Combination Products – FDA

Involved entities and how to approach them

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1. Introduction & Regulatory System Comparison

2. FDA – Departments and Divisions

3. Interaction and Communication

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System Comparison

- Differences between US-FDA and EU-MDR:

Example: Medical device classification – risk-based approaches

FDA:

Class I: Lowest Risk Class, minimal potential harm; **General Controls**; 510(k) / 510(k) exempt

Class II: Moderate Risk Class, higher risk than class I devices; General and **Special Controls**; 510(k) / 510(k) exempt

Class III: Highest Risk Class, sustain or support life, implanted, potential unreasonable risk; General Controls and **PMA** (premarket approval)

EU:

Class I (Is, r, m); Class IIa; Class IIb; Class III

→ Classification under consideration of the intended purpose and their inherent risks (Article 51 MDR)

→ Classification rules set out in Annex VIII MDR

→ See MDCG 2021-24 for explanations and examples

System Comparison

- Differences between US-FDA and EU-MDR:

  Example: Medical device classification – risk-based approaches

  - Similar: Risk classification

  - Differences:
    - **EU MDR** provides classification rules and guidance – classification ultimately a manufacturer decision.

    - **FDA** does not provide classification rules
      - Regulation number and product code provide a risk class
      - Manufacturers solely select the appropriate regulation number / product code and inherit the predetermined risk class.
      - Exception: The available categories do not fit

System Comparison

- Differences between US-FDA and EU-MDR:

  Example: Centralized authority

  - **FDA** regulates drugs, vaccines, medical devices and IVDs, tobacco products, food, veterinary medicine, and cosmetics.
    Different **centers** focus on individually regulated items
    Centers have **offices** and **divisions**

  - **EU** provides a large landscape of member state authorities and cross-union stakeholders (e.g., notified bodies, expert panels, reference laboratories etc.)

Centralized Authority

- For medical devices, drugs, biologic products, and combination products:
  - Center for **Devices** and Radiological Health (CDRH) → Medical devices
  - Center for **Biologics** Evaluation & Research (CBER) → Blood products, vaccines, gene therapy
  - Center for **Drug** Evaluation & Research (CDER) → Drugs

Example:

- Liposuction solely for fat removal: Medical device allocated to **CDRH** (product code “QPB”)
- Device for reinjection of autologous fat for contouring: Biologic product allocated to **CBER** (fat graft as biologic product, product code “QKL”)
- Excursion to FDA websites

Recap

- Manufacturers need to navigate a vast array of regulation numbers and product codes to come up at:
  - Risk class
  - Submission type
  - Center (office or division) inside FDA that has jurisdiction

- Challenges (especially for combination products):
  - Regulation number and product code identification: Not every device category is represented in the system
  - Determination that no suitable “address” exists: How to determine that a search was complete?

Approaching FDA with your combination product

FDA acknowledges that the line blurs between devices, drugs, and biological products.
Yet FDA does not surrender its authority for assigning jurisdiction, risk classes, or requirement identification to manufacturers.

Instead, FDA established a dedicated interface to guide and determine how a new combination product is regulated:

- Office of Combination Products (OCP, founded in Christmas 2002)
    - Office outside of individual medical product centers (device, biologic, drug)
    - Interface between industry and FDA centers and personnel
    - Tasks include:
        - Develop and provide guidance
        - Classify products as drugs, devices, biological products, or combination products
        - Assign one FDA center with primary jurisdiction to a proposed product

Interactions with the Office of Combination Products (OCP)

Request for Designation (RFD)

- Submission vehicle to have OCP:
    - Assess the regulatory identity of a proposed product
    - Determine (primary) jurisdiction for assessing the proposed product

- Pre-RFD results in **a preliminary, non-binding** regulatory identity assessment and primary jurisdiction determination

- RFD results in a **binding** regulatory identity assessment and primary jurisdiction determination

Interactions with the Office of Combination Products

Request for Designation (RFD) Contents and timeline

- Pre-RFD
  - Content **recommendations** are described, and a checklist is provided
  - Written feedback goal: 60 days after submission

- RFD
  - Content **requirements** (instead of recommendations)
  - Must include a recommended classification and identification of primary mode of action (PMOA)
  - Designation letter after 60 calendar days

