

## COMBINATIONAL PRODUCTS: A REGULATORY REVIEW

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## ABSTRACT

A regulation with respect to combination products and FDA over view .Advances in drug, biologic and medical device development relate to both single entities and combination of each type of medicinal product. Regulatory overview of combination products is complicated by the fact that although drugs are regulated primarily under section 505 of Food, drugs and cosmetic act and reviewed by CDER, CBER, and CDRH. Combination products increasingly include state-of-art, innovative technologies with great potential to advance patient care. Combining different regulated product types, however, triggers a panoply of issues with which the Food and Drug Administration, pharmaceutical, biologic and medical device manufacturers, and other stake holders have struggled through the years. Since 1991, FDA has worked toward resolving a number of these issues, and has made some inroads in assignment of jurisdiction for combination products. We are encouraged by FDA's preliminary efforts, and look forward to further improvement in the regulatory process for combination products.

**Keywords:** Combination products, CDER, CBER, CDRH, Food and drug administration, Drugs, Biologics, Medical devices

INTRODUCTION <sup>1,2</sup>:

Combination product is defined by regulation 21 CFR 3.2(e) and include the following:

- A product comprising two or more regulated components (i.e. drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity.
- Two or more separate products packaged together in a single package or as a unit and comprising drug and device products, device and biological products, or biological and drug products.
- A drug ,device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with the approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect where upon approval of proposed product the labeling of approved product would need to be changed.

Eg: to reflect a change in intended use, dosage form, strength, route of administration, or significant change dose.

- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device or

biological product where both are required to achieve the intended use, indication, or effect.

Examples of combination products where the components are physically, chemically, or otherwise combined include

- Monoclonal antibody combined with a therapeutic drug;
- A device coated or impregnated with drug or biologic, for examples, a drug- eluting stent, pacing lead with steroid-coated tip, catheter with anti microbial coating, condom with spermicide, or skin substitutes with cellular components or orthopedic implant with growth factors;
- Pre filled syringes, insulin injector pens, metered-dose inhalers, and transdermal patches.

Examples of combination products where the components are packaged together include

- A drug or biologic product packaged with a delivery device
- A surgical tray with surgical instrument, drapes, and lidocaine or alcohol swabs.

Examples of combination products where the components are separately provided but labeled for use together include

- Photosensitizing drug and activating laser or other light source



- An iontophoretic drug delivery patch and controller

### Types of Combination Products <sup>2</sup>

In assessing the current process, it became apparent that significance and complexity of issues may depend on the type of combination product involved.

Indeed, a combination product involving two clearly separate components give rise to very different issues than a combination product that is manufactured as a unit. For that reason, they need to be treated differently.

Following categories, which derive from the regulations defining combination products, include

- Integral combination products:

Two or more regulated products combined as an inseparable unit.

Example: drug-eluting stents, pre filled syringes

- Kits:

Combination product comprised of two or more regulated products packaged together, but with components that can be separated easily.

Example: anti bacterial scrub with catheter, drug additive with kit.

- Virtual combination products:

Products that, in concept and labeling, must be used together to achieve the intended use, indication or effect, but are not packaged together.

Examples: Herceptin and Herceptin test

### Intercenter Agreements <sup>2</sup>

In 1991, CBER, CDRH, and CDER entered into three Inter Center Agreements (ICAs) between CBER, CDRH, CBER AND CDER, and CDER AND CDRH.

Example for major provisions of the CBER-CDRH ICA include

- Identification of medical device for which CBER will have lead regulatory responsibility.

Eg: medical devices used or intended for collection, processing, storage, or administration of blood products, blood components.

- Identification of the devices to be regulated by CBER under the provision of public health services act;
- Determination of the center of primary jurisdiction is based on the primary mode of action

### Office of Combination Products: (OCP) <sup>2</sup>

FDA's Office of combination products was created in 2002.

