Combination Products Coalition
Clinical Trial Q&A

May 11, 2012

	Question	CPC Position/Understanding	Examples (Illustration of Question/Position)	Issues/Concerns/Inconsistencies (ie, reason for FDA guidance request)
1	Does the Agency agree that a separate (stand-alone) clinical investigation may be performed to establish safety and/or functionality of the drug delivery device (device constituent part) under an IDE? If yes, under what conditions would an abbreviated IDE (non-significant risk [NSR] study) be appropriate?	An IDE is an option for a drug delivery device clinical investigation when the study objectives are primarily device related and an active drug product will not be utilized. The clinical investigation can be performed under an IDE to assess the device feasibility, tolerability, performance, usability, and reliability when the 'delivered product' is a drug/biologic mimic solution, ie, saline or placebo (the formulation's excipients minus active substance). The investigation may be conducted under an abbreviated IDE (NSR study), subject to IRB review/approval, if the 'delivered product' has a known and non-toxic history (eg, sucrose, polysorbate) and use of the device meets the requirements for a NSR study (reference 21 CFR 812.3(m) and *Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies* (http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf). The IDE approach should be an option of the sponsor and CDER/CBER should agree to accept an IDE (significant risk [SR] or NSR study) as if it was conducted under an IND. Clinical investigations performed under either the IND or IDE regulations should equally support licensing of the drug delivery combination product as long as they maintain compliance with previously identified applicable	Example 1.1 - NSR IDE for tolerability clinical trial: Drug delivery device used to assess the tolerability (eg, patient comfort, pain, and/or bruising) of a drug delivery device using a known and non-toxic drug/biologic mimic solution. Example 1.2 – NSR IDE for device feasibility or design validation clinical trial: Drug delivery device used to inject saline for the purpose of assessing user interface (eg, device features, instructions for use, interoperability with other devices, preferred injection technique or site) or device injection specifications (eg, injection depth or injection time).	Industry would like assurance that results from drug delivery device protocols reviewed by CDRH under an IDE will be accepted by CDER/CBER as valid data and not discounted because the studies were not conducted under a drug-specific IND or reviewed by CDER/CBER reviewers. Likewise, industry would like clarification that the option to conduct studies under abbreviated IDE rules will be acceptable to CDER, CBER, and CDRH for submission in BLAs/NDAs.

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		regulations and are sound in design. Note: In order to ensure the device will perform as intended, design controls apply to the development of the drug delivery device, regardless of which investigational application is submitted (reference 21 CFR 812.1).		
2	What guidance can OCP provide on satisfying IND and BLA/NDA content and format requirements for a combination product a constituent part with a secondary mode of action (SMOA) (eg, drug delivery device)?	The content to be provided in the IND and BLA/NDA should adequately support the safety and efficacy of the combination product as a whole and take into consideration information that is recommended to be submitted for each type of constituent part of the combination product. For example, a marketing application for a drug-specific injector (BLA/NDA , or master file/510(k) by reference) should include information in accordance with FDA guidance[1], and the level of details/data included should be commensurate with the same type of general purpose, stand-alone device (eg, a class II injector, product code KZH, regulated under 21 CFR 880.6920, and subject to premarket notification requirements). Regarding format, there are several options for incorporation of of information for a constituent part of the combination product having a secondary mode of action, specifically, the drug delivery device information in the CTD structure, to include: • Incorporation by appropriate cross-reference to a master file or another marketing application (eg, 510(k)). • Incorporation by including device-specific information in one section of the CTD	Example 2.1 in Appendix A (submission to support Phase 3 IND or BLA/NDA) – Incorporation of drug delivery device information in sections 3.2.P and/or 3.2.R (including reference to master file or 510(k), as appropriate). Example 2.2 in Appendix A – Incorporation of drug delivery information in a single section, 3.2.P.7.	Industry welcomes recommendations from the Agency regarding the content and format of IND and BLA/NDA submissions for drug/drug delivery device combination products. Industry is concerned, however, that a single, prescriptive required contents list or format will be globally restrictive and not allow sufficient flexibility to assure that content is appropriate to the type, novelty or analogous risk based classification (Class I, II, III) of the device. However, if possible it would be helpful for the Agency to identify minimum requirements when possible.

[1] **Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products** (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf)