Interactions with the Office of Combination Products

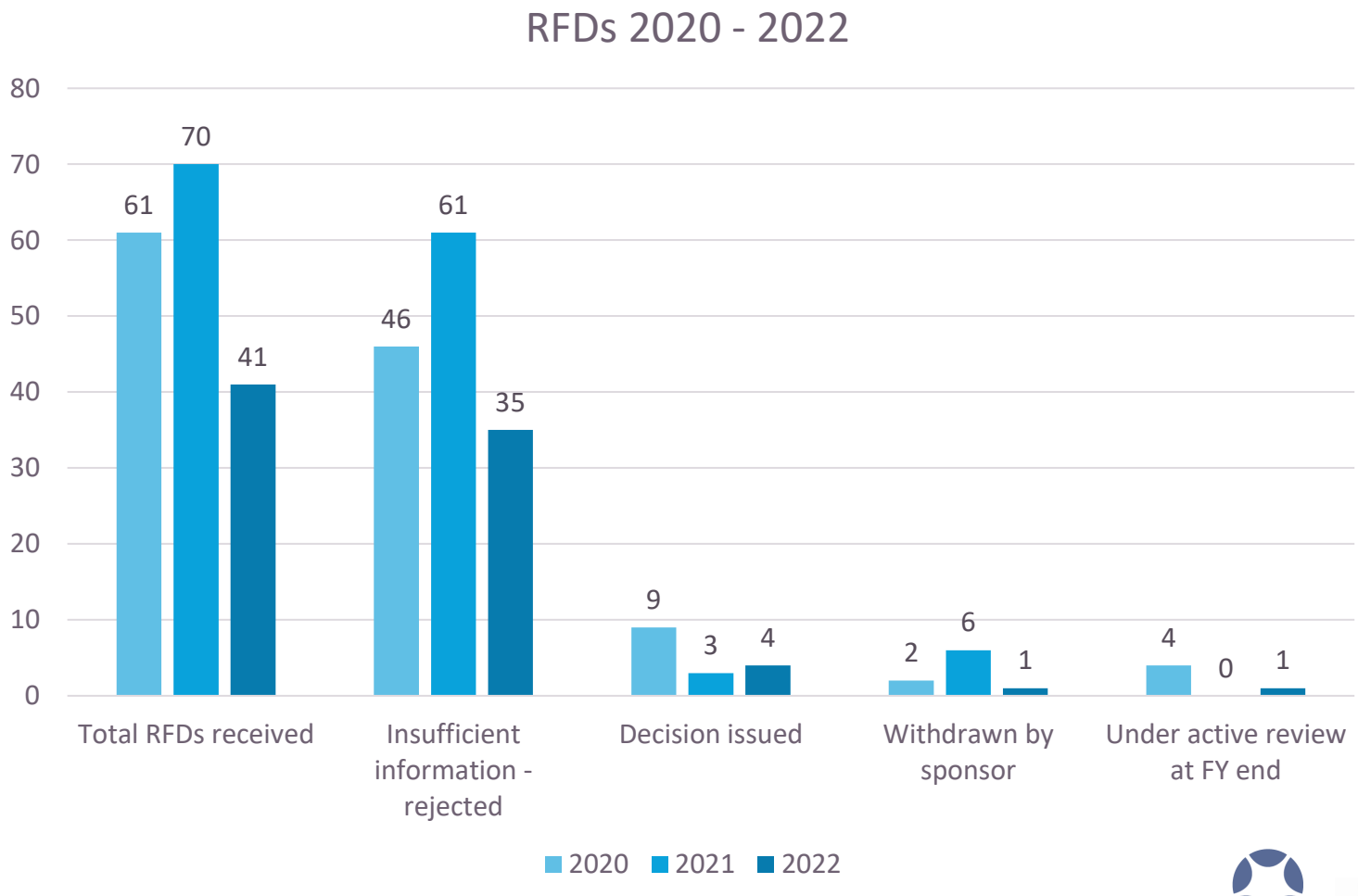
Request for Designation (RFD) Contents – all a **MUST** for RFD and **recommendation** for pre-RFD:

- Device description
- Proposed use or indications for use
- Manufacturing process and sources of all components
- Supportive data / studies
- Description of how effects are achieved
- Analysis and classification of PMOA
- Description or related products
- Sponsor (your!) recommendation
- Page limit (**only** RFD – 15 pages max)

Interactions with the Office of Combination Products

What's going on in the Combination Product sector?

- OCP Performance Reports to Congress (issued annually, most recent for fiscal year 2022)