Modernization Act that amended the FD&C Act to address concerns about the consistency, predictability,

and transparency of the process used by FDA to assign primary jurisdiction;

MDUFMA gives OCP broad responsibilities covering the regulatory lifecycle of drug-device, drug-biologic, and device-biologic combination product including

- Assigning an FDA center to have primary jurisdiction for review of a combination product.
- Ensuring timely and effective premarket review of combination products by overseeing reviews involving more than one center.
- Resolving disputes regarding the timeliness of pre market review of combination products.
- Updating agreements, guidance documents, or practices specific to the assignment of combination products
- Submitting annual report to congress on OCP's activities and impact.

It has significant responsibilities in the policy coordination, and oversight of FDA's regulation of combination product.

### Primary Mode of Action <sup>2</sup>

In 1990, congress amended the FD&C act to section 503(g), which requires FDA to assign lead jurisdiction for the regulation of a product consisting of a combination of a drug, device, or biological product to an FDA center based on a determination of the primary mode of action (PMOA) of the combination product. If the PMOA of a combination product is that of a biological product, the product is to be assigned to the FDA center responsible for review of biological products. In 1991 FAD issued a final rule establishing the procedures and information requirements for submitting a request for designation (RFD) to FDA. The RFD process outlined in these regulations was intended to provide a means for FDA, after reviewing information submitted by the sponsor, to determine the center that will have primary jurisdiction based on the agency's determination of the PMOA.

- The RFD process requires a sponsor to submit an RFD to identify the PMOA of combination product and recommend a lead center for its regulation. In some instances, sponsors experienced problems preparing the RFD because the PMOA of a combination product was not defined in statute or regulation.
- It may also be difficult to determine the PMOA if the product has two completely different mode of action, both apparently equally important.
- In these issue, FDA may make its jurisdictional designation of whether a mode of action is primary" as well as prior agency experience and current expertise.



- To the outside observer this could make the designation process appear subjective and perhaps inconsistent, particularly when jurisdictional assignments for apparently similar products differ.

