Combination Product Development

– Pre-filled Syringe and Injection Devices

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Agenda

- Introduction
- Market trends
- FDA Combination Product Regulations
- CGMP requirements for Combination products
  - Design Control
  - Human Factors & Usability study
- Primary container compatibility issue

What is Combination product?

- Under 21 CFR 3.2 (e) : A combination product is a product composed of any combination of drug/device; biological product/device; drug/biological product; or drug/device/biological product
- Single entity combination products: A product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity; examples: prefilled syringe, pen injector.

What is Combination product?

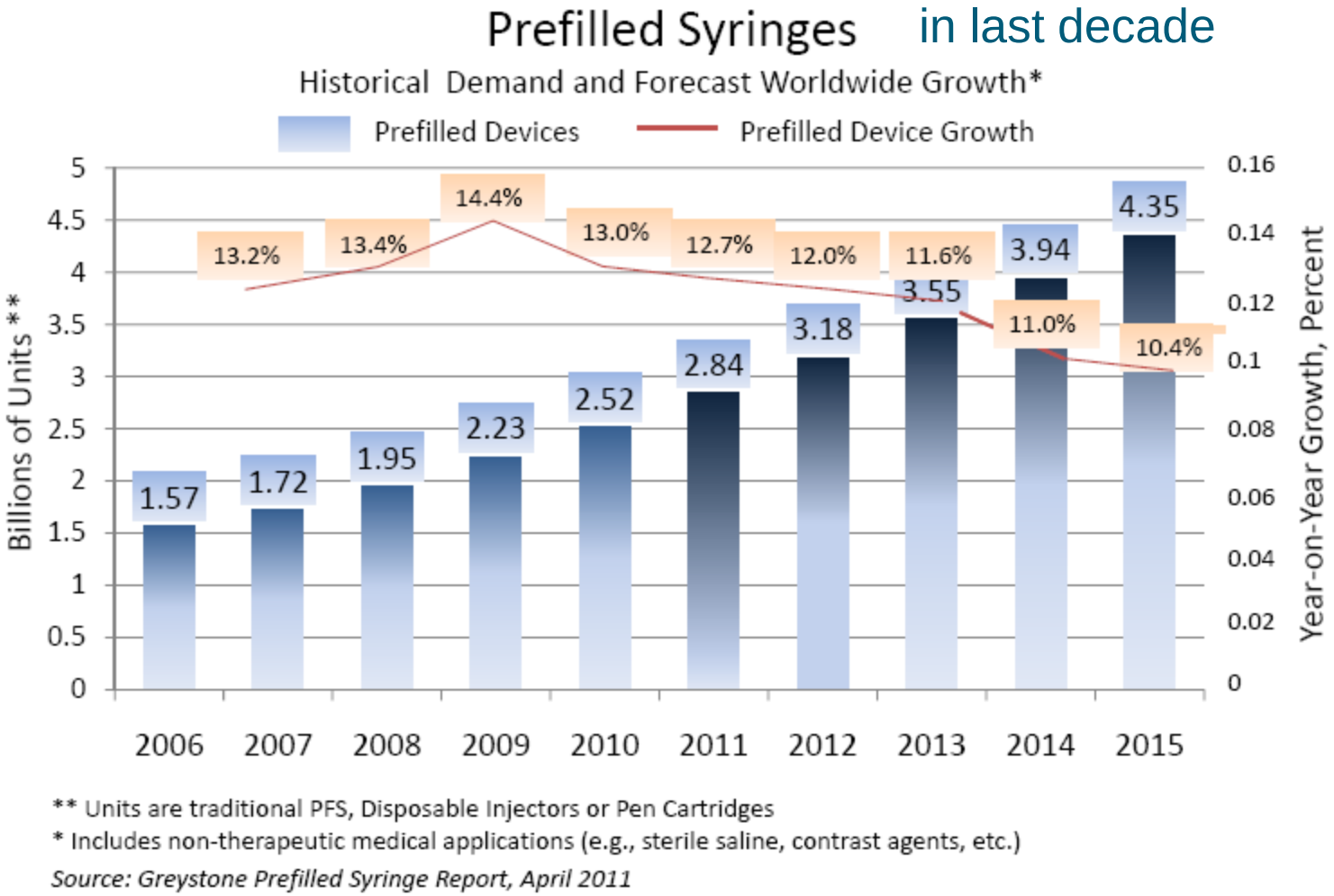
- Co-packaged combination products: Two or more separate products packaged together in a single package or as a unit and comprised of drug + device products, device + biological products, or biological + drug products; examples: drug + syringe + needle
- Cross-labeled combination products: A drug, device or biological product packaged separately that according to its proposed labeling is intended for use only with an approved individually specified drug, device or biological product; examples: photosensitizing drug x activating laser light source.