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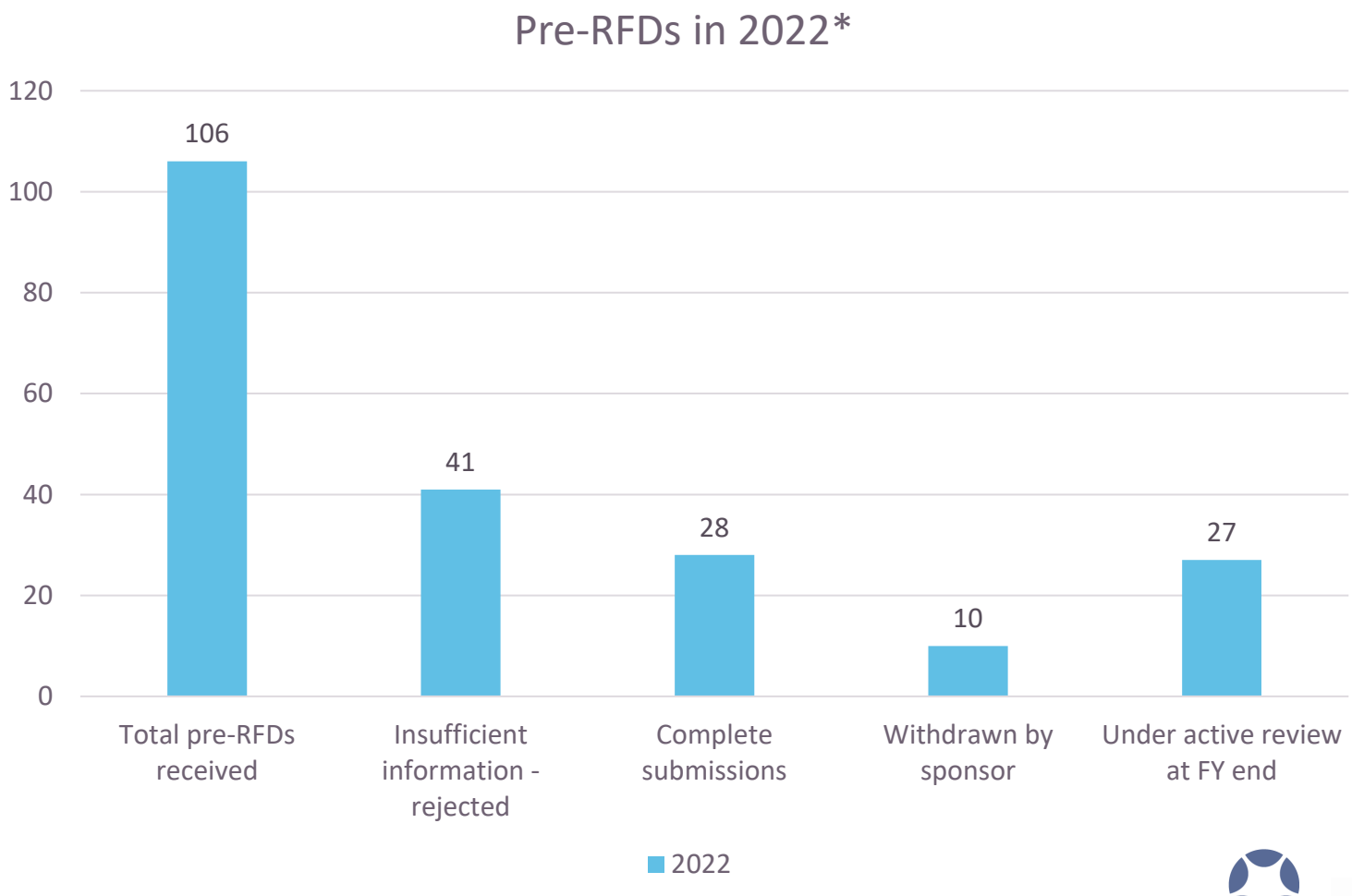

*: Pre-RFD data presentation consitent with RFD data presentation only for fiscal year 2022.

Interactions with the Office of Combination Products

What's going on in the Combination Product sector?

- OCP RFD Workload:
    - OCP receives about **one** RFD / **week**
    - About **80 %** of those lack information to allow review

- OCP Pre-RFD Workload:
    - OCP receives about **two** pre-RFDs / **week**
    - About **40 %** of those lack information to allow review

- For comparison:
    - FDA receives about **ten** 510(k)s / **calendar day**.
    - FDA receives about **ten** Q-Submissions / **calendar day**.

Recap

- FDA is a centralized entity for regulating medical devices, drugs, biological products, and combinations thereof.
- In contrast to EU, FDA will often determine classification and requirements for a type of product.
- Manufacturers must navigate existing structures and identify and apply requirements regarding their specific product.
- The OCP is the distinct entity to assess proposed combination products, determine its identity and identify primary regulatory jurisdiction.
- The OCP provides comprehensive tools to engage with them. These tools are regularly used by sponsors (RFD about once per week, pre-RFD about twice per week).
- OCP reporting requirements promote transparency.

Call to action

- Familiarize with the FDA regulation number and product code landscape.

- Determine: Does the right “address” (i.e., precedent) for my product already exist? Note: This can already be challenging!
    - If yes – Which requirements are defined, submission type, risk class?
    - If no – Get involved with FDA.

- Options for engaging with FDA:
    - RFD (if **fairly certain** the product is a combination product, **binding** response)
    - Pre-RFD (if **fairly certain** the product is a combination product, **non-binding** response)
    - 513(g) (if **fairly certain** the product is a medical device or IVD, own research into product code/regulation number without conclusion)
    - Q-Submission (not for determining classification; can be used to discuss how identified requirements will be applied – e.g., animal trial planning)

- FDA recommends and appreciates early regulatory interaction and engaging with them – my personal experiences with FDA officials were 100 % supportive, engaging, open-minded (yet unyielding on concerns / issues raised).

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Combination Products Guidances and Links

- OCP landing page
- OCP reports to congress
- Guidance on Principles of Premarket Pathways for Combination Products
- Pre-RFD guidance
- RFD guidance
- 513(g) guidance
- Q-Submission guidance
- Office of Orphan Products Development
- Breakthrough Devices Program
- Breakthrough Therapy

- Don’t hesitate to reach out to me:

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