

39 Before addressing the frequently asked questions on the clinical development of combination
40 products, we want to set forth some fundamental background on how combination products
41 are regulated by the agency.

42 **a. What is a combination product?**

43 As defined in 21 CFR 3.2(e), a combination product is a product comprised of any
44 combination of a drug and a device, a biological product and a device, a drug and a biological
45 product, or a drug, device, and a biological product. This includes:

- 46 • A product comprised of two or more regulated components; i.e., drug/device,
47 biologic/device, drug/biologic, or drug/device/biologic, that are physically,
48 chemically, or otherwise combined or mixed and produced as a single entity. This
49 guidance refers to these types of combination products as “**single entity**” combination
50 products.
- 51 • Two or more separate products packaged together in a single package or as a unit and
52 comprised of drug and device products, device and biological products, or biological
53 and drug products. This guidance refers to these types of combination products as
54 “**kit**” combination products.
- 55 • This guidance also refers to “**cross-labeled**” combination products, which are defined
56 as follows:
 - 57 ○ A drug, device, or biological product packaged separately that according to its
58 investigational plan or proposed labeling is intended for use only with an
59 approved individually specified drug, device, or biological product where both
60 are required to achieve the intended use, indication, or effect and where upon
61 approval of the proposed product the labeling of the approved product would
62 need to be changed; e.g., to reflect a change in intended use, dosage form,
63 strength, route of administration, or significant change in dose.
 - 64 ○ Any investigational drug, device, or biological product packaged separately
65 that according to its proposed labeling is for use only with another individually
66 specified investigational drug, device, or biological product where both are
67 required to achieve the intended use, indication, or effect.

68 For purposes of this guidance, a “**constituent part**” of a combination product is an article in a
69 combination product that can be distinguished by its regulatory identity as a drug, device, or
70 biological product, as defined in section 21 U.S.C. 321, Federal Food, Drug, and Cosmetic
71 Act (Act), and 42 U.S.C. 252 (i), Public Health Service Act, and as set forth in 21 CFR 3.2(k).
72 For example, a device coated or impregnated with a drug has two constituent parts, the device
73 constituent and the drug constituent.

74 **b. Generally speaking, how are combination products regulated?**

75 The OCP was established in 2002 as required by the Medical Device User Fee and
76 Modernization Act of 2002. OCP is responsible for the prompt assignment of a lead Agency
77 center that will have primary jurisdiction for the review and regulation of a combination
78 product; ensuring timely and effective premarket review by overseeing the timeliness of and

79 coordinating reviews involving more than one agency center; ensuring consistent and
80 appropriate postmarket regulation of combination products; and resolving disputes regarding
81 the timeliness of combination product review. OCP also works with agency centers to develop
82 guidance and regulations to make the regulation of combination products as clear, consistent,
83 and predictable as possible.

84 Under section 503(g)(1) of the Act, a combination product is assigned to a center with
85 primary jurisdiction, or a lead center, based on a determination of the primary mode of action
86 (PMOA) of the combination product. PMOA is defined as "the single mode of action of a
87 combination product that provides the most important therapeutic action of the combination
88 product." Based on its PMOA, a combination product is assigned to one of the Agency's
89 three human medical product Centers: the Center for Biologics Evaluation and Research
90 (CBER), the Center for Devices and Radiological Health (CDRH), or the Center for Drug
91 Evaluation and Research (CDER). The lead center has oversight responsibility for the review
92 and regulation of the combination product. The lead center often consults or collaborates with
93 other agency components and OCP, as appropriate, to identify and evaluate the information
94 needed for a regulatory submission (e.g., investigational application or marketing
95 authorization).

96 **c. What existing FDA guidance documents apply to combination products?**

97 FDA websites contain a wide variety of guidance documents for the development and testing
98 of drugs, devices, and biological products. In particular, OCP has posted a listing of guidance
99 documents that we believe are relevant to combination products, and included among these
100 are general and product-specific guidance documents that may assist with clinical study-
101 related issues: <http://www.fda.gov/oc/combo/guidance.html>.

102 However, currently few guidance documents address the specific issues encountered during
103 the pre-clinical and clinical development of a combination product. This guidance document
104 is intended to address questions pertaining to those issues, and, therefore, supplements
105 existing guidance documents developed by CBER, CDER, or CDRH, and OCP.