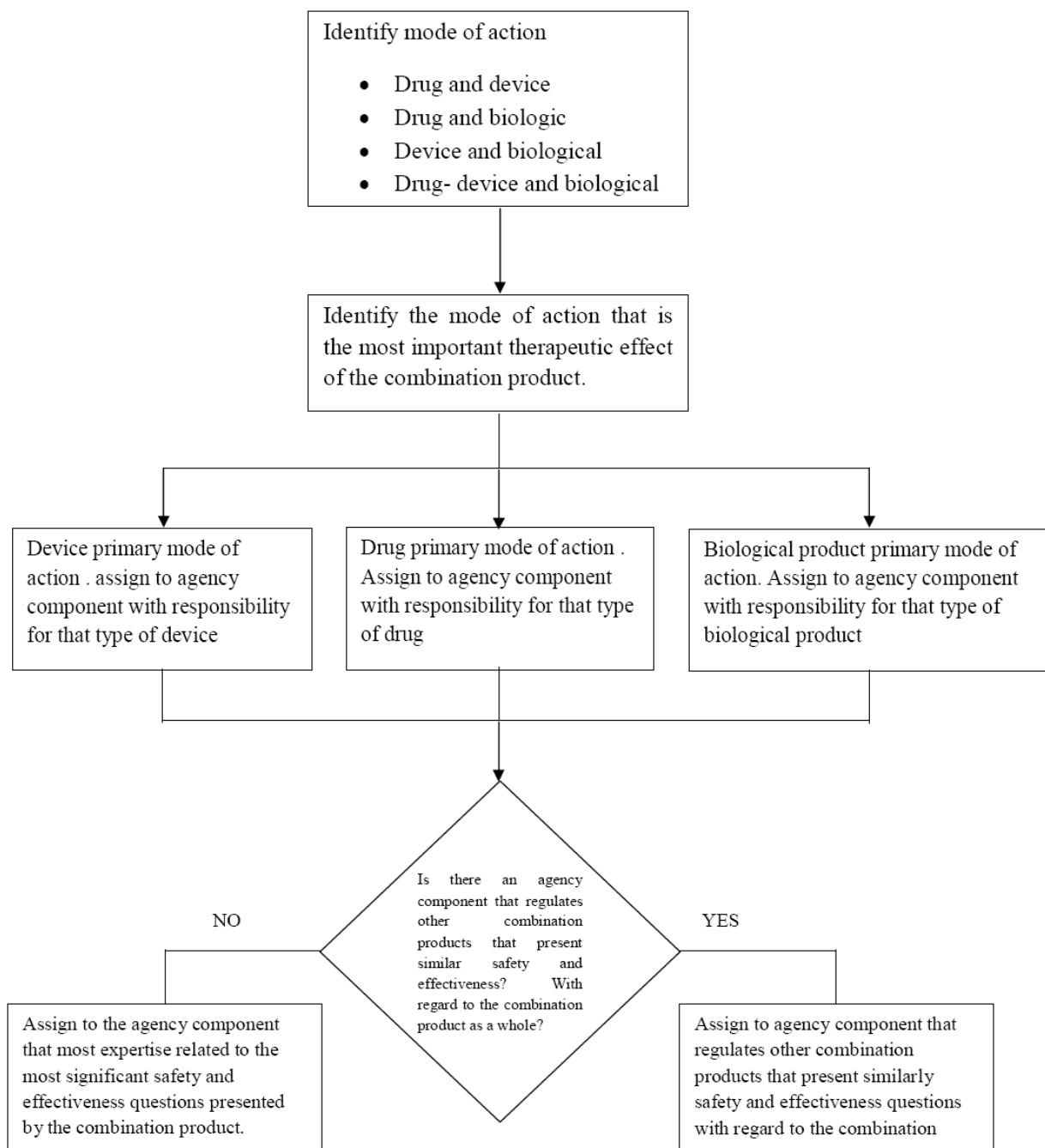
In response to these types of concerns, the FDA amended its combination product regulation (5) to

- Defined “mode of action “ (MOA) and primary mode of action” PMOA
- Describe an algorithm to assign combination products to a center for regulatory oversight when

