COMBINATION PRODUCTS SUMMIT

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Investigational Combined Use: Industry Perspective & Proposal

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on behalf of: **Combination Products Coalition (CPC), Cross-Labeling & Combined Use Working Group**

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2020

Cross-Labeling and Combined Use – Industry Perspective

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Agenda

- Introduction
  - US Regulation of Combination Products
  - Cross-Labeled Combination Products
  - Combined Use
  - Examples
  - Cross-labeling vs. Combined Use
  - Software/Digital Health
  - History
- Impact
  - Impact on: industry, patients, HCPs regulators
  - Value in Clarity, Uncertainty
  - Specific concerns
  - Complexities
  - Designation Impact
  - Opportunity
- Proposal: Guidance
  - Definitions
  - Regulatory requirements/expectations

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Cross-Labeling and Combined Use – Industry Perspective

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Conclusion

- Cross-Labeling/Combined Use is area of ambiguity with impact on FDA, industry, and patients
- Longstanding concerns, dating back to enactment of the regulation
- Multiple areas of impact
- Opportunity for clarity via guidance
- Drive via continued collaboration

2021

Cross-Labeling and Combined Use – Industry Perspective

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Investigational Combined Use

- Combined Use in investigational setting
  - Investigational drug/biologic (studied under IND) used with medical device
    - Legally marketed device (approved/cleared/granted/exempt) used per intended use.
    - Legally marketed device used outside of intended use.
    - Investigational device.
  - Investigational device (IDE or abbreviated/exempt requirements) used with drug/biologic
    - Approved drug/biologic used on-label.
    - Approved drug/biologic used off-label*
      - *in certain situations, when explicitly allowed by FDA.
    - [Investigational drug/biologic – see above]

Today's focus: practical matters relating to investigat… classification)

Cross-Labeling and Combined Use – Industry Perspective

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Proposal: Risk-Based Approach

*Examples for delivery devices, other types of risks may apply

Higher cumulative risk – more suited to be treated as a combination product

- Drug/biologic or device status: (Higher Risk)
  - Investigational
  - Legally marketed (used off-label)
  - Legally marketed (used on-label)
- Drug/biologic modality: (small molecules, oligonucleotides, monoclonal antibodies, recombinant protein, gene therapy) (Higher Risk)
  - Unknown/highly unstable/novel modalities
  - Less-understood/unstable in some scenarios/relatively newer modalities
  - Well-understood/stable/broadly used modalities
- Route of administration: considering qualitative invasiveness and legally marketed devices intended for that route (Higher Risk)
  - High risk: epidural, intracerebral, intracisternal, intrathecal, intravitreal, intraocular, or implanted/indwelling
  - Medium risk: intravenous, subcutaneous, intramuscular, intradermal
  - Low risk: transdermal, oral, ophthalmic (drop), nasal, otic

