi-Product Facilities

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469 In addition to the recommendation in section VI.B, we recommend that multi-product facilities
470 have cleaning and testing procedures in place that ensure prevention and/or detection of
471 contamination by adventitious agents. To the extent possible, dedicated equipment and/or
472 disposable parts (e.g., tubing) is recommended. For multi-product areas, we recommend that
473 procedures be established to prevent cross-contamination and that demonstrate removal of the
474 previously manufactured product from shared equipment and work surfaces, especially if live
475 viral and vector processing occurs in a production area.

3. Gene Therapy and Cellular Therapy Products

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479 Due to the wide variety and unique production aspects of investigational gene and cellular
480 therapy products, producers should consider the appropriateness of additional or specialized
481 controls. Although we recommend that investigational cell and gene therapy products be
482 produced following the recommendations in this guidance, we recognize that it may not be
483 possible to follow each recommendation. For example, with some cellular products, it may be
484 impossible to retain samples of the final cellular product due to the limited amounts of material
485 available. We recommend that reasons for adopted approaches be included in the records on the
486 investigational product.

4. Multi-Batch Producers

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490 We are aware that, in some cases, investigational biological and biotechnology products covered
491 by this guidance may be produced as frequently as one batch per subject in phase 1 studies (e.g.,
492 therapeutic vaccines, cell therapies, gene therapies). Production of multiple batches will allow
493 additional production and testing information to accumulate in an accelerated manner as
494 compared to more conventional products. It is also important to have and adhere to appropriate
495 control procedures that enable the consistent manufacture of comparable drug substance and
496 drug products.

497
498 When producing multiple batches of the same investigational product, we recommend that
499 producers periodically conduct and document internal performance reviews. We recommend
500 that such a review assess the control and consistency of the production process and overall
501 product quality. This review would fall outside of routine production operations and would be
502 conducted to assess procedures, practices, and information, including data generated from
503 production and investigational new drug testing. Based on the review, appropriate modifications
504 and corrective actions can be taken to control procedures and production operations. The data
505 generated with each batch can also allow the producer to establish and/or refine acceptance
506 criteria as experience and knowledge permits and, therefore, to achieve more consistent
507 investigational new drug production.

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D. Sterile Products/Aseptically Processed Products

We recommend that special precautions be taken for investigational new drugs intended to be sterile. Thorough consideration should be given to controls for aseptic processing. The following examples are recommendations that should be considered:

- Conducting aseptic manipulation in an aseptic workstation under laminar flow conditions (e.g., an air classification of Class 100). Some examples of workstations include a laminar air flow workbench, biosafety cabinets, or barrier isolator system.
- Disinfecting the entire aseptic workstation as appropriate (e.g., before aseptic manipulation, or between different operations during the same day).
- Ensuring that items within a laminar airflow aseptic workstation not interrupt the airflow.
- Disinfecting gloves or changing them frequently when working in the laminar flow hood.
- Disinfecting the surface of nonsterile items (e.g., test tube rack, and the overwrap for sterile syringes and filters) with sterile disinfectant solution before placing them in the laminar flow hood.
- Performing manipulations of drug or components subsequent to a sterilizing step under appropriate conditions.
- Documenting and following all procedures intended to maintain the sterility of the components, in-process materials, and final product.
- Qualifying sterility tests (e.g., USP <71>) to demonstrate that the test article does not interfere with the test.
- Employing aseptic technique and control of microbiological impurities in components designed to prevent microbial and endotoxin contamination.
- Training personnel using aseptic techniques in those techniques.
- Qualifying for use equipment used for sterilization; performing appropriate calibration; keeping maintenance records.
- Creating documentation to support the use of sterile components and disposable equipment (e.g., filters, bags, containers) in the form of Sterilization/certification of analysis, or demonstration that the sterilization method is validated.
- Ensuring that release of the final product by the QC unit, or person, include an acceptable review of production records demonstrating that aseptic procedures and precautions were followed.
- Ensuring that final products are not released until acceptable results of sterility testing are known. We understand that products with a short shelf-life (e.g., radiopharmaceuticals, cellular products) may have to be released while results of the sterility test are pending based on results from other relevant tests (e.g., assessment of sterile filtration by bubble

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550 point filter integrity test, cell product — a negative gram stain, or other rapid microbial
551 detection test and negative endotoxin test)). We recommend that positive results from
552 sterility or other relevant tests result in an investigation to determine the cause of
553 contamination followed by corrective action if warranted.

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GLOSSARY

Acceptance Criteria - numerical limits, ranges, or other suitable measures for acceptance of test results that the drug substance or drug products or materials at other stages of their manufacture should meet

Active Pharmaceutical Ingredient (API) (or Drug Substance) - any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Batch - a specific quantity of a drug or other material intended to have uniform character and quality, within specified limits, and produced according to a single production order during the same cycle of manufacture

Component - any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product

Contamination - the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, in-process material, or IND product during production, sampling, packaging, or repackaging, storage or transport

Cross-Contamination - contamination of a material or IND product with another material or product

Drug product - a finished dosage form (e.g., tablet, capsule, solution) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient, but is intended to be used as a placebo.

In-process material - any material fabricated, compounded, blended, or derived by chemical reaction (e.g., intermediate) that is produced for, and used in, the preparation of the drug product

Investigational new drug (IND product) - a new drug or biological drug that is used in a clinical trial. The term also includes a biological product that is used in vitro for diagnostic purposes.

Microdose studies - studies in which participants are administered a single dose of less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained in vitro and in vivo (typically doses in, or below the low microgram range) and at a maximum dose of ≤ 100 micrograms.

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600 **Production** - all operations involved in the preparation of an IND product from receipt of
601 materials through distribution including processing, storage, packaging, labeling laboratory
602 testing and quality control

603
604 **Screening study** - a study that is performed under an exploratory IND application, is intended to
605 compare the properties of related active moieties to screen for the preferred compound or
606 formulations for additional clinical development under a traditional IND application.

607
608 **Specification** - a list of tests, references to analytical procedures, and appropriate acceptance criteria
609 that are numerical limits, ranges, or other criteria for the tests. It establishes the set of criteria to which a
610 drug substance or drug product should conform to be considered acceptable for its intended use.

611 *Conformance to specification* means that the material, when tested according to the listed
612 analytical procedures, will meet the listed acceptance criteria

613
614 **Sponsor** - person who takes responsibility for and initiates a clinical investigation

615
616 **Quality Units** - an organizational unit that fulfills quality control responsibilities. This can be in
617 the form of separate QC units or a single individual or group, depending upon the size and
618 structure of the organization.

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