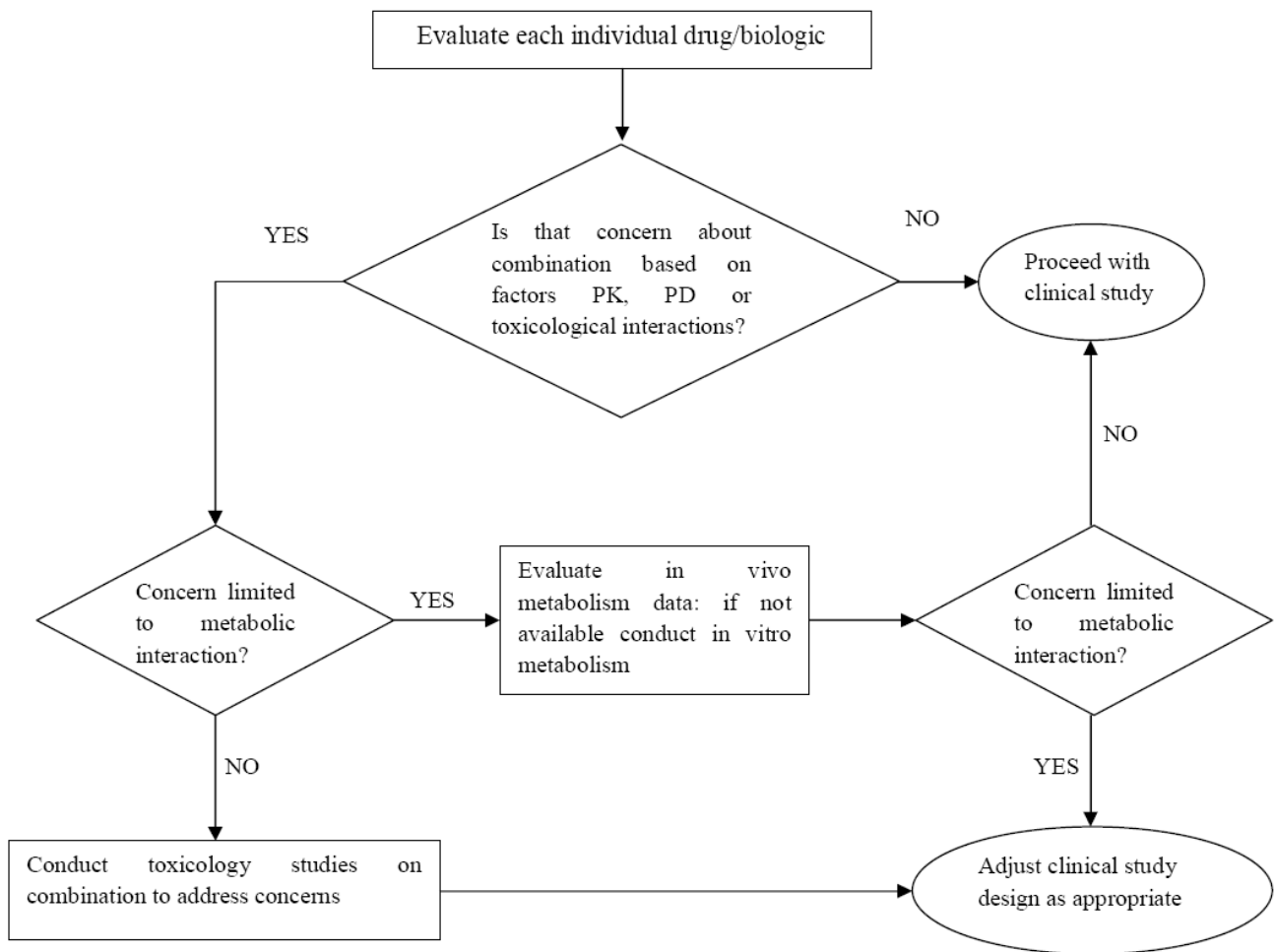
the agency cannot determine with reasonable certainty which mode of action provides the most important therapeutic action of the combination product.

- Require a sponsor, in its RFD, to base its recommendation of the center with primary jurisdiction for regulatory oversight of its combination product on the PMOA definition and, if appropriate, the assignment algorithm

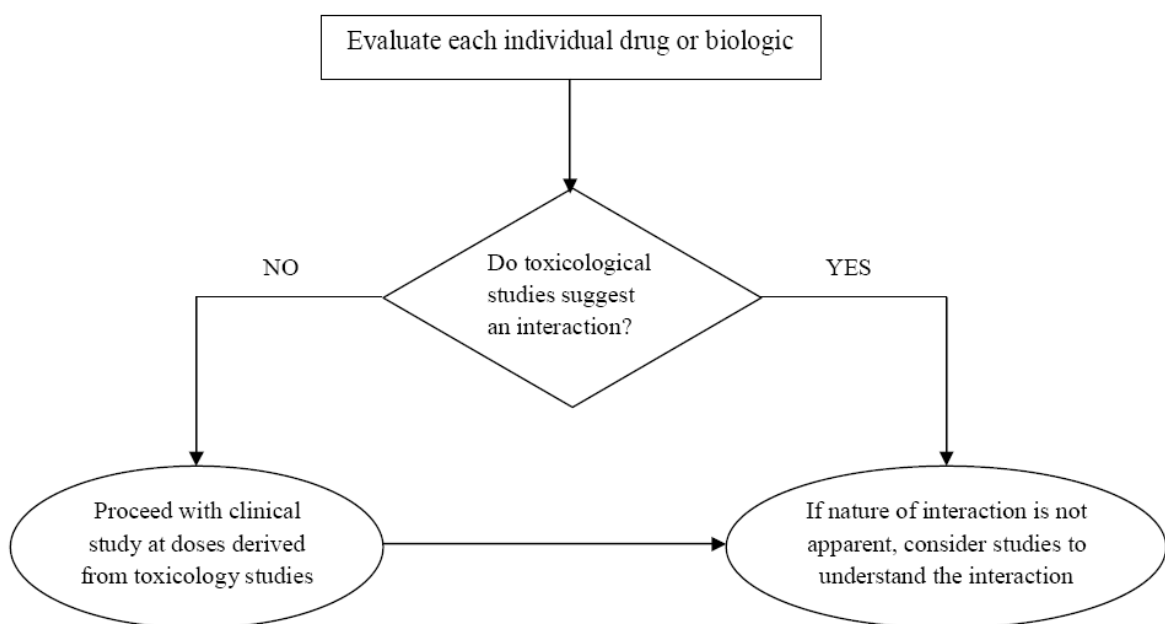
**Algorithm for assigning a combination product to an FDA center for regulatory Oversight<sup>2</sup>**