106 **III. Pre-Clinical Safety Studies**

107 **a. How can combination product sponsors ensure that preclinical studies are**
108 **appropriately designed?**

109 The design of preclinical studies varies by the type of product studied and the data that will
110 ultimately need to be included in an IND or IDE. Because of these individualized and unique
111 factors, FDA recommends that sponsors contact their lead Center review division to discuss
112 this issue. Sponsors can also obtain insight into study design by reviewing approval
113 documentation for approved combination products. Finally, FDA also encourages sponsors to
114 consult the guidance documents that are applicable to combination products (*See*
115 <http://www.fda.gov/oc/combo/guidance.html>). Examples of guidance documents that
116 might be helpful in the design of preclinical studies include *Exploratory IND Studies, Format*
117 *and Content of the Nonclinical Pharmacology/Toxicology Section of an Application*, and
118 *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

119 **b. How does conducting clinical studies under an IDE versus an IND affect**
120 **preclinical studies?**

121 FDA believes that this factor alone should not have a substantial impact on preclinical studies.
122 Whether an Investigational New Drug (IND) or Investigational Device Exemption (IDE)
123 application is used, the application may contain information on the entire combination
124 product, as appropriate. With respect to preclinical studies, the focus should remain on
125 safety-related issues applicable to a constituent part that would typically be included.

126 **IV. IND and IDE Applications**

127 OCP receives numerous questions about how the IND and IDE requirements apply to a
128 sponsor. The questions in this section are designed to apply to those process-oriented issues.

129 **a. What determines whether a sponsor should file an IND and/or an IDE?**

130 For most combination products, applicants should submit only one investigational application
131 (IND or IDE) for the clinical investigation(s) of the combination product as a whole. The
132 FDA center with primary jurisdiction over the combination product will determine whether a
133 sponsor should file an IND or IDE. Typically CDRH will require an IDE, and typically
134 CDER or CBER will require an IND.

135 **b. Generally speaking, what content should an applicant include in an IND**
136 **or IDE for a combination product?**

137 Whether an IND or IDE application is used, the application may contain information on the
138 entire combination product, as appropriate. For example, if the product is a drug-device
139 combination product, the IND or IDE may need to include the details on the drug and device
140 that typically would be submitted in an IND for the drug or biological constituent part **and** in
141 an IDE for the device constituent part. Of course, the specific content of an IND or IDE will
142 vary based upon the product and its constituent parts. If a sponsor wants to deviate from the
143 typical content of the IND and IDE, FDA recommends discussing the desired approach with
144 the applicant's lead center.

145 Additionally, as stated above, there are a number of existing guidance documents that can
146 assist sponsors with issues surrounding the development of combination products. Moreover,
147 generally, the regulatory guidance for INDs and IDEs provides substantial flexibility in
148 considering how to address the issues posed by a particular product. For example, two
149 guidance documents that may be of interest to combination product developers are: (1)
150 *Exploratory IND Studies*, which provides an alternative for exploring candidate products
151 during research and development prior to selecting the composition for further development,
152 (See *Guidance to Industry and Reviewers: Exploratory IND Studies* at
153 <http://www.fda.gov/cder/guidance/7086fnl.pdf>) and (2) guidance on changes that may occur
154 during investigational development of a device (See *Guidance to Industry: Changes or*
155 *Modifications During the Conduct of a Clinical Investigation* at
156 <http://www.fda.gov/cdrh/ode/guidance/1337.pdf>).

157 However, because sponsors have approached the agency with a number of questions specific
158 to combination products, this guidance document is intended to supplement the existing
159 guidance to address issues that pertain specifically to combination products.

160 **c. How should an applicant incorporate device-related information into a**
161 **“regular” IND for drug-device or biological-device combination product,**
162 **and how should an applicant incorporate drug-related information into an**
163 **IDE for a drug-device or biological-device combination product?**

164 To the extent that an IND needs to include information about a device constituent part, the
165 agency believes that the IND format and sections are sufficiently flexible to capture device-
166 related information. For example, many applicants have successfully used the CMC section
167 of an IND to capture device-related information.

168 Similarly, to the extent that an IDE needs to include information about a drug or biological
169 constituent part, the IDE format and sections are sufficiently flexible to capture drug- or
170 biological-related information.