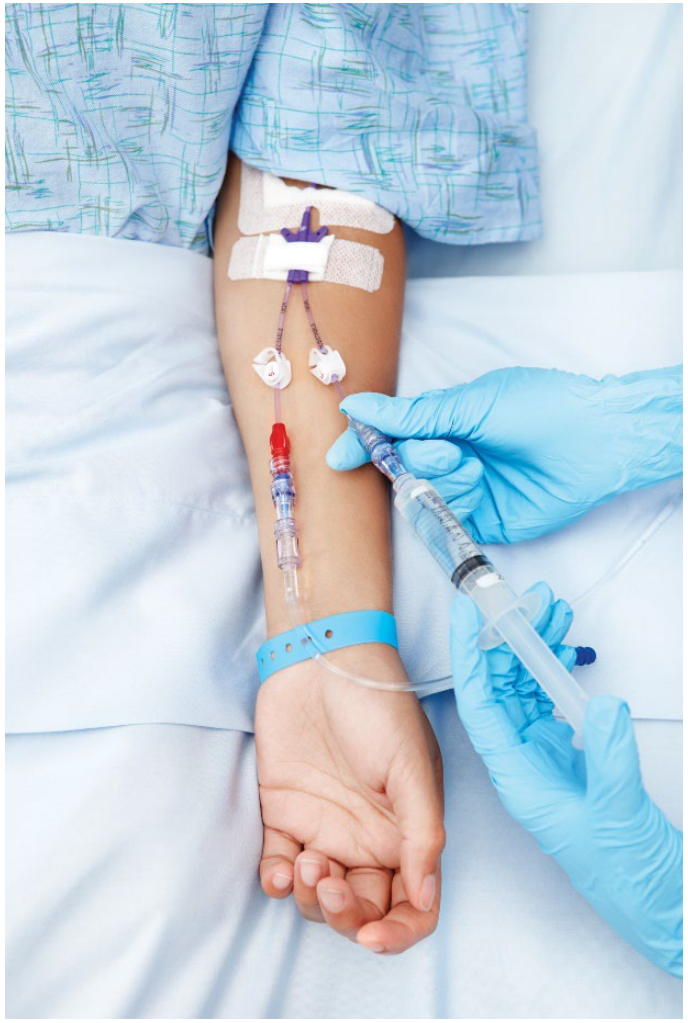
Reminder: Combined Use Definition

FDA-regulated products (drugs/devices/biologics) that may reference another general class or specific product, but *do not* meet the definition of a combination product (e.g. concomitant use, 'one-way' labeling).

Drug Delivery in the Investigational Space

Source: utah.edu

Source: baxter.com

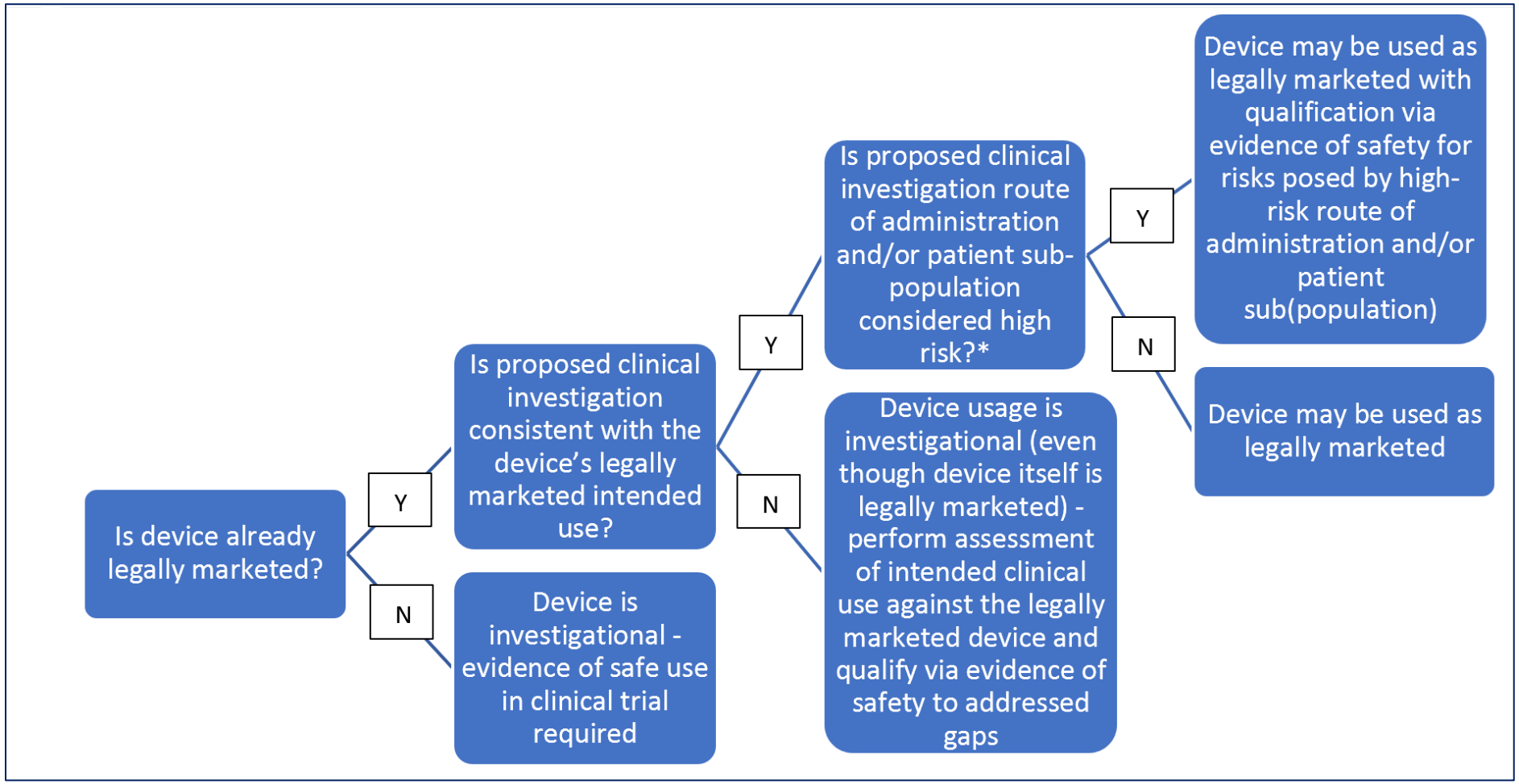


Source: wikipedia.org

Source: cannondesign.com

Source: bd.com

Industry Proposal: Risk-Based Framework



Note that device used for preparation, such as reconstitution, admixture, etc. are being included in the term "delivery" for the purpose of this document. This includes any drug-contacting devices used in preparation or administration.