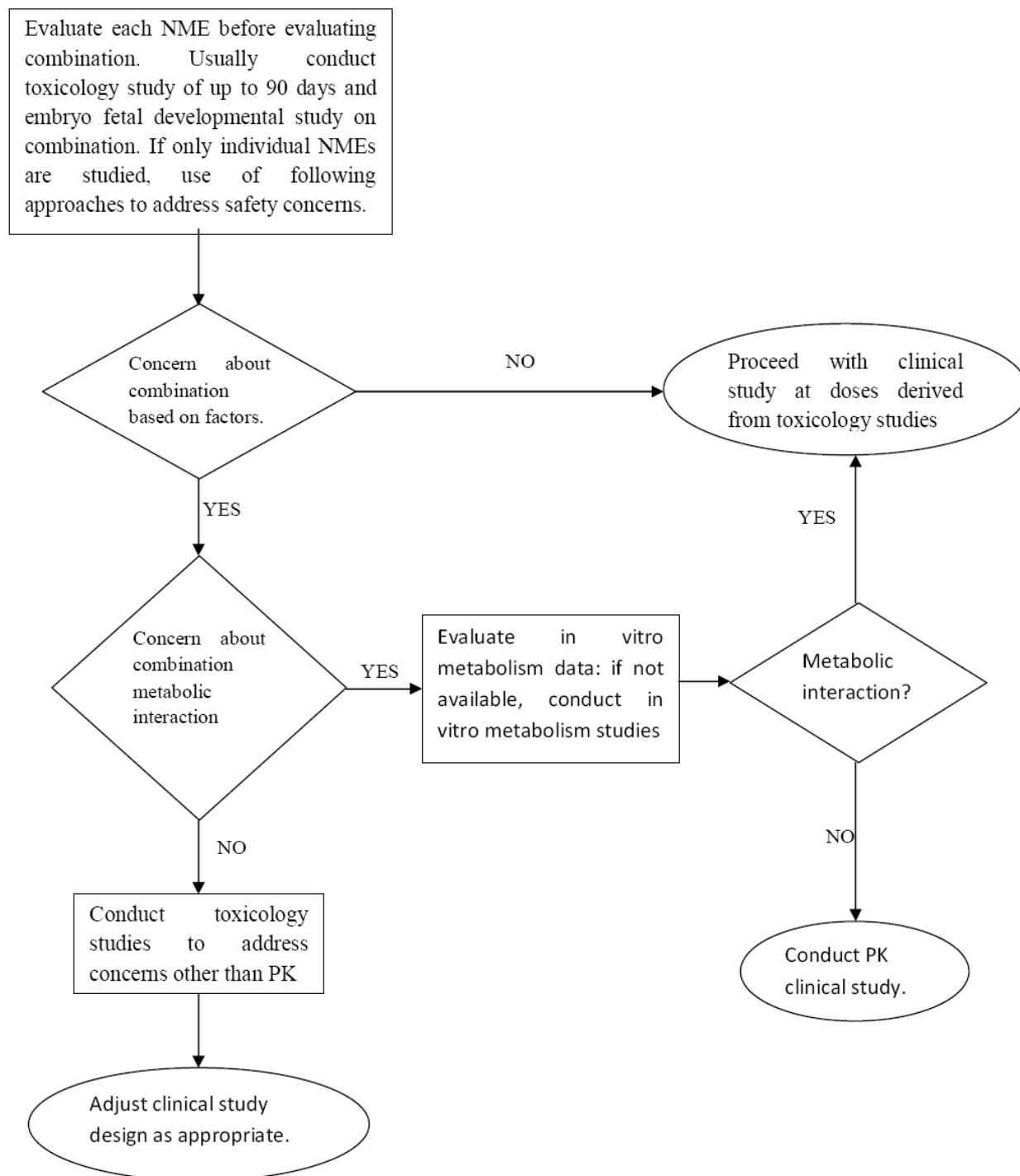
**Combination of previously marketed drug or biologics<sup>3</sup>**