171 **d. How should an applicant incorporate device-related information into an**
172 **IND in the Common Technical Document (“CTD”) format for drug-**
173 **device or biological-device combination product?**

174 FDA recognizes that INDs in the CTD format may be less flexible in their application to
175 combination products than traditionally formatted INDs. However, the agency believes that
176 an applicant should be able to adapt the CTD format to encompass device-related information.
177 In particular, many applicants have successfully created new sections in the CTD IND as
178 required to capture device-related information. One example of this approach would be an
179 applicant’s use of the regular, drug-related CMC section and creation of a separate, device-
180 related CMC.

181 **e. To what extent may an applicant suggest or request coordination among**
182 **Centers, branches, or divisions in establishing submissions requirements**
183 **for a clinical study on a combination product?**

184 The Agency has established policies regarding coordination among Centers, branches, and
185 divisions with regard to combination products. Additionally, the Agency encourages
186 applicants to make requests and offer suggestions for how such coordination should occur.
187 Some ways in which applicants may make these requests and suggestions are by working with
188 the relevant Project Manger or Branch Chief, or through meeting requests. Please also see
189 question X.c. in this guidance for more information about meeting requests.

190 **V. Clinical Study Design**

191 **a. How does an applicant assess what clinical data are needed for a**
192 **combination product?**

193 FDA considers the entire combination product in assessing the data required to support the
194 product submission. For example, while one part of the product might already be approved,

195 another part might be new and raise questions about safety or efficacy. The combination of
196 constituent parts may also raise important safety and efficacy issues. Therefore, in planning
197 for clinical studies to support a marketing submission for a combination product, sponsors
198 should consider what parts of their combination product are investigational and require
199 clinical data to support marketing approval, as well as how the parts interact and what data are
200 needed to support claims relevant to that interaction.

201 For example, in a drug-device delivery system, the data should support claims that the
202 constituent parts are safe and effective for their individual intended purposes, as well as that
203 the product as a whole is safe and effective for its intended use. Clinical data may be required
204 to support all of these uses, although the specific data needed for the product at issue may
205 vary depending upon the approval status of the constituent parts and the type of device part.

206 Additionally, whether the constituent parts should be evaluated separately, as a system, or
207 both, is a highly variable issue that varies depending on the product, the approval status of the
208 constituent parts, and the applicant's desired claims (e.g., does each individual product have
209 effectiveness claims). To expand on the drug-delivery delivery system example, consider a
210 needle-free autoinjector. While the applicant should consider the autoinjector's efficacy
211 separately, the applicant should also evaluate the interaction between the autoinjector and
212 drugs, considering issues such as the rheological effect of shearing forces on macromolecules.
213 However, an efficacy study may not be required if initial testing shows that the drug is not
214 impacted by interaction with the device. As with other individual product issues, the Agency
215 encourages early and frequent discussions between the applicant and the Agency to determine
216 the appropriate development pathway for the product.

217 **b. What inputs should a sponsor use for planning its clinical studies?**

218 In terms of specific inputs for the assessments described above, the impact of the constituent
219 parts together may be evaluated by *in vitro* testing, CMC/bench testing, or other assessments
220 that are appropriate for the specific product. Another major input is risk assessments, such as
221 end user or usability assessments. These assessments can inform important considerations,
222 such as:

- 223 - User training/design validation and the training aspect on how to use the product.
- 224 - Anticipated complaints and adverse events.
- 225 - Questions and issues to aide in complaint and adverse event investigation. For
226 example, such questions should seek to differentiate which constituent part caused a
227 complaint/adverse event.
- 228 - Product packaging and labeling that allows subjects and clinicians to distinguish
229 among the various parts of the investigational product.
- 230 - For a drug constituent part, potential over- or under-dosing issues.
- 231 - Product return issues and how the product can be appropriately controlled to the extent
232 it represents a biological hazard (e.g., sterilization, EH&S handling specification).

233 **c. What sample size requirements apply to sponsors of clinical studies on**
234 **combination products?**

235 Beyond the general inputs above, sponsors have asked how they can best assess and
236 determine appropriate sample size for combination product studies. Because combination
237 products involve such a wide range of technology and corresponding risk levels, there may be
238 a multitude of factors impacting issues such as sample size. Specifically:

239 - The product's investigational parts and the science and technology of the combination
240 product.

241 - As with other clinical studies, the type, phase, and objectives of a study are significant
242 factors.

243 - Existing clinical data.