* For general use devices, i.e. (devices where route of administration or patient populations are not specified). Examples of high-risk route of administrations include CNS – intrathecal, intracerebral, ophthalmic. High-risk subpopulations could include pediatrics or geriatrics.

Factors Considered in Risk-Based Assessment

- Regulatory Status of Device
- Drug modality and use of surrogates for performance testing
- Issues related to new routes of administration
- Human Factors Evaluation
- Leveraging publicly available data sources

Regulatory Considerations:

- **IND** (Drug): 'phase-appropriate' contents per 21 CFR 312.22 & 312.23.
- **IDE** (Device): significant/non-significant risk devices per 21 CFR 812.3(m) & 812.2(b).

Factor: Regulatory Status of Device

- Use within legally marketed intended use – *leverage marketing status*
- Use outside of legally marketed intended use – *supplemental data*
- New/investigational device – *complete data*

- Emphasis on relatively few performance and safety attributes needed rather than comprehensive “design controls” program
- Investigation-specific performance confirmation and characterization should be performed in lieu of design verification testing.
- Testing should be limited to specific use and performance specifications defined in the IND study protocol.

Factor: Drug modality and use of surrogates for performance testing

- Consider known attributes about drug product
- Assess ability to use surrogates (placebo, formulated buffers) for device performance testing

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- When devices are in contact with investigational biologic or drug, in-use compatibility of the device with study agent needs to be assessed from product quality standpoint
- Risk-based use of placebo or formulated buffer that mimic the study agent can effectively be used for certain device performance testing
- Acknowledge minimum requirements of testing for endotoxins and particulates may be necessary

Factor: Issues related to new routes of administration

- Use in high-risk routes of administration, populations, etc. – *specified data*

- When specific route of administration is proposed, sponsor must show combined device use is safe for the clinical investigation.
- In some cases, device performance is drug- and route-agnostic – this should not require additional testing unless there are contraindications or specific characteristics of concern identified in risk assessment.
- Characterization testing of combined use system, vs. 'comprehensive design verification' should be sufficient to determine system performance issues or new significant risks.

Factor: Human Factors Evaluation

- Existing data (for legally marketed devices) should be considered and leveraged
- Clinical documentation (Clinical Protocol, Pharmacy/Surgical Manual, training, etc.) should be considered
- URRA can be used to determine whether a formative HF study should be conducted

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- Consideration for HF/UE is appropriate, however many leverage legally marketed devices with existing labeling.
- Sponsor would not have authority to alter labeling (including Instructions for Use) of the marketed device.
- Newly identified use-related risks may be addressed via clinical documentation (Protocols, Manuals, training, etc.) noting higher level of control for clinical studies.
- Full HF/UE, including Design Validation, should be considered for marketing application.

Factor: Publicly available data sources

- Regulatory documentation (510(k) clearance summary, PMA summary basis of approval)
- Device labeling (IFU, manuals, supplier documentation)
- Scientific literature

- Right of reference (e.g. Letter of Authorization, LoA) not needed for publicly available information
- LoA may be needed when evidence from the device needed to support use outside of cleared indications or is contraindicated.
- Clarity when LoAs are required would be useful due to timing and constraints involved in clinical investigations.
- Uncertainty for sponsor when LoA may not be available.

Data Expectations (1 of 3)

Device Status	Impact	Sponsor internal Documentation Expectations	IND Submission Expectations
Legally Marketed, used within existing intended use	Device used in accordance with its marketed label including IFU. Device is used per its specifications. Drug/device interactions do not introduce new risks and reduce regulatory burden. Design controls leveraged from marketed device.	• Device information referenced: DMF/MAF, 510(k), PMA, and/or registration/listing. • DP compatibility (CQAs) and in-use stability • Appropriate controls on purchased supplies that are implemented commensurate with risk applicable for that stage and linkage between clinical intended use and device specifications. (or as defined in publicly available information). • Drug agnostic design requirements may be leveraged. • Instructions for Use (IFU) from manufacturer for legally marketed intended use. • Relevant interoperability testing for devices that may be used in combination (if applicable). • Risk-based assessment of the device use in the clinical study (biocompatibility, sterility)	• Reference to device regulatory information (510(k) number, PMA number registration/listing). • Right of Reference (Letter of Authorization) only if referencing contents of a DMF/MAF. • Justification for device selection based on specifications linked to clinical intended use. • Summary of results from DP compatibility. Reference to the 510(k) device labeling (e.g., User Manual) for recommended device use rather than requiring this same content in drug labeling (e.g., IFUs) • Summary of risk-based assessment consistent with device selection, drug/device compatibility study, investigational use and interoperability if additional devices are required for adequate delivery of drug

