

Welcome to today's FDA/CDRH Webinar

Thank you for your patience while we register all of today's participants.

If you have not connected to the audio portion of the webinar, please do so now:

Dial: 800-369-2040

International: 1-773-756-4813

Passcode: 1397061

Conference Number: PWXW6784811

Combination Product Updates for “Acceptance and Filing Reviews for Premarket Approval Applications” and “Refuse to Accept Policy for 510(k)s”

March 20, 2018

James Bertram, Ph.D.

Policy Analyst

Center for Devices and Radiological Health

Office of Device Evaluation

March 22, 2018

PURPOSE

The purpose of this webinar is to help clarify the Agency's recommendations related to the content of these guidance documents

- The 21st Century Cures Act (“Cures”) amended section 503(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and requires sponsors of device led combination products to
 - Accurately self-identify the product as a combination product
 - If the drug constituent has been previously approved by CDER:
 - Provide patent certification/statement if they contain a “listed drug”
 - Consider whether any new drug application (NDA) is protected by exclusivity that could affect approval/clearance
- FDA has updated refuse to accept (RTA) checklists to take into account necessary elements and contents of a complete application
- These provisions do not apply to non-combination products

OUTLINE

- Introduction to New Statutory Provisions
- Identification of Combination Products
- Patent Provisions
- Exclusivity Provisions
- Review and Conclusions
- Case Studies
- Questions

INTRODUCTION TO NEW STATUTORY PROVISIONS

INTRODUCTION



Drug Price Competition and Patent Term Restoration Act of 1984

- Also known as the Hatch/Waxman Amendments
- Speeds entry of generic drugs into the market and provides additional protection to innovators
- Provided for “Exclusivity”
 - Gives certain holders of an approved NDA limited protection from new competition in the marketplace
 - Could preclude submission or approval of a 505(b)(2) application or an abbreviated NDA (ANDA) for a prescribed time period
- Patent Protections
 - Innovators provide relevant patents to FDA
 - FDA lists in Orange Book
 - Applicants of 505(b)(2) applications and ANDA must certify to patents listed for relied-upon listed drug

INTRODUCTION



The 21st Century Cures Act applies these provisions to device-drug combination products

We have updated the PMA and 510(k) RTA Checklists to address these provisions

RTA Updates apply to submissions received after April 2, 2018 (provisions in effect since December 13, 2016)

Introduction

Section 503(g) of the Food, Drug and Cosmetic Act (FD&C Act) was amended and now requires sponsors of combination products to:

- Accurately self-identify the product as a combination product (**FD&C Act sec. 503(g)(8)(C)(v)**)
- Provide patent certification/statement if they contain an ‘approved drug’ (**FD&C Act sec. 503(g)(5)(A)**)
- Consider whether the drug constituent is covered by exclusivity (**FD&C Act sec. 503(g)(5)(C))**)

INTRODUCTION



FD&C Act sec. 503(g)(5)(B) - ‘Approved drug’ means an active ingredient –

- that was in an application previously approved under section 505(c);
- where such application is relied upon by the applicant;
- for which full reports of investigations that have been made to show whether such drug is safe and effective for use were not conducted by or for the applicant; and
- for which the applicant submitting the application or request has not obtained a right of reference.



INTRODUCTION

These provisions apply to the following device led combination product submission types:

- 510(k)s (traditional, special and abbreviated)
- De Novo Requests
- Original PMAs
- Panel Track, 180 day, and Real Time PMA Supplements

We recommend you provide similar patent and exclusivity information in submissions with and without RTA checklists

IDENTIFICATION OF COMBINATION PRODUCTS

New Statutory Provisions

- Accurately self-identify the product as a combination product

FD&C Act sec. 503(g)(8)(C)(v)

“In seeking agency action with respect to a combination product, the sponsor of such product shall identify the product as a combination product”

Identification of Combination Products



- Sponsors of combination products must self identify as such
- CDRH will verify the sponsor's identification of their combination product
- Failure by the sponsor to identify a submitted combination product as a combination product is grounds for refusal to accept (i.e., RTA1 decision)

Types of Combination Products



- Drugs/devices/biologics that are:
 - Physically or chemically combined into a single entity (21 CFR 3.2 (e)(1))
 - Copackaged/kit (21 CFR 3.2 (e)(2))
 - Sold separately but labeled for use together (21 CFR 3.2 (e)(3),(4))
 - May be submitted in separate drug/biologic and device applications or in one single device application if device PMOA
 - Select “N/A” for containing approved drug as a constituent part question if application only contains a device

Classification of Products

- Refer to final [Classification Guidance](#)
- Provides interpretation of “chemical action” and “primary intended purposes” in the device exclusionary clause

“which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes”