244 - Complaint projection rates as determined by internal or external benchmarking. For
245 example, these considerations may drive the development of the sample size
246 necessary to assess and establish adverse event occurrence ratings.

247 - Primary mode of action of the combination product and which Agency Center is the
248 lead Center for the combination product.

249 Clearly, these issues are individual to the combination products, and as such, FDA encourages
250 early discussion with the Agency around these concerns. Additionally, existing guidance,
251 including International Conference on Harmonization (ICH) guidelines, can offer assistance
252 to sponsors.

253 **d. How do study design requirements change based upon the type of**
254 **combination product being studied (e.g., single entity, kit, cross-labeled)?**

255 As mentioned above, FDA considers the entire combination product in assessing the data
256 required to support the product submission, so the type of clinical data needed (and hence
257 study design) will be affected by the parts of the product that require clinical data to support
258 marketing approval. For some new combination products, the clinical data may need to
259 support the entire combination product, particularly when the product's efficacy claims relate
260 to both constituent parts or when the product is highly integrated. On the other hand, as
261 discussed above, clinical studies may be more limited in scope in situations where a
262 constituent part is already approved, there will be no efficacy claims relating to a product, or
263 the constituent part would not otherwise require data (e.g., a low risk device).

264 That said, because combination products represent such a wide variety of risk levels, it is
265 difficult to generalize the permutations of study design requirements.

266 **e. How can a sponsor best demonstrate safety across a range of drugs for a**
267 **drug delivery platform that can be used with a variety of drugs?**

268 One central question here is whether and to what extent sponsors may bridge studies for one
269 drug to the other. If the drug and study population are sufficiently similar, such bridging
270 studies may be possible. Typically, bridging studies will be more suitable when the drug
271 products contain the same drug substance (i.e., are “generational” changes), rather than for a
272 completely new drug product. For example, in terms of drug similarities, sponsors should
273 consider issues such as viscosity, acidity, and light sensitivities. Sponsor should also consider
274 similarities in the study already conducted and the study that would otherwise be needed if a
275 bridging study were not conduct. Factors to conduct include endpoints, patient population
276 and size, inclusion/exclusion criteria, and clinical setting.

277 Additionally, for drug delivery devices that will be used with a variety of drugs, the applicant
278 may need to conduct testing on multiple drugs and/or representative drugs in a class, in order
279 to support the device’s intended use.

280 **f. If a combination product uses a device as a delivery system and intends**
281 **the product for home use, what clinical data should be collected (if any) to**
282 **support a “home use” claim?**

283 Medical devices, like other FDA-regulated products, must be safe and effective for the uses
284 for which they are intended. If a device is intended for home use, the sponsor must be able to
285 demonstrate that the intended users are able to operate the device safely and effectively under
286 realistic conditions. For combination products that include a device constituent part, this
287 assessment will likely include an evaluation of the impact of human factors on the safety and
288 effectiveness of the combination product. Such an assessment would evaluate how users
289 operate the system in the home use setting and would cover all components and accessories
290 necessary to operate and properly maintain the device; e.g., controls, displays, software, logic
291 of operation, labels, instructions, analysis of critical tasks, use error hazard and risk analysis.

292 FDA has also issued guidance on home use claims specific to diagnostic devices that may be
293 useful input for other products. Here, at a high level, sponsors should demonstrate that:

- 294 • the user will get acceptable results from the test compared to the results obtained when
295 a professional performs the test;
- 296 • the user will be able to interpret test results correctly; and
- 297 • the benefits of the test outweigh its risks.

298 However, such data development may not necessarily occur in a clinical study setting (see
299 below, Question IV.c.v. Further guidance on home use claims for diagnostic devices can be
300 found at: <http://www.fda.gov/cdrh/oivd/doc-fdareview.html>

301 **VI. Specific Regulatory Requirements**

302 In addition to questions about investigational product submissions and clinical study design,
303 sponsors often pose questions concerning how specific regulatory requirements that typically
304 apply in the drug, biologic, or device setting should be applied to the development of a
305 combination product.

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a. Labeling

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i. In a study that is not completely blinded, how should constituent parts be labeled?

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Generally, applicants should use the rules that apply to their investigational application – i.e., the IND or IDE rules. As discussed above, clinical studies for most combination products will be conducted under either an IDE or IND (not both). In cases where compliance with these rules presents a conflict or problem for a sponsor, we suggest discussing the issue with your lead Center.

