

Regulatory Update on Combination Products

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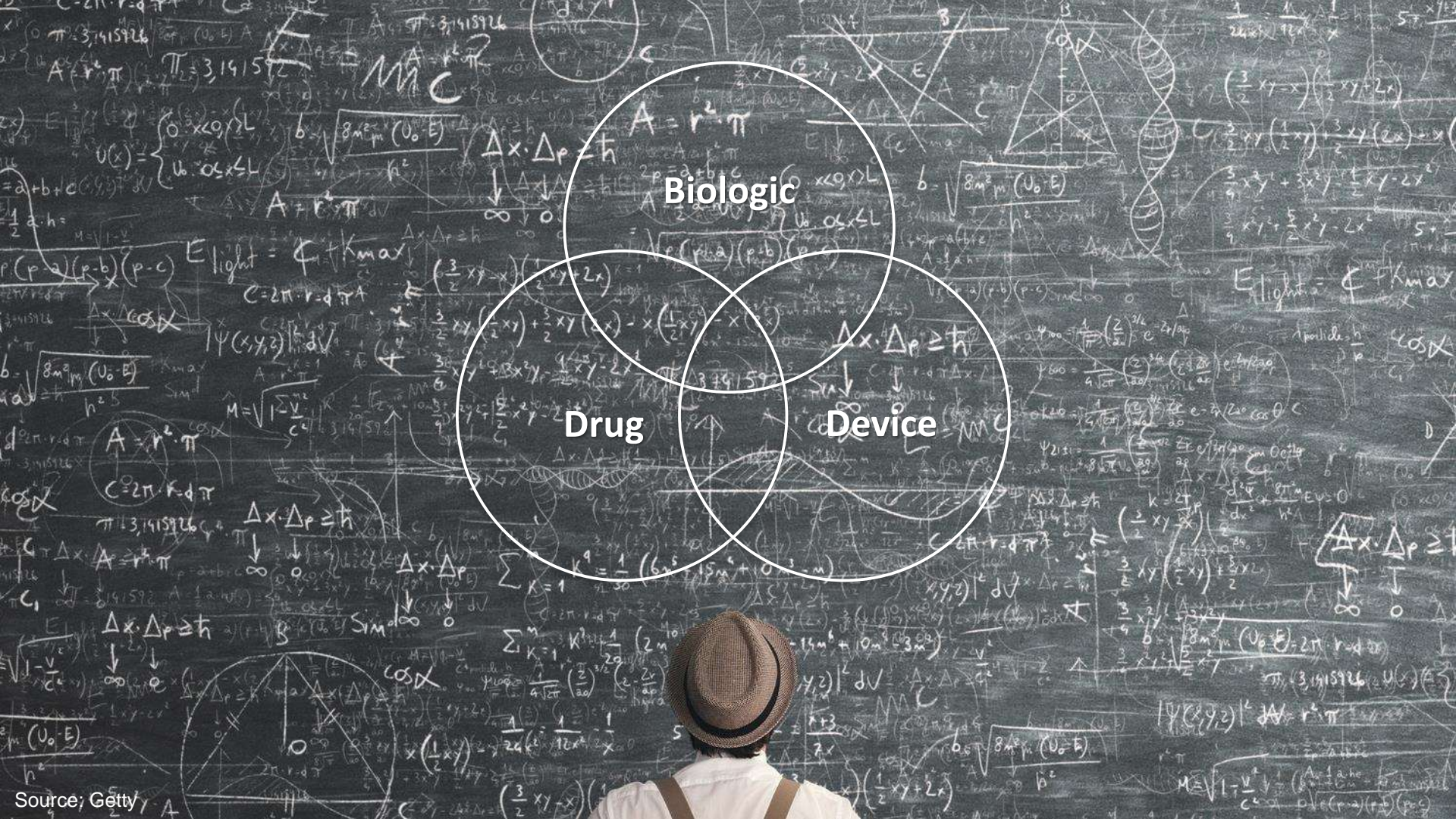
CDER | US FDA

Generic Drugs Forum 2020 – April 16th, 2020

Unlocking Combination Products



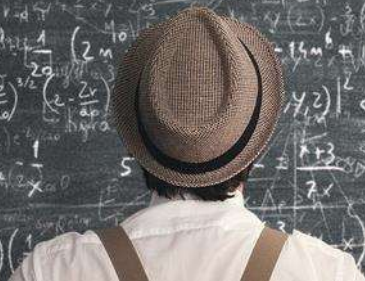
3... 7346.832... 4...
820... 211... 3038...
506H... 356h...