Combination Product Assignment

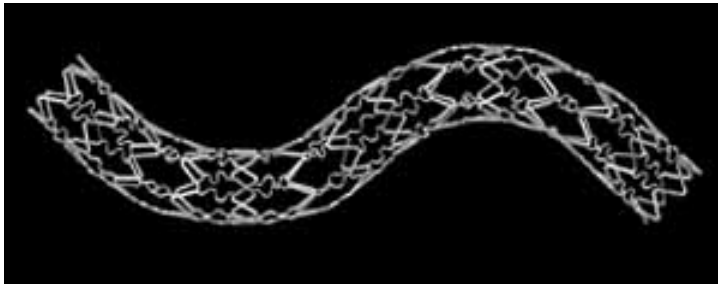


- CDRH regulates combination products with a device primary mode of action (PMOA)
 - PMOA is the single mode of action (MOA) of a combination product that provides the most important therapeutic action of the combination product (21 CFR 3.2 (m), 3.4 (a))

OR

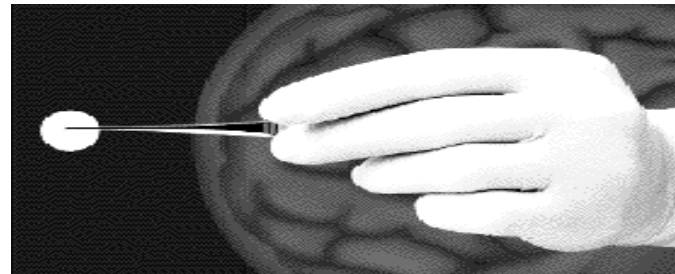
- That are assigned to CDRH based on the product assignment algorithm (21 CFR 3.4 (b))
 - Center that regulates products raising similar questions of safety and effectiveness
 - Center with most expertise to evaluate the most significant safety and effectiveness questions raised by the product

PMOA Examples



Drug Eluting Stent

- PMOA – stent opens artery (device)
- Secondary MOA – drug prevents inflammation and restenosis
- Assigned to **CDRH**



Drug Eluting Disk

- PMOA – chemotherapy for brain tumor (drug)
- Secondary MOA – local delivery of drug by the device
- Assigned to **CDER**

Example CDRH Combination Products



- Oral/dermal wound dressings with drugs
- Sutures with antimicrobials
- Heparin/antimicrobial coated catheters
- Steroid-eluting leads
- Drug-eluting stents
- Surgical mesh with antimicrobials
- Breath tests
- Lock flush solutions
- Bone void fillers with antimicrobials
- Dermal fillers with lidocaine

Classification of Combination Product Procedures



- Recommend including the following statement in cover letter and product description:
 - We are identifying [insert product name] as a combination product.
- Recommend in product description clearly identifying the drug constituent parts
- CDRH may refuse to accept (RTA) applications for combination products that do not self identify as such
- If you have questions about the classification of your product contact CDRHProductJurisdiction@fda.hhs.gov or the Office of Combination Products at combination@fda.gov

PATENT PROVISIONS

New Statutory Provisions

- Provide patent certification/statement if product contains an approved drug

FD&C Act sec. 503(g)(5)(A)

“If an application is submitted under section 515 or 510(k) or a request is submitted under section 513(f)(2), consistent with any determination made under paragraph (1)(D), for a combination product containing as a constituent part an approved drug

- *the application or request shall include the certification or statement described in section 505(b)(2); and*
- *the applicant or requester shall provide notice as described in section 505(b)(3)”*

Patent Procedures

- Sponsors of combination product applications should determine whether the drug component (active ingredient) has been previously approved by CDER
- If yes, the sponsor should identify a listed drug (LD) under an NDA in the Orange Book for which they rely
- Sponsors should provide appropriate patent certification or statement to all patents listed for the LD
- Right of reference from the NDA holder may be provided in lieu of patent information
 - Recommend stating in cover letter that a right of reference is included and identify its location in the submission

Patent Certifications

- For each RLD that is relied on, sponsors should provide either a statement that there are no relevant patents or one of the following certifications based on the Orange Book to each listed patent (21 CFR 314.50(i)):
 - **Paragraph I:** The patent information has not been submitted to FDA
 - **Paragraph II:** That the patent has expired
 - **Paragraph III:** The date on which the patent will expire
 - **Paragraph IV:** That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted

Patent Certifications

- When providing a paragraph IV certification, sponsors must provide notice to each owner of the patent and to the NDA holder and include a statement of such certification (21 CFR 314.52(b)(3))
 - Owner/holder has 45 days to file infringement suit

Patent Certifications

- CDRH plans to RTA combination product submissions that do not contain appropriate patent certifications or statements
- If a Paragraph III certification is provided, CDRH cannot grant final clearance or approval until the patent has expired
- If a Paragraph IV certification is provided, CDRH must wait 45 days before granting final clearance or approval
 - If an infringement suit is filed within the 45 day period, CDRH must delay clearance or approval for up to 30 months

Patent Certifications

- Patent provisions are met/ no delay on approval/ clearance/ granting when:
 - The submission does not contain an approved drug, or
 - A right of reference to the NDA is provided, or
 - a complete data set to establish safety and effectiveness of the drug is included in the submission such that reliance on a LD is not required, or
 - An appropriate ‘no relevant’ patent statement or Paragraph I or II certification is provided

EXCLUSIVITY PROVISIONS

New Statutory Provisions

- Consider whether the drug constituent is covered by exclusivity

FD&C Act sec. 503(g)(5)(C)