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b. Manufacturing Issues and GMPs

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i. Are sponsors permitted to manufacture investigational combination products manually?

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Yes, sponsors may manually manufacture investigational combination products as long as the product complies with all controls that ordinarily apply, such as applicable Good Manufacturing Practices (see following questions). Manual manufacturing could be employed throughout the research process. We anticipate that manual manufacturing would most commonly be used for combination products incorporating device constituent parts.

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ii. For drug-device combinations under an IND, what drug GMP requirements apply to the device constituent part, given that devices under an IDE are typically exempt from GMP requirements, except for design controls?

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For drug-device investigational products under an IND, the relevant drug GMP requirements will depend on the type of combination product. Specifically, for combination products that are produced as a single-entity or are co-packaged, our September 2004 draft guidance on GMPs applicable to combination products recommended that the relevant drug GMPs would apply to the device constituent part during and after joining the constituent parts together. In contrast, under the draft guidance, the drug GMPs would not apply to the device constituent of a cross-labeled combination product, because the device constituent part will only be provided and manufactured separately from the drug or biological constituent parts. For more information, please consult the September 2004 draft guidance on GMPs applicable to combination products: <http://www.fda.gov/oc/combinations/OCLove1dft.html>.

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iii. For drug-device combinations under an IDE, what device GMP requirements apply to the drug constituent part? For example, do design validation and/or verification requirements apply to the drug constituent part?

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Devices approved under an IDE are exempt from the Quality System regulation (QSR), except for the design control requirements under 21 CFR § 820.30 and those requirements with which the sponsor states its intention to comply in the IDE. As recommended in our September 2004 draft guidance on GMPs applicable to combination products, design controls are one element of the QSR that does not overlap with drug GMPs and should, therefore, be

345 applied to a drug-device combination products when and to the extent that the constituent
346 parts are physically combined or merged. Therefore, following the recommendations in the
347 draft guidance, for combination products that are produced as a single-entity or are co-
348 packaged, design controls would apply to the drug constituent part during and after joining the
349 constituent parts together. However, the QSR, including design controls, would not apply to
350 the drug constituent of a cross-labeled combination product, because the drug constituent part
351 will be provided and manufactured separately from the device constituent parts. Note that if
352 the sponsor elects to comply with other parts of the QSR these may also apply to a single
353 entity or kit combination product, to the extent those QSR requirements do not overlap with
354 the drug GMPs (e.g., CAPA and purchasing controls – *See* September 2004 Draft GMP
355 Guidance).

356 **iv. How do risk assessments performed on devices apply to the drug**
357 **constituent part of a drug-device combination product?**

358 Risk management is essential to and required for the development and control of medical
359 devices and its importance has also been recognized in the pharmaceutical industry. For
360 example, the ICH Q9 guidance outlines the application of risk management for
361 pharmaceuticals and is very similar to ISO 14971, a recognized standard for risk management
362 to medical devices. In all, the Agency and stakeholders alike are increasingly recognizing
363 that quality risk management is a valuable component of any effective quality system.
364 Therefore, we anticipate that most effective quality systems for combination products will
365 incorporate principles of risk management, whether as a direct requirement under applicable
366 device regulations or as an industry best practice.

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368 In this regard, when performing a risk assessment, the manufacturer should consider the
369 probability and severity of the harm or physical injury or damage to health (including the
370 damage that can occur from loss of product quality or availability), or damage to property or
371 the environment¹, that can be caused by a failure of the product. As applied to a combination
372 product, this harm should be assessed with respect to the product as a whole and its
373 constituent parts, regardless of whether the constituent parts are provided as a single entity or
374 otherwise. This stage of the assessment could be completed through performance of a
375 Preliminary Hazard Analysis or a similar assessment. Additional risk assessment techniques
376 should focus on the risk contribution of specific parts of the product or process. The potential
377 problems and/or failures of the drug constituent part, including the process of formulating,
378 storing and combining with the device (if applicable), can be assessed separately in a
379 component or process Failure Modes and Effects Analysis (FMEA) to establish and determine
380 the appropriate mitigation to reduce or eliminate these risks.

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382 One example of the risk assessment process as applied to combination products is with
383 respect to clinical studies. Here, preliminary risk assessments should be completed before the
384 start of the study (based on in-vitro and pre-clinical work) and should be revised based on
385 results provided during the study. Such risk assessments would be applicable to the drug
386 constituent part of a drug-device combination product.