Biologic

Drug

Device



A slice of strawberry cheesecake is presented on a white surface. The cake has a thick, creamy white filling and a golden-brown crust. It is topped with several fresh, sliced strawberries and a sprig of green mint. A vibrant red strawberry sauce is drizzled over the top and sides of the slice. In the foreground, another strawberry half and a small mint leaf are placed on a pool of the red sauce. To the right of the main slice, there are more strawberries, a small white cream swirl, and another mint leaf, also with some sauce.

CP CGMPs



PMSR

CGMPs

ICCRS

MDSAP

OBJECTIVES

1: CP Updates

2: 21 CFR Part 4

3: CDER-led Submissions

4: Device Specific Info

5: Summary

- 21 CFR Part 3 (Product Jurisdiction)
 - **Regulation**
 - <https://tinyurl.com/21CFRPart3>
 - **Preamble**
 - <https://tinyurl.com/PMOApreamble>
 - **Proposed rule**
 - <https://tinyurl.com/ProdJuris>

- 21 CFR Part 4 (Regulation of CPs)
 - **Regulation**
 - <https://tinyurl.com/21CFRPart4>
 - **Preamble**
 - <https://tinyurl.com/CGMPpreamble>
 - <https://tinyurl.com/PMSRpreamble>
 - **Guidance**
 - <https://tinyurl.com/CGMPguidance>
 - <https://tinyurl.com/PMSRguidance>
 - **AAMI TIR48:2015**
 - <https://tinyurl.com/TIR48>

- 21st Century Cures Act
 - Sec. 3038 (CP innovation)
 - Amendments to 503(g) & 520(h)(4)
 - ✓ PMOA, single submission, meeting requests, submission data, ICCRs, pre-submission interactions, dispute resolution metrics...
 - CP CGMP Variations
 - ✓ <https://tinyurl.com/CGMPvariations>

- FDA Reauthorization Act of 2017
 - Sec. 803 → FD&C Act, Sec. 506H (competitive generic therapies)
 - “Involve senior managers and experienced review staff, as appropriate, in a collaborative, coordinated review of such application, including with respect to drug-device combination products and other complex products.”

- Agency Program Directives
 - SMG 4101 (CP ICCR Process)
 - <https://tinyurl.com/SMG4101>
 - SMG 4103 (Agency CP Engagement)
 - <https://tinyurl.com/SMG4103>
 - SMG 4104 (Human Factors ICCRs)
 - <https://tinyurl.com/SMG4104>

- Subpart A – CGMPs for CPs
 - 21 CFR Part 4.4(b)(1)
 - Drug CGMP OS w/ QSR call-outs
 - ✓ 820.20 (mgmt responsibility)
 - ✓ 820.30 (design controls)
 - ✓ 820.50 (purchasing controls)
 - ✓ 820.100 (CAPA)
 - ✓ 820.170 & 820.200 (installation & servicing [as applicable])

- Subpart A – CGMPs for CPs
 - 21 CFR Part 4.4(b)(2)
 - QSR OS w/ drug CGMP call-outs
 - ✓ 211.84 (incoming testing)
 - ✓ 211.103 (yield calculation)
 - ✓ 211.132 (OTC tamper evident packaging [as applicable])
 - ✓ 211.137 (expiration dating)
 - ✓ 211.165 (finished product testing)
 - ✓ 211.166 (stability testing)
 - ✓ 211.167 (special testing)
 - ✓ 211.170 (reserve samples)

- Subpart B – PMSR for CPs
 - Goals
 - Complete and consistent reporting
 - Appropriate postmarket surveillance
 - Avoid unnecessary duplicative reporting requirements
 - Clarify how requirements apply to CPs

- Subpart B – PMSR for CPs
 - Rule applies to...
 - “Combination product applicants”
 - “Constituent part applicants”
 - Application-based reporting requirements apply to...
 - NDAs/ANDAs– 21 CFR Part 314
 - BLAs– 21 CFR Parts 600 and 606
 - Device applications– 21 CFR Parts 803 and 806

- Subpart B – PMSR for CPs
 - Individual case safety reports (ICSRs)
 - Follow lead Center's procedures
 - Non-ICSRs
 - Procedures in associated regulations and guidance
 - Reports may be streamlined