“The following provisions shall apply with respect to an application or request... to the same extent and in the same manner as if such application or request were an application described in section 505(b)(2) that referenced the approved drug:

- *(i) Subparagraphs (A), (B), (C), and (D) of section 505(c)(3)*
- *(ii) Clauses (ii), (iii), and (iv) of section 505(c)(3)(E).*
- *(iii) Subsections (b) and (c) of section 505A, Section 505E(a), Section 527(a).”*



Exclusivity Provision

- Sponsor does not need to provide information related to exclusivity
- FDA will be checking for exclusivity, so we do recommend being aware of any unexpired exclusivity and contacting us with questions
- Contact CDRHProductJurisdiction@fda.hhs.gov for any questions on exclusivity

IMPLEMENTATION PROCEDURES

Implementation Procedures

- CDRH will evaluate information related to these provisions at RTA phase and issue RTA1 if provisions are not met/submission or marketing authorization is blocked
- CDRH will also conduct evaluation of patent and exclusivity information prior to clearance/approval
- If clearance/approval is blocked, CDRH may not issue a “clean” clearance/approval decision
- Evaluation prior to clearance/approval applies to submissions received on/after Dec 13, 2016
- RTA updates apply to submissions received on/after 4/2/2018

CASE STUDIES

Case Studies

- Just a reminder, considerations for evaluating your obligations in addressing these provisions:
 - Self-Identification as a Combination Product
 - Listing in the Orange Book
 - Patents listed in the Orange Book
 - Exclusivities listed in the Orange Book

Case Study 1: No patents or exclusivities for drug



- Product Description: Combination Product (Device coated w/Drug A)
- Background:
 - LD for Drug A was approved under NDA 012345
 - No unexpired patents and no unexpired exclusivities affecting Drug A
- Sponsor Obligation:
 - Self-Identify as a combination product
 - Provide a Paragraph I or II Certification (or ROR) to NDA 012345 in cover letter:

“Paragraph I Certification to NDA 012345 - To the best of our knowledge no patent information has been submitted to the FDA.”

Case Study 2: Drug with unexpired patent



- Product Description: Combination Product (Device coated w/Drug B)
- Background:
 - LD for Drug B was approved under NDA 543210
 - No unexpired exclusivities affecting Drug B
 - Patent does not expire until 2/2/2020
- Sponsor Obligation:
 - Self-Identify as a combination product
 - Provide a ROR from holder of NDA 543210 and identify in cover letter its location in your submission
OR
 - Provide a PIII or PIV certification (delays clearance/approval)

Case Study 3: Drug not listed in Orange Book



- Product Description: Combination Product (Device coated w/Drug C)
- Background:
 - Drug C not listed in Orange Book
- Sponsor Obligation:
 - Self-Identify as a combination product

If drug is not listed in Orange Book, it would be helpful to note this in the cover letter.

Case Study 4: Product with 2 Drugs



- Product Description: Combination Product (Device coated w/Drugs D & E)
- Background:
 - LD for Drug D was approved under NDA 102345
 - LD for Drug E was approved under NDA 543201
 - No unexpired patents and no unexpired exclusivity affecting Drug D or Drug E
- Sponsor Obligation:
 - Self-Identify as a combination product
 - Provide a Paragraph I or II Certification (or ROR) to NDA 102345
 - Provide a Paragraph I or II Certification (or ROR) to NDA 543201

“Paragraph II Certifications to NDAs 102345/543201 - To the best of our knowledge patent information that has been submitted to the FDA has expired.”

SUMMARY

Summary

- Provisions do not apply if
 - Product is not a combination product
- Provisions are met if
 - Sponsor identifies product as combination product and
 - Product contains a drug component that has not been previously approved by CDER, OR
 - A right of reference is provided to the NDA holder, OR
 - A complete data set to establish S + E of the drug is included, OR
 - No unexpired patents for the relied-upon LD(s), no unexpired exclusivity and the sponsor provides an appropriate patent statement or certification

Summary

- Provisions are not met/ marketing authorization delayed if
 - Sponsor does not identify product as combination product
- OR
- Product contains a drug listed in the Orange Book and
 - Sponsor does not provide an appropriate patent certification, statement, or right of reference, OR
 - Sponsor provides a Paragraph III or IV certification to unexpired patent(s) listed for the relied-upon LD, OR
 - There is unexpired exclusivity that affects the submission

Resources

- [Approved Drug Products with Therapeutic Equivalence Evaluations \(Orange Book\)](#)
- [FAQs on the Orange Book](#)
- [Frequently Asked Questions on Patents and Exclusivity](#)
- [Classification Guidance](#)

Questions?

If you have questions please contact
CDRHProductJurisdiction@fda.hhs.gov

Slide Presentation, Transcript and Webinar Recording will be available at:

<http://www.fda.gov/training/cdrhlearn>

Under the Heading: How to Study and Market Your Device;
Subheading: Cross-Cutting Premarket Policy

Please complete a short survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/CDRHWebinar immediately following the conclusion of the live webinar.