**Combination of previously marketed drugs or biologics in combination with NMEs<sup>3</sup>**



### Combination of NMEs with NMEs<sup>3</sup>



### General Safety Considerations<sup>3</sup>

In combinations when one is a new molecular entity

- Conduct general toxicology of the NME:- Genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicology, Reproduction and developmental toxicology, carcinogenicity.
- Conduct 90-day bridging study with the combination in most appropriate species.

In combinations of two or more new molecular entities.

- Conduct general toxicology of the NME.
- Pharmacology, safety pharmacology, PK/ADME, developmental toxicology, carcinogenicity.
- Conduct in 90 days

### Strategic Regulatory Considerations<sup>2</sup>:

Strategic planning activities can include all steps necessary to satisfy the applicable regulatory



requirements. Sponsor must also aware of the potential impact of product changes (e.g., intended use and indications, technology) on how the product may be regulated. It is important to take specific steps during the earliest stages of development to understand how their combination product will be regulated, the impact this will have on their strategic development plan, and how the plan might be affected by product changes made as development progresses.

Key early steps in identifying the combination

Product regulatory path

- Determine the intended use of the combination product.
- Determine product modes of action and the primary mode of action (PMOA)
- Determine the likely jurisdictional assignment based on the PMOA determined, apply the assignment algorithm to determine the likely jurisdictional assignment. Verify the jurisdictional assignment with FDA if possible.
- If necessary, submit a request for designation (RFD) to the FDA office of combination products.

### The Request for Designation Process (RFD)<sup>2</sup>

The RFD process is described in 21 CFR parts 3.

After a company has decided to submit a formal RFD to OCP, the process is as follows:

- Sponsor preparation and submission of the RFD
- FDA notification of the sponsor within five days of receipt that the RFD has either filed or that it has not been filed
- FDA technical review and issuance of a designation letter within 60 days of filing.
- Sponsors who disagree with the determination may request reconsideration of the determination and, if the request is denied, request an appeal in accordance with provisions of 21 CFR 10.75.

The RFD process flow is described .OCP has published a guidance document that specifies the information to be included in the RFD and provides a recommended format.

The regulations require that the RFD submission be limited to 15 pages, so it is important for sponsors to include the required information.

### Required content of a request for determination for a combination product

- The identity of the sponsor, including company name and address, establishment registration number, company contact person, and telephone number.