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		structure (3.2.R or 3.2.P.7). • Incorporation by including device-relevant information that is common to established CTD sections (3.2.P.1, 3.2.P.2.2, 3.2.P.2.4, etc.). • A mixture of one or more of the above options. The CPC does not believe that a single format should be required by CDER; rather, the sponsor should be able to submit the information in a format/structure and with sufficient detail to best facilitate efficiency of review by the Agency.		
3	Can data for a drug delivery device be submitted in a device or drug master file in support of a clinical investigation and/or marketing application when the same entity (sponsor/applicant) holds both the master file and the investigational or marketing application?	We understand that the use of master files was originally intended to facilitate the effective review of an application when a subset of the required information is proprietary to one entity. However, use of a master file should be an option available to the sponsor/applicant and CDER/CBER should agree to accept information in a master file as long as the file is appropriately referenced in the application (IND/IDE, BLA/NDA) and a letter of authorization (if necessary) is included. Use of a master file may provide the following benefits: • Consolidation of drug delivery device information for ease of CDER/CBER and CDRH review. • Reference to platform technology utilized in a drug delivery device where multiple drug product applications may need to incorporate the information (eg, IND and BLA for a single drug product or multiple BLAs for different drug products). • Simplify notification of post-approval changes by allowing the sponsor to report the change and provide detail about the change to one document and file	Similar approaches to this have been successfully implemented for products regulated by CBER. For example, BLA for Further Manufacture for Human Thrombin and Drug Master Files for cell lines for vaccines. An example of a device master file table of contents in support of a marketing application is located in Appendix B.	During multiple industry/Agency interactions in 2011, to include informal discussions and formal meetings, OCP, CDRH, and CDER have communicated the use of master files as an acceptable alternative to including device-specific information directly in the investigational or marketing application. The Agency has acknowledged that drug delivery device information can be under a Drug Master File (DMF) or Device Master File (MAF), and this master file then referenced in the relevant drug submission (eg, BLA). Further, the Agency has stated that the master file approach allows a company to store performance data for the drug delivery device that are not specific to or dependent on a particular drug or biologic in a common location for ease of reference by multiple applications. The CPC seeks confirmation from the Agency that the master file approach is acceptable across all divisions within the Centers and that it may be used

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		subsequent supplements to each applicable license application based on applicable regulatory requirements for the license application and a risk-based impact assessment.		either traditionally (ie, when a subset of the required information is proprietary to one entity) or non-traditionally (ie, submitted by the same sponsor/applicant that will submit the investigational or marketing application). Additionally, the CPC would like clarification that either type of master file, device or drug, may be utilized in this manner.
4	What are the clinical requirements, if any, to bridge from: (a) an approved drug product presentation that has proven safety and effectiveness to a new presentation that includes a device constituent part; (b) a new drug product where the pivotal Phase 3 data was not generated using the desired commercial drug delivery device for initial approval with the Phase 3 presentation and the desired commercial drug delivery device?	The CPC proposes that a stepwise approach be used to establish the comparability of the clinical and to-be-marketed presentations of a product. Each step would be based on the risks to safety and effectiveness presented by the design and/or test results. 1) If the key administration specifications for the two presentations are equivalent (or fall within the approved labeling for the approved presentation), clinical data is not required in support of the marketing application. See Appendix C for a summary rationale supporting the justification that subcutaneous injections should be viewed as a "single mode of administration" unless there is a compelling question as to the substantial equivalence of the delivery technologies. This appendix provides additional supporting information regarding the following topics: anatomic similarity of the Injection with respect to dose delivery in subcutaneous (SC) or intramuscular (IM) tissue, the relevance of delivery precision, the appropriateness of leveraging of "platform" technologies, interchangeability concerns, historical CDRH precedents, the influence of a therapeutic window and overall PK variability on delivery device comparability, the need to be harmonized with international standards and guidelines, and the experience learned from use	Example 4.1: Approved drug product in pre-filled syringe (PFS) presentation; addition of autoinjector that has design verification data assuring same injection depth, delivered volume, rate of injection (defined as key injection specifications). Conduct simulated use summative HFE/UE to support self-administration of the drug product. No clinical bridging data required. Example 4.2: Conducting Phase 3 pivotal study using PFS and then obtaining additional pre-launch data for an autoinjector from an open label extension study (or bioequivalence study) plus clinical use studies for self-administration in addition to conduct of simulated use summative HFE/UE.	Over the last two years, industry has received numerous comments from CDER Divisions regarding the comparability of injection technology. These comments suggest that different presentations are different combination products requiring unique safety and efficacy trials (or at least bridging studies). These comments have included: • One Division's view that a PFS and "platform" autoinjector presentation [that had been approved for a monoclonal antibody (mAb) for treatment of Rheumatoid Arthritis (RA)] were each new and different combination products for an investigational mAb (also intended for RA), that needed to be studied in separate trials as different modes of administration. FDA's preferred approach was to conduct the pivotal trials in one presentation (eg, PFS) and, after demonstrating safety and effectiveness (eg, through BLA review), conduct a second study