For Combination Product Applicants...

| NDA/ANDA or BLA (if combination product includes a device constituent part), must also submit... | BLA or device application* (if combination product includes a drug constituent part), must also submit... | NDA/ANDA or device application* (if combination product includes a biological product constituent part), must also submit... |
|---|---|---|
| | ICSRs | |
| 5-day (remedial action) reports (21 CFR 803.3, .53, .56) Malfunction reports (21 CFR 803.50) | 15-day (serious unexpected adverse event) reports (21 CFR 314.80) (with 30-day deadline if marketed under a device application) | 15-day (serious unexpected adverse event) reports (21 CFR 600.80) (with 30-day deadline if marketed under a device application) |
| | Non-ICSRs | |
| Correction or removal reports and records (21 CFR 806.10, 806.20) | Field alert reports (FARs) (21 CFR 341.81) | Biological product deviation reports (BPDRs) (21 CFR 600.14, .171) |

*Device applications = PMA, 510(k), de novo, PDP, HDE (see 21 CFR 4.101)

Other reports:

- Combination product applicants marketing under an NDA, ANDA, and BLA applicants must address 5-day and malfunction reports in periodic reports (21 CFR 314.80, 600.80).
- Combination product applicants marketing under a device application must provide additional reports only as required and specified in writing by FDA.

- Subpart B – PMSR for CPs
 - PMSR resources
 - Preamble and guidance
 - ✓ Slide 8
 - FDA webpage
 - ✓ <https://tinyurl.com/PMSRresources>

Inter-center Consultation Requests FY2018

- The number of inter-center consultation requests related to combination products continued to increase.
- The number of inter-center consultation requests increased from 1419 in FY17 to 1445 in FY18.
- Requesting Center:
 - CDRH: 460
 - CDER: 867
 - CBER: 118

Combination Product Premarket Submissions FY2018

- The total number of original applications for combination products submitted for review decreased from 566 in FY17 to 497 in FY 18
- Of the 497 combination product premarket submissions received in FY18:
 - CBER Lead: 51 (10%)
 - CDER Lead: 339 (68%)
 - CDRH Lead: 107 (22%)
- 47% of the premarket submissions are original INDs followed by ANDAs (22 percent).

- Compliance Program Updates
 - Changes to 7346.832 (pre-approval inspections) implemented 9/16/2019
 - <https://tinyurl.com/7346-832>
 - Align with CDER/ORR ConOps
 - <https://tinyurl.com/FDAConOps>

- 356h Updates
 - Form and instructions updated August 2018
 - Specific fields for CP info
 - <https://tinyurl.com/356hInfo>
 - Establishment information
 - Include manufacturing, packaging, and control facilities for DS/DP/CP
 - Also include device constituent part manufacturers and specification developers

- 356h Updates
 - Level 2 GFI finalized October 2019
 - *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*
 - <https://tinyurl.com/356hQ-A>

- CDRH Reorganization
 - Phased approach that began in March 2019, implementation complete by end of CY 2019
 - <https://tinyurl.com/CDRHreorg>

- Transition to ISO 13485:2016
 - Harmonizing and modernizing regulation of medical device quality systems
 - MDSAP stakeholder FDA update
 - ✓ <https://tinyurl.com/FDA13485>
 - AAMI TIR102:2019 (CFR mapping)
 - ✓ <https://tinyurl.com/TIR102>

EU MDR...?

SaMD...?

Digital health...?

ICH Q12...?



- If you have CP questions about **X**, contact **Y**
- Application info → Center RPM or Lead Reviewer
- Inspection observations → ORA (Centers will assist if needed)
- CP guidance and policy → OCP



Pearl Jam's CP Tour

2013

"Indifference", "Down", "No Way",
"Help, Help", "In Hiding", "Sad"...

2020

"Smile", "Just Breathe", "Unthought
Known", "It's Okay"!!!

Which of the following is **not a combination product?**

- A. An insulin pre-filled syringe
- B. An IV container filled with 0.9% normal saline
- C. Elexacaftor/ivacaftor/tezacaftor tablets
- D. A buprenorphine transdermal patch

Which of the following does **not have to be listed on the Form FDA 356h?**

- A. Device specification developers
- B. Device component manufacturers
- C. Device constituent part manufacturers
- D. Finished combination product manufacturers

Questions?

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<https://www.fda.gov/combination-products>