- Classification, name of the product and all component products
- Proprietary name of product
- Identification of any component of the product that has already received premarket approval, is marketed as not being subject to premarket approval, or has received an investigational exemption, the identity of the sponsors regarding use of this product as a component of a new combination product.
- Chemical, physical, or biological composition
- Status and brief reports of the results of developmental work, including animal testing.
- Description of manufacturing processes including the sources of all components.
- Proposed use or Indications
- Description of all known modes of action, the sponsor's identification of single mode of action that provides the most important therapeutic action of the product, and basis for that determination.
- Schedule and duration of use.
- Dose and route of administration of drug or biologic.
- Description of related products, including the regulatory status of those related products.
- Any other relevant information
- The sponsors recommendation as to which center should have primary jurisdiction.

### User Fees<sup>2,4</sup>

- Combination product reviewed by CDRH will normally be subject to device user fees and perhaps other fees like registration fees.
- Combination product assigned to CDER, CBER for review will be subject to Prescription drug user fee requirements.
- PDUFA establishments and renewal fee on products. Sponsors may be eligible for fee waiver or reductions under PDUFA and MDUFMA.

Eligibility criteria for fee waiver:

- The combination product as a whole is innovative.
- FDA is requiring two fee-eligible marketing applications for the combination products.
- The applications only request approval of the two components of the combination product for use together. Applications that uses of one or both components outside the combination generally would not be eligible for this waiver.



**Table 1: User Fees**

Single application/fees	Available waiver/reduction
NDA/PDUFA fees BLA/PDUFA fees	Waiver applicable to single PDUFA applications: <ul style="list-style-type: none"> <li>• Small business</li> <li>• Barrier to innovation</li> <li>• Necessary to protect the public health</li> <li>• Fees will exceed the anticipated present and future review cost incurred by FDA</li> </ul>
PMA, BLA, or 510(k)/MDUFMA fees	Waivers applicable to single MDUFMA applications <ul style="list-style-type: none"> <li>• Small business</li> <li>• Humanitarian device exemption</li> <li>• BLA for a product licensed for future manufacturing use only</li> <li>• Third party 510(k)</li> <li>• Any application for device intended solely for pediatric use</li> </ul>

**Table 2: Current Good Manufacturing Practice**

If the Operating Manufacturing Control System is Part 820 (QS Regulation)		If the Operating Manufacturing Control System is Part 210/211 (CGMP Regulation)	
Carefully Consider These Specific CGMP Requirements	Title	Carefully Consider These Specific QS Requirements	Title
§ 211.84	Testing and approval or rejection of components, drug product containers, and closures	§820.30	Design controls
§211.103	Calculation of yield	§820.50	Purchasing controls
§211.137	Expiration dating	§820.100	Corrective and preventive actions
§211.165	Testing and release for distribution		
§211.166	Stability testing		
§211.167	Special testing requirements		
§211.170	Reserve samples		

### Current Good Manufacturing Practices for Combination Products<sup>5</sup>

Under the FD&C act, drugs and devices are considered to be adulterated if they are not manufactured in accordance with CGMP.

- The quality system regulation describes GMP requirements for finished devices according to 21 CFR part 820.
- CGMP regulations for all finished products according to 21 CFR part 211.
- Additional manufacturing requirements may be applicable under the biological products regulations 21CFR parts-600-680 for drugs and devices that are biological products, FDA develops additional rules that may be applicable to one or more components of a combination product.
- FDA recognizes that many manufacturing facilities operate under one type of current good manufacturing practice system.

- Key Current Good Manufacturing Practice Provisions to Consider During and After Joining Together Co-packaged and Single-Entity Combination Products.

### Pre-Clinical Safety Studies<sup>1</sup>

The design of preclinical studies varies by the type of product studied and the data that will ultimately need to be included in an IND or IDE.

Sponsors can also obtain insight into study design by reviewing approval documentation for approved combination products.

FDA considers the entire combination product in assessing the data required to support the product submission, so the type of clinical data needed (and hence study design) will be affected by the parts of the product that require clinical data to support marketing approval. For some new combination products, the clinical data may need to support the entire combination product, particularly when the product's efficacy claims relate to both constituent parts and when the product is highly integrated.