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		of commercial products. The non-clinical supplement to the file will be supported by in-vitro Design verification data and Design Validation provided through a simulated use summative HFE/UE study. If the technology or design of the system is novel, a clinical use study confirming an acceptable device failure rate (including those due to use errors) and device adverse event profile as compared to pivotal clinical data may be required. 2) If the key administration specifications are not equivalent (or fall outside the labeling of the approved presentation), then evidence of clinical comparability will be needed for bridging the clinical data to the new delivery system. For most products, bridging data will only require a determination of Bioequivalence through Human PK comparing the proposed system to the system used in the clinical study. The PK studies will confirm how the body acts on a drug – how the drug is absorbed, distributed, metabolized, and eliminated. Since the drug is the same, a PD study measuring how the drug acts on the body, the drug's biochemical and physiologic effects on the body, would not be required as part of the clinical bridging data. 3) It is only if the design of the system raises significant new risks regarding the safety or effectiveness of the therapeutic, or the pK study does not establish bioequivalence, that clinical safety or effectiveness data will be required. The specific clinical trial requirements will be product specific and will be reviewed with the agency to confirm acceptability.		with the alternative presentation (eg, autoinjector); this study should include PK/PD, usability and robustness studies even if the devices were already approved and marketed. At different times, FDA also has taken the following positions, which suggest inconsistencies either within Divisions or between acceptable elements of device development and Design Controls. • Concern that autoinjectors may inject too deeply or too shallow resulting in adverse events. • Concern that patients may remove the autoinjector from the skin before receiving the full dose and result in "wet injections". • Prior usability studies have been insufficient to detect post marketing problems. • Studies should be conducted with the to-be marketed presentations and any design change to them that could alter injection technique, even slightly, would raise a question of comparability. • Because companies cannot be demonstrate with 100% certainty that PFS and autoinjector delivery is the same, they must be presumed to be different with a potential for different safety and effectiveness.

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		A data package may be submitted in the original BLA/NDA that includes not only the pivotal Phase 3 data, but also additional non-clinical and clinical bridging studies supporting the safe and effective use of all presentations intended for approval. Alternatively, the additional data may be submitted in support of a supplemental filing. Regardless, the decision-making process for determining the type of data to be submitted should follow the rationale as outlined above and be based on a robust risk management and design verification/validation planning.		
5	Does the Agency agree that a simulated use HFE/UE study (ie, study where a material is not injected or delivered/administered to the study participant) is not subject to clinical trial requirements (Part 312 or 812)?	A simulated use study is a non-clinical research and development (R&D) study. It is not a clinical investigation per the definition in 21 CFR 312.3(b) as it does not involve any use or administration of drug. Neither does it meet the definition of an investigation under 21 CFR 812.3(h), and it may also be exempt under 21 CFR 812(c)(4). Simulating the use of the device does not constitute medical use and the study participants are not subjects in a clinical investigation. If a study involves actual injection of a solution into humans, the classification of the substance being injected would determine whether or not an IND would need to be considered. If the substance met the definition of a drug, determination of whether or not studies can be conducted without an IND should follow 21 CFR 312 and FDA's draft guidance for industry and researchers, *Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf). If the substance does not meet the definition of a drug (saline or a placebo	Example 5.1 – Non-clinical R&D study: Hand-held injector being used to inject saline into a skin pad (ie, needle present but no injection into human subject). Example 5.2 – Clinical study under NSR IDE: Hand-held autoinjector being used to inject saline for the purpose of assessing user interface (eg, device features, instructions for use, interoperability with other devices, preferred injection technique or site) or device injection specifications (eg, injection depth or injection time).	Seeking clarity from the Agency on this topic.

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		[formulation's excipients minus active – if they have a known history, or information on their toxicity is provided (e.g., sucrose, polysorbate)], then determination of whether or not studies can be conducted without an IDE should follow 21 CFR 812 and FDA's guidance, *Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies* (http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf).		
6	Does the Agency agree that a simulated use HFE/UE study (ie, study where a material is not injected or delivered/administered to the study participant) is not subject to human protection requirements (Part 50 and 56)?	Often these studies will not be subject to Parts 50 and 56 because they do not meet the definition of "clinical investigation" in those parts: "Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." (21 CFR 50.3(c), 56.102(c)). Under the regulations and this definition, studies are subject to Parts 50 and 56 if they are first "an experiment" and second either (a) meet the requirements for prior submission to FDA under section 505(i) or 520(g) of the Federal Food Drug & Cosmetic Act (the Investigational New Drug ("IND") or Investigational Device Exemption ("IDE") requirements, respectively), or (b) do not meet those requirements, but the study results are intended to be later submitted to, or held for inspection by, the FDA as part of	Example 6.1 – Non-clinical R&D study: Hand-held injector being used to inject saline into a skin pad (ie, needle present but no injection into human subject). Not subject to Parts 50 and 56. Example 6.2 – A study to assess consumers' preferences for different autoinjectors (e.g., color, packaging, hand comfort) is not an investigation subject to Parts 50 or 56.	Seeking clarity from the Agency on this topic due to absence of guidance and information specific to drug delivery products.