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¹ *See* ISO 14971:2007 and ICH Q9.

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v. Should product design validation/user testing requirements be incorporated into clinical studies on combination products?

390 Combination products that incorporate device constituent parts may need to consider a variety
391 of usability and human factors inputs. For example, the use of the investigational product
392 might be far more controlled (e.g., clinic or in-patient setting) with significant amounts of
393 patient follow-up, than in the final user setting. Therefore, sponsors should consider how
394 users operate the system under stressful conditions. This analysis should encompass all
395 components and accessories necessary to operate and properly maintain the device; e.g.,
396 controls, displays, software, ergonomics, logic of operation, labels, instructions, analysis of
397 critical tasks, use error hazard and risk analysis. Importantly, however, clinical studies are
398 often not required to evaluate these portions of design validation. Indeed, the instructions for
399 use (IFU) and training implemented under a clinical study are necessarily different than those
400 that will be implemented for a final marketed product. One purpose of a clinical study is
401 often as a source of Design Input, in that they help to identify changes, additions or revisions
402 to user training and instructions for a final product.

403 For products where the PMOA is drug or biologic, the role the device constituent part plays in
404 the safety and/or effectiveness of the drug is a critical factor in determining the need for and
405 implementation of device validation and user studies. If the safety and effectiveness of the
406 drug can be established independently from the device constituent part, sponsors may conduct
407 non-clinical, simulated use studies with both quantitative and qualitative measures to validate
408 the usability of the products, including the IFU. These non-clinical methods can be used for
409 the device validation separate from a clinical study, for example, in a small post-Phase III
410 bridging study. The results of these types of studies should be used to evaluate the impact on
411 the drug and can result in product design changes, changes in the IFU, and the identification
412 of the need for and the design of a training program. Unless the product changes arising as a
413 result of these studies impact the drug's effectiveness, clinical studies should typically not be
414 required. These studies should be discussed and summarized as part of the final submission
415 approval and should be maintained in the master file, thus available for FDA inspection.

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417 For products in which the safety or effectiveness of the drug or biologic cannot be separated
418 from the performance of the device, the inherent nature of the product may necessitate a
419 clinical approach. For example, in highly integrated and high risk products, such as
420 implantable drug-eluting stents, design validation has been a part of clinical study design.
421 However, the use of clinical trials for design validation should not preclude use of pre-clinical
422 and simulated user studies to develop and refine the device use, including instructions and any
423 required training.

424 Finally, for products in which the drug or biologic plays an ancillary role, if clinical studies
425 are required, these studies may be the culmination of the device validation and should include
426 elements that satisfy the requirements to establish the "usability" of the device and the
427 required instructions, in addition to establishing its safety and effectiveness for the intended
428 use. Earlier (pre-clinical) user groups and/or simulated use user studies may be also be
429 required to fully develop the product that is used in the clinical trial.

430 **VII. Safety Reporting**

431 **a. How does a sponsor determine what adverse event reporting requirements**
432 **apply in a clinical study on a combination product?**

433 Sponsors should use the rules that apply to their investigational application – i.e., the IND or
434 IDE rules. As discussed above, clinical studies for most combination products will be
435 conducted under either an IDE or IND (not both).

436 **b. What adverse event reporting requirements apply when a study involves a**
437 **combination product comprised of an unapproved or uncleared**
438 **constituent part and a cleared or approved constituent part?**

439 Adverse event reporting for the investigational constituent part will be governed by the rules
440 of the applicable investigational application – i.e., the IND or IDE rules. If the sponsor
441 markets the cleared or approved product, then the sponsor would report adverse events under
442 the rules that apply to that product (e.g., drug safety reporting requirements, medical device
443 reporting, etc). If a firm other than the sponsor markets the cleared or approved product, we
444 recommend that the sponsor report adverse events pertaining to the marketed product to the
445 firm that markets the product, although the regulations may not require such reporting.

446 For example, consider a situation in which a sponsor imports a device into the U.S. and has
447 the device shipped to a distributor. The distributor then distributes the device to various
448 clinical sites participating in the research. Here the sponsor may have an obligation to report
449 an adverse event about the marketed device to the original manufacturer because the sponsor
450 is likely to be considered the “importer” of the approved product under the medical device
451 reporting regulations.² On the other hand, if the sponsor did not import the device into the
452 U.S. and simply purchased it from a U.S. manufacturer or distributor, the sponsor would
453 ordinarily not have a regulatory obligation to report an adverse event to the manufacturer.