Data Expectations (2 of 3)

Single application (IND)

Device Status	Impact	Sponsor internal Documentation Expectations	IND Submission Expectations
Legally Marketed, used outside of existing intended use	Device requirements for clinical investigation met through leveraging studies from the marketed device and bridging to address new risks through gap assessments. Design controls leveraged from marketed device. Modified use, or design, bridged.	• DMF, 510(k), appropriate controls on purchased supplies providing access to device specifications and DHF, Risk assessment to establish leveraging and bridging studies. • Device information referenced: DMF/MAF, 510(k), PMA, and/or registration/listing. (or as defined in publicly available information). • **URRA** in the proposed clinical context • **Multiple device** compatibility/use • DP **compatibility** (CQAs) via in-use stability • Appropriate controls on purchased supplies that are implemented commensurate with risk applicable for that stage and linkage between clinical intended use and device specifications. (or as defined in publicly available information). • Drug agnostic design requirements may be leveraged or require bridging contingent to modification for investigational use. • Instructions for Use (IFU) from manufacturer for legally marketed intended use. Assessment of investigational use and conditions of use to determine risk to safety and functionality of device in Clinical Study. • Applicable drug/device interaction studies ('in-use stability') with relevant DP quality data. • Relevant interoperability testing for devices that may be used in combination (if applicable). • Risk-based assessment for clinical intended use.	• Reference to device regulatory information (510(k) number, PMA number registration/listing). • Right of Reference (Letter of Authorization) *only* if referencing contents of a DMF/MAF • Summary of device specifications linked to clinical intended use. Including adequate design verification for bridging to new investigational use (if applicable). • For significant risk investigational combined use device. Comparative use analysis of investigational use to intended commercial use of device. Major differences may require adequate justification or design validation studies for bridging to new investigational use • Summary of results from drug/device interaction studies. • Summary of results from interoperability testing (if applicable). • Reference to the 510(k) device labeling (e.g., User Manual) for recommended device use rather than requiring this same content in drug labeling (e.g., IFUs). • Summary of risk assessment including drug/device compatibility study, and Interoperability if additional devices are required for adequate delivery of drug • Summary of literature review demonstrating common clinical use of device outside of existing intended use (if applicable)

Data Expectations (3 of 3)

Single application (IND)

Device Status	Impact	Sponsor internal Documentation Expectations	IND Submission Expectations
Investigational	Device requirements for clinical investigation met. Design controls adequate to meet safety and functionality for intended investigational use.	Meets expectations for IDE requirements for investigational device.	The device content may be submitted and reviewed under a single investigational application with the drug. Alternately, the device design may also be provided through an LOA reference to a DMF/MAF.

Challenges for Future Consideration

- Although framework is limited to drug delivery, proposals may also apply to other devices used in combination with drugs/biologics.
- Regulatory pathways of cross-labeled combination products remain a challenge, including accommodating concurrent reviews of separate applications for marketing drug & device constituents, and communication options for obtaining timely and efficient FDA feedback during development.
- Commercial labeling considerations including need for “mutually conforming labeling”.

References

- CPC White Paper: Combined Use Drugs-Devices in the Investigational Setting (Oct 24, 2023): https://www.linkedin.com/posts/combination-products-coalition_cpc-investigational-combined-use-drugs-devices-activity-7125579406776913923-LVfn?utm_source=share&utm_medium=member_desktop
- CPC White Paper: Cross-Labeled Combination Products, Request for Guidance and Considerations (Sep 2020): starts on p. 59 at https://www.linkedin.com/posts/combination-products-coalition_archive-6-of-6-january-2020-to-november-activity-7049093990763089923-ytFX?utm_source=share&utm_medium=member_desktop
- Presentation at Xavier Health Combination Product Summit, Oct 26, 2020: *The Possibilities of Cross-Labeling and Combined Use*
- Presentation at Xavier Health Combination Product Summit, Sep 24, 2021: *Combined Use and Cross-Labeled Products: Overcoming Investigational Challenges*

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Q&A

Thank you!

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