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		an application for a research or marketing permit (e.g., a premarket notification submission ("510(k)"), premarket approval application, new drug application, etc). A simulated use study is, in principle, observational research rather than strictly an experiment. An experiment is typically defined by subject matter experts as a study in which there is an active intervention to make one or more variables change in relation to another variable in order to determine whether cause precedes effect (i.e., establish the causal association of a factor or factors). Observational research is typically defined by subject matter experts as a study whose purpose is to observe and analyze what is occurring in order to describe what took place. As such, a simulated use study typically observes how study subjects would use or assemble a test article---no variables are manipulated in order to establish a causal relationship. Therefore, a simulated use study is a non-clinical research and development (R&D) study that does not meet the definition of a "clinical investigation" or "experiment." Because there is no "clinical investigation" or "experiment", a simulated use study is not subject to Parts 50 or 56. This question does not address the applicability of other DHHS/OHRP requirements for research.		
7	What are the data requirements for drug delivery device-related labeling (including promotional) claims such as 'ease of use'/'simplicity of use', convenience, user preference, reduction of accidental needle-stick	Advertisements for prescription drugs that relate to "safety or effectiveness must [be] supported by substantial evidence derived from adequate and well-controlled studies" (21 CFR 202.1(e)(6)). Device promotional labeling must not be false or misleading; many do not require clinical data for clearance (eg, class II devices	Example 7.1: A promotional claim (eg on a website) stating, "The drug delivery device is easy to use" could be adequately supported by data from a questionnaire employed in a simulated use summative HFE/UE study. The questionnaire would include affirmative	Because there are differences in the regulations and guidance governing drug and device promotional claims, it is unclear how to apply these requirements to combination product constituent parts such as drug delivery devices. It would be helpful if FDA

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	claims?	such as autoinjectors or pen injectors). Therefore, if promotional claims are related to the use of the device constituent part of a drug delivery combination product, it is appropriate to apply device requirements. Medical devices can be evaluated using bench/non-clinical methods, to include simulated use summative HFE/UE studies. These methods provide valuable evidence to support the device's safe and effective use (reference *Draft Guidance for Industry and FDA Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design,* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm). Therefore, results from HFE studies should be adequate to support device-related promotional claims. For autoinjectors, the device features such as those aiding usability or convenience that are present as a *matter of fact*, can be described in promotional materials. Beyond describing *matter of fact* device features, if there are comparison claims, the data in support of such claims can also be supported by bench/non-clinical or human factors comparative studies.	statements about whether specific features on the device are easy to use. Study participants would be asked to indicate their relative agreement with the statements based on a 7-point Likert scale after simulated use of the device.	could provide guidance on what supporting information is considered adequate justification for drug delivery device promotional claims.
8	Is there anything unique about the combination product dispute resolution process for product specific disagreements (FDA review process or a decision) on a clinical trial matter?	OCP should be available as a resource to industry and agency reviewers to help facilitate the review process, to help clarify and/or develop appropriate regulatory pathways, and/or to provide any other assistance as appropriate to OCP's mission. Explicit in the mission is OCP's role as the focal point for combination product issues. It is, therefore, appropriate for OCPs to be available at all levels of dispute resolution for combination products. Clinical Trial matters	Example 8.1: After receiving End-of-Phase 2 meeting feedback about the Phase 3 study requirements for two combination products for subcutaneous injections, the sponsor was asked by the Division to consult with OCP for further discussion about why the Division was requiring pivotal studies for each unique presentation. The sponsor contacted OCP to request a	OCP should generate a guidance document that explains their direct role in dispute resolution for combination products and clarifies what OCP is allowed to do during and through the dispute resolution process (ie, set transparent boundaries). The manner/method in which OCP interacts with a Division on combination products policies, either in general or

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		should be addressed in the same way as any other topic of dispute. OCP's participation in dispute resolution may be requested by industry or the FDA lead Center. If a dispute arises concerning the timeliness of premarket review, to include review of an IND or IDE, industry should follow OCP's published guidance document on this topic (*Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product*, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126006.htm). Other disputes should be addressed in accordance with applicable regulatory pathways (eg, 21 CFR 312.48 for IND dispute resolution, 21 CFR 314.103 for NDA/ANDA dispute resolution) and Agency guidance (*Formal Dispute Resolution: Appeals Above the Division Level, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126015.pdf, CDRH Resolution of Differences of Opinion - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOmbudsman/ucm113713.htm*). (Reference: **Frequently Asked Questions About Combination Products [**http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm**])**	meeting and sent a summary of the feedback and its concerns with a copy to the Division and CDRH. OCP immediately contacted the Division and CDRH and discussed the matter and then responded back to the sponsor that the sponsor's concerns were relayed but that OCP could not intervene further due to the product-specific nature of the issues and that these needed to be addressed by the Division. However, OCP's intervention was an effective mechanism to communicate concerns over restrictive policies to the Centers and OCP's feedback suggested that the Division would be interested in discussing more flexible Phase 3 study approaches. This is an example of a positive experience with OCP taking an interest in resolving barriers to drug development.	product-specific issues, should be well-defined. Written guidance is needed to clarify the role OCP can and cannot take (ie, when is an issue too product-specific for OCP to set over-arching policy that all Divisions must conform too?). For matters specific to the non-PMOA constituent part of a combination product (ie, drug delivery device), the CPC also believes that OCP should take an active role in supporting and conveying the importance of a collaborative review process, where the Center holding the subject matter expertise (SME) for the non-PMOA constituent part (ie, CDRH) has a strong voice in defining submission content and requirements for that part. If a dispute arises between the Lead Center (CDER/CBER) and CDRH, OCP should actively support the SME position given their functional responsibility for this area within the Agency.

Appendix A: Sample/Example IND or BLA/NDA Structure

Example 2.1:
The following format may be used as a guide for where to provide information for a drug delivery device constituent part of a combination product in a Phase 3 IND or BLA/NDA application. Note that any of this content can be located in a master file or another license application if it is appropriately cross referenced (also reference Appendix B).