454 In any event, duplicate reporting of an adverse event to the agency (e.g., from the sponsor and
455 the manufacturer) is not required.

456 **VIII. IRB/Ethics Committee Review**

457 **a. How does FDA ensure that IRBs and ECs have adequate combination**
458 **product expertise?**

459 FDA regulations require that IRB members have “varying backgrounds to promote complete
460 and adequate review of research activities commonly conducted by the institution”, and the
461 experience and expertise of IRB members must qualify the IRB to “to promote respect for its
462 advice and counsel in safeguarding the rights and welfare of human subjects.” (See 21 CFR §
463 56.107). Thus, pursuant to agency regulation, it is the IRB’s responsibility to ensure that its
464 members are qualified to review the research that is the subject of IRB’s jurisdiction, and the
465 IRB’s compliance with these requirements would be within the scope of FDA’s inspection of
466 an IRB.

² 21 CFR §§ 803.3; 803.40.

467 With respect to combination products, sponsors have been confronted with situations in which
468 IRBs are unclear on the regulatory issues surrounding combination products. For example,
469 some IRBs may try to impose drug requirements or standards in a clinical study of a drug-
470 device combination product, even when the PMOA of the product is that of a device and the
471 study is conducted under an IDE. Thus, FDA believes a need exists for IRBs to become more
472 familiar with issues impacting clinical studies of combination products, and this guidance
473 represents one step in that direction.

474 The agency also believes that sponsors can help ensure IRBs have adequate expertise and
475 experience by researching relevant member experience and, if necessary, by providing
476 materials to help educate IRB members on the investigational product and combination
477 products generally. Taking the example above, such materials could describe the PMOA of
478 the combination product, the significance of the PMOA determination, and how it affects the
479 clinical study process. Such education and informative materials may help in expediting the
480 IRB review process for the combination product.

481 **IX. Specific Technologies – Prefilled Injection Devices**

482 In addition to questions on specific regulatory requirements, we also frequently receive
483 questions about the development of a specific type of combination product. In particular,
484 applicants have posed many questions regarding combination products incorporating prefilled
485 injection devices. Therefore, in addition to the general guidance above regarding clinical
486 studies on combination products, below we address some common questions we have
487 received on products incorporating prefilled injection devices.

488 **What bioequivalence or other bridging studies are required in order to make the** 489 **following product changes?**

490 **a. a vial to a prefilled injection device in a drug-device combination product?**

491 Here the product is being changed from either a drug or biological to a combination product.
492 Therefore, this change involves a significant change to the primary and secondary container
493 closure and should require complete characterization of compatibility and stability, including
494 performance and functional device testing (design verification studies) and design validation
495 studies (user testing). In terms of specific requirements, if there is automated injection with
496 an external power source, the effect on the drug must be assessed. An example of a potential
497 effect on the drug is the rheological effect of shearing forces on macromolecules. Further, if
498 there is a significant change in the method that the needle penetrates the injection site (e.g.,
499 needle free injection), a small crossover study establishing the necessary equivalence of the
500 syringe versus the injection device product may be warranted.

501 **b. a syringe to a prefilled injection device in a drug-device combination** 502 **product?**

503 In contrast to the situation above, here the product is already starting from one type of
504 combination product (as opposed to a stand-alone drug or biological product) and is changing
505 to another combination product. Therefore, this change may be more limited than the above
506 example. For example, it may not involve a change to the primary container closure, only to

507 the functional secondary packaging. (Note, however, that this is not true if the syringe itself is
508 changed and/or the pre-filled injection device has a unique container.) For this more limited
509 change, appropriate supporting data should include performance and functional device testing
510 (design verification studies) and design validation studies (user testing). Generally speaking,
511 no new leachables and extractables, biocompatibility or stability studies would be warranted
512 unless the specific change raises issues in these areas. Additionally, if the additional
513 packaging provides additional light stability, then a photostability study should be done. As
514 with the above example, studies on the rheological effect of shearing forces on
515 macromolecules may also be warranted in order to fully assess the effect on the drug.

516 X. Agency Process and Communications

517 Finally, we want to address how a sponsor can obtain agency input on questions regarding
518 combination product development and how to resolve those instances where a conflict arises
519 between a sponsor and the agency.