## Post Marketing Considerations <sup>2</sup>

Combination products are subject to same type of post marketing regulatory requirements as their components (drug, device, or biologic).

Planning for PM regulatory compliance should therefore include ongoing GMP requirements, adverse event reporting, post marketing commitments associated with a products specific marketing approval or clearance.

## Adverse Event Reporting

Manufacturers of combination products should request that post marketing requirements be included in pre approval discussions with the agency.

1. Device malfunction reporting (21 cfr 803.3(r)(2)(II), 21 CFR 803.20) Malfunctions associated with a death or serious injury reporting may be necessary.
2. Five-day MDR reporting: The MDR regulation requires reporting of :-
  - Any reportable event that necessitates premedical action to prevent an unreasonable risk of substantial harm to the public health
  - Any MDR reportable event for which FDA has made a written request for the submission of 5 day report
3. Drug and biologic product “alert” reporting (21 CFR 314.80(c)(1) and 600.80(C)(1))
  - For drugs and biological products, post market safety reporting emphasizes adverse events that are both serious and unexpected.
  - Device safety reporting requires 30 days, they would submitted at 30 days rather the earlier “alert” reporting period of 15 days.
4. Blood related deaths(21 CFR 606.170)
  - FDA believes that early notification of blood related death may be necessary to ensure consistent and appropriate post market regulation for some blood containing combination products regulated under the device or drug provisions of the FD&C act.
  - Blood related reports has to submit within 7 days to CBER.

## Examples of FDA Approved Products <sup>6</sup>

- Absorbable Collagen Sponge with Genetically Engineered Human Protein
- Iontophoretic transdermal system for fentanyl
- Dermal Iontophoresis System

- Absorbable Collagen Sponge with Genetically Engineered Human Protein
- Surgical Mesh with Antibiotic Coating
- Paclitaxel-Eluting Coronary Stent System
- Tositumomab and Iodine I 131 Tositumomab
- Antibiotic Bone Cement
- Dermal Collagen Implants for Aesthetic Use
- Peginterferon alfa-2a in Combination with Ribavirin
- Iontophoretic Drug Delivery Patch and Controller
- Photodynamic Therapy
- Sirolimus-Eluting Coronary Stent

## CONCLUSION

- Scientific advancement gives rise to more and more combination products, FDA and manufacturers will continue to struggle with the issue raised by regulation of combination products, unless those issues are addressed now.
- For that reason, FDA works with combination product manufacturers and other stake holders to develop and implement appropriate solutions to address these issues.
- Combination products require us to think careful about our prescribing. In some circumstances they might simply, or even improve, therapy.
- We should consider if using a combination product help us to prescribe according to accepted guidelines.

## REFERENCES

1. Combination product coalition: guidance document submission, draft guidance for industry and FDA staff: FAQs on Pre-clinical and clinical research on combination products February 27, 2009.: [http://combinationproducts.com/images/CPC\\_ClinTrialFAQFINAL.pdf](http://combinationproducts.com/images/CPC_ClinTrialFAQFINAL.pdf)
2. Evan B. Siegel .Development and approval of combination products, A Regulatory perspective.p.1,16-20,34,44,59-63,67-73
3. Guidance for Industry Nonclinical Safety Evaluation of Drug or Biologic Combinations. . <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079243.pdf>
4. Application user fee for combination products. April 2005. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126017.htm>
5. Guidance for industry and FDA current good manufacturing practice for combination products.





- September 2004 <http://www.emergogroup.com/files/Current%20Good%20Manufacturing%20Practice%20for%20Combination%20Products.pdf>
6. Examples of combination product approvals Available from: URL: <http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm>
  7. Combination products: proposed policies to enhance the FDA regulatory process. <http://www.combinationproducts.com/images/policypaper.pdf>
  8. Combination products-love them or loathe them? <http://www.australianprescriber.com/magazine/24/5/127/9/>

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