Module	Overview: PROPOSED
1	Administrative Information –Cover letter and forms –Letters of authorization • Device manufacturer MAF or 510(k) –Labeling -Device Index - description of where device content can be found.
2	Introduction and Overall Summaries
3	Quality
5	Clinical –Listing of clinical studies (5.2) –Comparative bioequivalence study reports (5.3.1.2) –Reports of post-marketing experience (5.3.6) –Literature references (5.4)

Section	PROPOSED Phase 3 IND	PROPOSED BLA/NDA
	Description and Composition of the Drug Product	Description and Composition of the Drug Product
3.2.P.1	Describe the device constituent/component(s) (e.g., injector presentation, kit components) in a brief descriptive sentence and include in component table.	Describe the device constituent/component(s) (e.g., injector presentation, kit components) in a brief descriptive sentence and include in component table.
3.2.P.2.1	Components of the Drug Product	Components of the Drug Product
	No Device Content	No Device Content
	Pharmaceutical Development - Drug Product	Pharmaceutical Development - Drug Product
3.2.P.2.2	Describe the device constituent/component(s) (e.g. injector presentation, kit) briefly and generally.	Describe the device constituent/component(s) (e.g. injector presentation, kit) briefly and generally. Limit device development history.
	Manufacturing Process Development	Manufacturing Process Development
3.2.P.2.3	No device content	Describe device constituent/component(s) (e.g., injector presentation, kit) briefly and generally outline how manufacturing process or assembly was developed. Link to 3.2.P.3.3.
3.2.P.2.4	Container Closure System	Container Closure System
	Provide a brief summary of "suitability" of the device constituent/component(s).	Provide "suitability" information for the device constituent/component(s). For delivery devices, high level overview of drug-specific data showing that delivery is accurate, 510(k) history, summary of Human Factors studies of target population, shear studies, component ageing, ISO 10993 data, etc. Link to 3.2.R (medical devices).
	Microbiological Attributes	Microbiological Attributes
3.2.P.2.5	Information regarding testing to confirm container closure integrity is maintained	Information regarding testing to confirm container closure integrity is maintained (development, stability, shipping studies)
	Compatibility	Compatibility
3.2.P.2.6	Brief description of compatibility of device with drug product, if there is contact.	Describe compatibility of device with drug product, if there is contact and provide summaries of compatibility studies if conducted.
3.2.P.3.1	Manufacturers	Manufacturers

	Name and address of the sites performing assembly, kitting or packaging operations.	Name and address of the sites performing assembly, kitting or packaging operations.
	Description of Manufacturing Process and Process Controls	Description of Manufacturing Process and Process Controls
3.2.P.3.3	Includes a process flow diagrams and brief description of major and/or critical steps of the final combination product assembly steps - not detailed component manufacturing (parts molding or machining). May include hold times, assembly or packaging, etc.	Includes a description of the final combination product assembly steps - not detailed component manufacturing (parts molding or machining). May include hold times, process flow diagrams, assembly or packaging equipment, etc.
	Control of Critical Steps and Intermediates	Control of Critical Steps and Intermediates
3.2.P.3.4	For integral combination products, define in-process controls (IPCs), and critical process parameters (CPP) of the manufacturing or assembly process. Content dependent on product complexity. NA for kit components.	For integral combination products, define intermediate checks, in-process controls (IPCs), and critical process parameters (CPP) of the manufacturing or assembly process. Content dependent on product complexity. NA for kit components.
	Manufacturing Process Validation and/or Evaluation	Manufacturing Process Validation and/or Evaluation
3.2.P.3.5	Provide available information on evidence that IQ/OQ/PQ and Process Validations are in process or were completed (e.g., device release test data on multiple clinical/stability/commercial lots).	Provide evidence that IQ/OQ/PQ and Process Validations were completed (e.g., device release test data on multiple clinical/stability/commercial lots). May or may not require assembly steps validation.
3.2.P.5.1	Specifications	Specifications
	Provide table of release specifications for the combination product with limited, key device quality inspection or performance test specifications (ranges). Do not include device component design specifications. Kit component specifications typically reported elsewhere (3.2.P.7, 3.2.R)	Provide table of release specifications for the combination product with limited, key device quality inspection or performance test specifications (ranges). Do not include device component design specifications. Kit component specifications typically reported elsewhere (3.2.P.7, 3.2.R)
3.2.P.5.2	Analytical Procedures Provide an adequate summary of the release test method/protocol for each reported device component specification.	Analytical Procedures Provide an adequate summary of the release test method/protocol for each reported device component specification.
3.2.P.5.3	Validation of Analytical Procedures	Validation of Analytical Procedures
	If "novel", provide summary validation information (e.g., Gauge R&R) with data for measured parameters or cite standards. Descriptive device inspections may not require validation.	If "novel", provide summary validation information (e.g., Gauge R&R) with data for measured parameters or cite standards. Descriptive device inspections may not require validation.
3.2.P.5.4	Batch Analysis	Batch Analysis