520 a. What can a sponsor do if they believe that FDA is being too demanding 521 with respect to what preclinical or clinical studies are required for a 522 combination product?

523 Sponsors have several different avenues for approaching disputes with the agency. In
524 particular, sponsors are always welcome to contact either the Agency-wide or Center
525 Ombudsmen for assistance in resolving issues and disputes involving the regulatory process
526 and/or the application of Agency policies and procedures. FDA regulations also set forth a
527 process for internal agency review of decisions, such as how sponsors may request review of
528 a scientific controversy by an appropriate scientific advisory panel or an advisory committee
529 (21 CFR § 10.75). The agency has published guidance documents on these procedures as
530 well (See, for example, *Guidance for Industry; Formal Dispute Resolution: Appeals Above
531 the Division Level*, available at <http://www.fda.gov/cber/gdlns/dispute.htm>; and *Medical
532 Device Appeals and Complaints: Guidance on Dispute Resolution*, available at
533 <http://www.fda.gov/cdrh/modact/dispresl.pdf>; and *Resolving Scientific Disputes Concerning
534 The Regulation Of Medical Devices, A Guide To Use Of The Medical Devices Dispute
535 Resolution Panel; Final Guidance for Industry and FDA*, available at
536 <http://www.fda.gov/cdrh/resolvingdisputes/1121.html>).

537 In addition, OCP is available as a resource to sponsors anytime throughout the product
538 development process for issues pertaining to the development and regulation of combination
539 products. For example, OCP is often a useful resource in assisting sponsors with issues
540 involving inconsistency between or among agency divisions that a sponsor believes is
541 unjustified. In particular, we have found that OCP may act as a “mediator” to help resolve the
542 issues a sponsor has within the Centers.

543 b. Do sponsors of clinical studies on combination products have the ability to 544 meet with FDA on clinical research issues in addition to existing avenues 545 for pre-IND or pre-IDE meetings?

546 The agency recognizes that, currently, sponsors have limited access to FDA for input on
547 combination product clinical studies, other than formal pre-IDE and pre-IND meetings.
548 Moreover, FDA recognizes that the special circumstances surrounding clinical trials on
549 combination products demonstrate a need for alternative and additional informal and formal
550 mechanisms for early and continued agency-sponsor communication regarding these
551 products. In particular, many of these sponsor companies are small, start-up companies with
552 limited resources and, for the most cutting-edge combination products, even larger companies
553 are unlikely to have expertise in both device and drug or biologic requirements and will
554 therefore need more “basic” assistance and guidance. Further, to date, very little guidance
555 and precedent exists for many of these products. For these reasons, agency requirements and
556 expectations are likely to evolve on a case-by-case basis and in a manner that is best
557 facilitated by strategic and interactive meetings, rather than the question and answer format of
558 current meetings. Finally, FDA also benefits from education and discussion on the
559 technologies and unique elements of these products, and again, the current meeting format is
560 not always optimal for the type of educational and informative meetings that can provide a
561 foundation for the agency.

562 In light of the above, sponsors are invited to submit written requests for meetings to discuss
563 product development and clinical research issues to OCP. This request should describe the
564 combination product at issue, describe the issues and relevant questions, and suggest agency
565 personnel who should attend the meeting. OCP will then coordinate with the responsible
566 Centers and individuals. If appropriate, these meetings, which may occur both before and
567 during the clinical development process, may be treated as Type C meetings under existing
568 agency rules.

569 Additionally, sponsors also have existing regulatory avenues under which they may request
570 agency input. For example, under 21 C.F.R. § 10.85, sponsors may submit a request for an
571 advisory opinion to the Division of Dockets Management. In general, the regulations require
572 the agency to respond within 180 days of receipt of such a request. One benefit of requesting
573 an advisory opinion is that the agency’s response represents the formal position of the agency
574 on the issues involved, thus, except in unusual situations where an immediate and significant
575 danger to health is involved, the agency is obligated to follow its response unless it is
576 amended or revoked pursuant to the relevant regulatory requirements. The agency will not
577 recommend legal action against a person or product with respect to an action taken in
578 conformity with an advisory opinion that has not been amended or revoked pursuant to
579 applicable regulatory requirements. Please see 21 CFR § 10.85 and related sections for
580 additional information about requesting an advisory opinion.

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