	Provide release test results for device characteristics for clinical and/or process validation lots as part of overall combination product batch data.	Provide release test results for device characteristics for clinical and/or process validation lots as part of overall combination product batch data.
3.2.P.5.6	Justification of Specifications Provide overview of device Design Inputs that justify specifications - e.g. force to actuate. Supporting design verification data may be necessary.	Justification of Specifications Provide overview of device Design Inputs that justify specifications - e.g. force to actuate. Supporting design verification data may be necessary.
	Container Closure System	Container Closure System
3.2.P.7	High level description of device and device components. Link to 3.2.R (medical device)	High level description of device and device components. Link to 3.2.R (medical device)
	Stability Summary and Conclusion	Stability Summary and Conclusion
3.2.P.8.1	Provide summary of device constituent aging test program and combination product functional stability test program, stability indicating parameters, and proposed shelf life for the combination product (country dependent). Present and discuss stability data.	Provide summary of device constituent aging test program and combination product functional stability test program, stability indicating parameters, and proposed shelf life for the combination product. Present and discuss stability data.
	Post-approval Stability Protocol and Commitment	Post-approval Stability Protocol and Commitment
3.2.P.8.2	Not Applicable	Provide commitments (e.g., annual stability lots) and protocol summaries
3.2.P.8.3	Stability Data Provide functional stability testing data.	Stability Data Provide functional stability testing data.
	Facilities and Equipment	Facilities and Equipment
3.2.A.1	No device specific information (country specific).	Description of the combination product (final assembly/kitting) facility, flow diagrams, principle equipment, other products, cross-contamination procedures.
	Regional Information (medical devices)	Regional Information (medical devices)
3.2.R	Not relevant for clinical trial applications	US: 510(k)-like document for review by CDRH EU: Technical file-like document for review by Notified Body or Competent Authority

Example 2.2 (Supplied by Patricia Love, OCP – September 2011):

PRELIMINARY RECOMMENDATIONS
Autoinjector data in eCTD format

The following provides advice and recommendations on submitting a combination drug and device product which includes an autoinjector in an eCTD application. The following suggestions and information being provided, is information from the CDER OBI DRRS (eCTD staff) and Reviewer's that would specifically focus on module 3.

1. For eCTD format and use of the system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say "Container Closure System."

2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.

3. We recommend the following when including and referencing device information:

    a. You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.
    b. In 3.2.P.7 you could include a leaf titled something similar to the following, "Table of Contents for Drug-Device Autoinjector. This leaf/document, could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.
    c. The leaf titles should be clear, concise and indicative of the document's content.

4. Module 1.4.4 cross reference to other applications is a location where you can provide references to other applications and you can include copies of an application's table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of authorization, 1.4.2 Statement of right of reference, 1.4.3 List of authorized persons to incorporate by reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

5. Although it's not required, providing a "Information to Reviewers" or "Reviewers Guide" document in Module 1.2 Cover letters can be helpful. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it would identify where drug, device and combination product information is located.

For other specific eCTD questions, you may send an email to esub@fda.hhs.gov and or refer to the eCTD website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm which has links to all the specifications.

For combination product questions, you may send an email to combination@fda.gov or directly contact the staff member with whom you are working.

Appendix B: Sample/Example - Master File Structure (MAF) in Support of Marketing Application(s)

Section Reference	Key Information/Data
1 - Administrative	• MAF Cover Letter • Master File Table of Contents • Executive Summary • Financial Interests and Arrangements of Clinical Investigators (Forms FDA 3454/3455) if clinical data is included • Guidance/Standards Conformity Summary (applicable guidance documents, special controls, and/or standards; statement of compliance)
2 - Description and Design Features	• Device Names: Common, Trade/Proprietary (if available), and Classification (§880.6920, KZH, Class II) • Indication Information, in relation to use in combination with drug product (eg, for SC or IM injection) • Description of Conditions of Use: – Principles of Operation (including Use Steps and Injection Sites) – Performance Specifications – Drug Product of Intended Delivery – Drug Product Dose Capability – How Supplied to the End User (to include distribution plan) – Type of Use • Identification of Model(s) and Accessories • List of Components and Materials (chemical, grade, brand name and which materials are in or will affect the fluid path) • Device Design Requirements, such as physical, mechanical, electrical, operational, and biological specifications (high level, not design control documentation)
3 – Manufacturing Information	• Manufacturing Summary (including packaging and labeling, and manufacturer's information) – Assembly/Manufacturing Flowchart – Quality Controls (critical control points) • Facility, location, statement of compliance with GMPs in alignment with 510(k) expectations for class II devices (statement of compliance is optional; this section does not include manufacturing process validation data)
4 - Labeling	• Proposed labeling (device/package labels and instructions/directions for use), if not included in sBLA
5 - Device Life	• Shelf-life Test Summary • Usable Life Test Summary
6 - Biocompatibility	Biocompatibility Test Summary, to include justification for selected biocompatibility

Section Reference	Key Information/Data
	tests (body contact and contact duration)
7 – Software (if applicable)	• Software Level of Concern (category based on risk) • Software Verification and Validation Testing [documentation in accordance with *Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005, CDRH/CBER)*]
8 - Safety	• Risk Analysis Summary • Device Safety/Component Safety Features and Summary • Electromagnetic Compatibility/Electrical Safety Summary (if applicable)
9 - Functionality and Performance Testing	• Design Verification Test Summary (bench testing) • Simulated Use Summative HFE Study Summary [documentation in accordance with *Draft Guidance for Industry and FDA Staff: Applying Human Factors and Usability Engineering to Optimize Medical Device Design (June 22, 2011, CDRH)*] • Clinical Study Summaries
10 - Attachments	• Material Safety Data Sheets (for components/materials used in the autoinjector) • Engineering Drawings (subassembly and component, as appropriate) • Views and Photographs/Illustrations of the autoinjector (showing the drug product delivery stages) • Design Verification and Validation Test Reports (including Biocompatibility, Shelf-life/Usable Life, Simulated Use Summative HFE Study, Clinical Studies) • Quality System Certificates for Manufacturing Facilities (optional)

Appendix C: Additional Rationale

The following are the key points that we believe FDA should be considering in developing its policy or guidance:

1. **Geometric Similarity of the Injection** Dose presentations in manual PFS and autoinjector (or prefilled pen) technologies (that use that same PFS) are designed to deliver the same volume of drug to the same location in subcutaneous tissue over the same or similar time interval. The typical autoinjector or pen's needle extension is 5-7 mm which would reach about the same depth as the typical subcutaneous PFS needle [½" (12.7 mm)] directed at a 45° angle for subcutaneous injection. The injection will then be performed over 2-6 seconds for manual technique or slightly longer for autoinjector injection. Subcutaneous tissue is generally uniform and there is little anatomical rationale to believe that the depot of drug will be significantly affected by these delivery technologies when used as intended. Even when the Instructions for Use (IFU) suggest the option of injecting into a pinched fold of skin/subcutaneous tissue, or not, there may be still be little subcutaneous variability (e.g., from any compression of the skin layers) or inadvertent injection into intramuscular tissue). The minor differences in the injection technology's needle specifications or injection technique do not appear to be clinically or anatomically relevant for subcutaneous injection. FDA's feedback has suggested that subcutaneous injection and delivery are as device dependent as nasal sprays and metered dose inhalers are for aerosol delivery. CPC would agree that the aerosolized dose fraction delivered from these devices depends highly on device design and patient technique and a thorough understanding of particle size and distribution in an open body cavity is needed for a specific device. However, these kinds of issues do not appear to be a significant clinical concern for subcutaneous injection devices.

2. **Phase 3 pivotal studies could use a manual presentation to collect and assess the drug's safety and effectiveness**. The manually-controlled needle insertion and delivery would be expected to vary slightly from user to user, regardless of their experience, whereas an automated delivery method would have a fixed needle insertion angle and depth. Therefore, a company could choose to use the manual presentation in its pivotal study as the presentation with the most potential for variability in dose delivery technique. The automated delivery method, with a greater potential for precise, repeatable delivery, would therefore be encompassed within the range of dose delivery variations that were studied when the manual method was used. Viewing the manual injection as potentially more variable than an automated delivery method is the same approach as used in assessing and setting biochemical specifications (e.g., potency) for the final product using specifications derived from the clinical batches. Final (commercial) drug product specifications could ultimately be tighter than, but within, those biochemical specifications studied in the clinical studies, but do not typically raise a clinical concern. Thus, the manual presentation would be the preferred and only presentation needed to collect the "base-case" (most variable) response to the drug product under study. The effect of technique precision and repeatability would not likely be clinically relevant for many drugs, particularly those that do not have a narrow therapeutic window and that have an established safety profile.

3. **Platform delivery device technology**. For autoinjector or pens that are platform technologies and are already approved, choosing to study only the PFS presentation in the pivotal trials for an initial NDA/BLA, as has been suggested by FDA, may result in a second filing for the autoinjector or pen. Therefore, there would be a delay in the availability of a presentation (e.g., platform autoinjector or pen) that is already approved as a suitable delivery device and would be best suited for self-administration. This delay would not be in the best interest of patients who would prefer to self administer, especially with respect to autoinjectors designed for and intended for patients with hand impairment.

4. **Interchangeability of dose presentations.** If the PFS was studied in a pivotal trial for an initial /NDABLA, with a follow-on study using the autoinjector or pen, there would be some risk that the drug label might have to distinguish the clinical outcomes from these different trials and that the two presentations might not be considered "interchangeable" for the same dose volumes. However, any differences in safety and effectiveness could be an artifact related to the variability typical of certain drugs (e.g., mAbs) that might be seen in the small study conducted and not related to the delivery devices.

5. **CDRH precedence on hypodermic needles**. CDRH has cleared many subcutaneous needles and syringes through the 510(k) process with needle lengths from 4 mm to 25 mm and in a variety of needle gauges. These devices accommodate commonly taught subcutaneous injection techniques and have been acceptable for this intended use for many subcutaneously administered drug

products. In fact, many vialed drug products simply instruct physicians (and patients) to "Inject Subcutaneously" and provide no further recommendations on syringe type, needle length or gauge. This wide variation in syringe or needle selection and administration technique, used to administered many liquid drugs, has not significantly impacted the safety or effectiveness of these drugs such as to require the restriction or specification of these devices.

6. **CDRH precedence on injection technology.** CDRH has cleared several reusable autoinjectors (Introducers, Needle Syringe; Product Code KZH) dating back over 15 years. Some of these are generic autoinjectors that can accommodate any 1 mL glass pre-filled syringe approved as a drug product. Certain reusable autoinjectors were cleared as Over the Counter devices intended for patient self administration from pre-filled syringes in a home setting (K993385, K013362). Use of these devices has not resulted in a new subcategory of the subcutaneous mode of administration or new restrictions on their use with specific drugs. However, these devices have aided many patients with hand impairment and needle phobia, and any issues related to their widespread use have not led to significant public health issues.

7. **Factors related to a drug's therapeutic window and PK variability**. Preclinical animal data and Phase 1 and 2 data clinical data can often be used to demonstrate, at least on a preliminary basis, that a biologic drug has a wide therapeutic window and a wide safety margin for the doses to be studied in the Phase 3 trials. In the past FDA has indicated that, for biologics or drugs exhibiting these characteristics, where dose precision is not critical, demonstrating bioequivalence in normal healthy volunteers may not be necessary. FDA's recent feedback, in some cases, seems to be a departure from this position. No company can provide 100% certainty that PFS and autoinjector delivery will demonstrate bioequivalence without performing a study, even if its purpose is to rule out this concern. However, the real issue is whether there is actual clinical concern based on the respective design of the devices and the clinical requirements for the drug.

As a class, mAbs do not appear to require precise or device-specific administration into a particular location in the subcutaneous space to be safe and effective. This is further supported by the following subcutaneous dosage information:

Anti TNFs for RA administered by subcutaneous injection
- Humira® doses are 40 mg /0.8 mL in both a PFS and an autoinjector presentation
- Enbrel® doses are 50 mg / 1.0 ml in both a PFS and an autoinjector presentation
- SIMPONI® doses are 50 mg / 0.5 mL in both a PFS and an autoinjector presentation
- CIMZIA® doses are 200 mg / 1.0 mL (reconstituted lyo) and 200 mg/ 1 mL in prefilled OXO Good Grip injector)

Anti-IL 6 for RA administered by subcutaneous injection
- Actemra® (tocilizumab) – Not yet approved for subcutaneous administration. However, as reported in Clinicaltrials.gov, a Phase III trial has been initiated to study 162 mg doses in both a prefilled syringe and autoinjector in a single Phase 3 trial.

Other Biologics supplied in PFS and autoinjector presentations

- Aranesp® (darbepoetin alfa): Single-dose prefilled syringes and prefilled SureClick™ autoinjectors are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp®.

While several bioequivalence studies have been performed on these drugs, the results of those studies have not demonstrated a need to distinguish the dosage between the commercial auto-injector presentations and prefilled syringe presentations. If FDA is aware of clinically relevant differences in bioequivalence or safety of mAbs or other drugs in comparative studies of delivery devices, it still would not be certain that those differences can be attributed to the delivery devices as the root cause of those differences. Most mAb responses are inherently variable and subcutaneous tissue deposition differences due to delivery device technique would likely be small in comparison.

8. **Published studies have not found significant clinical concerns over subcutaneous injection variability**. There are numerous studies referenced in the literature on subcutaneous administration technique and device variation that have both raised concerns and minimized concerns related to dose delivery. For example, studies have shown needle lengths as short as 4 mm do not impact subcutaneous dosage in comparison to longer needles, that injection sites can alter PK levels of drugs, that drugs intended for

IM administration can inadvertently be administered subcutaneously, and that drugs intended for subcutaneous administration can inadvertently be administered intramuscularly (See References). However, the studies have generally shown that the subcutaneous space is a single mode of administration and that this space generally provides for reliable dosing where any differences have only a minimal effect on patient therapy. In most cases, the clinical concerns are limited to drugs with short half lives (insulin or epinephrine). This literature does not support an urgent need to study autoinjectors or pens as a unique subcutaneous delivery mode for drugs and biologics.

9. **Post marketing experience**. CPC is concerned that FDA is basing the need for conducting repeat clinical studies of autoinjectors during development based on the experience from post market reports of marketed autoinjectors and pens. Post market reports are based on hundreds of thousands of uses, and identification of all potential field failure rates may not be predicted during development and are best identified once on the market.

Conclusions

In developing its policy, FDA should consider that the subcutaneous mode of administration is a single mode of administration and that, while there may be slight variations in pharmacokinetics, these differences have not been critical for most biologics and drugs. Considering a 'specific autoinjector design' to be a unique subcutaneous mode of administration does not seem to clinically warranted and the need to study them only after the PFS presentation has been determined to be safe and effective is not in the best interest of patients who wish to self administer when a new drug becomes available. We urge FDA to develop a policy that would allow both a PFS and an autoinjector, housing the identical PFS with the same dose volumes, to be studied for approval in an initial BLA.

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