Market Trends

- Prefilled syringes and injection devices are gaining strong acceptance as delivery systems for injectable drugs.
- The main use of the delivery system is for treatment of chronic conditions requiring patients to self-administer medication.
- Interest in combination products is high due to opportunities they offer to enhance product safety and efficacy.

Prefilled syringe & injection devices market growth

Double-digit growth in last decade



** Units are traditional PFS, Disposable Injectors or Pen Cartridges

* Includes non-therapeutic medical applications (e.g., sterile saline, contrast agents, etc.)

Source: Greystone Prefilled Syringe Report, April 2011

Market Trends

- The combination products provide:
  - Ease of use
  - Reduced drug waste
  - Patient centric design
  - Customization
  - Market differentiation
- The global Prefilled syringe market is likely to achieve sales of USD 6.9 BN by 2018, growing at a compounded annual growth rate of 13.8% from 2012 to 2018*.

* Pre-filled Syringe Market, 2013-2023, Roots Analysis, business research & consulting.

Prefilled Syringe & Needle Safety Device (OSHA regulation)

Amgen: Enbrel auto injector

http://www.enbrel.com

Schering Plough/Merck: Dual chamber injector

West SmartDose® Electronic Patch Injector

- Large volume sub-q
- High viscosity
- Cartridge based

FDA Combination Products Regulation

- FDA ‘s office of combination products is an organizational component in the office of the commissioner; its role is to facilitate and coordinate consistent FDA regulation of combination products
- A combination product can be formed in three ways, through integration, co-packaging and labeling
- FDA can apply whatever regulatory resources it deems necessary to assure the safety and effectiveness of a combination product; this produces developmental and regulatory complexity

Jurisdiction of Combination products

- Single entity Combination product:
  - Drug (or biologic): Primary Mode of Action
  - CDER (or CBER): Primary Jurisdiction
  - CDRH: Consultation
- Co-packaged or Kit Combination product:
  - Drug (or biologic): Primary Mode of Action
  - CDER (or CBER): Primary Jurisdiction
    - Device may already be regulated by CDRH as a general use device (needs specific use labeling)
  - CDRH: Consultation

Quality Regulations for Combination Products

- Quality Regulations:
  - Drug & Biologic cGMP
    - 21CFR 210, 211
    - 21CFR 600 through 680
  - Quality system Regulation (QSR, Device cGMP)
    - 21CFR820
  - CGMP Requirements for Combination Products
    - 21CFR4
- Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Requirements for Combination Products (2015)

CGMP for Combination Products

- For a combination with drug and device constituent parts, must be compliant with **both CGMP and QSR**
- A drug CGMP Quality System based **Streamlining Approach** 21CFR4.4(b)(1)
  - 21CFR 820.20 Management responsibility
  - **21CFR 820.30 Design Control**
  - 21CFR 820.50 Purchasing Control
  - 21CFR 820.100 Corrective and preventive action
  - 21CFR 820.170 Installation
  - 21CFR 820.200 Servicing

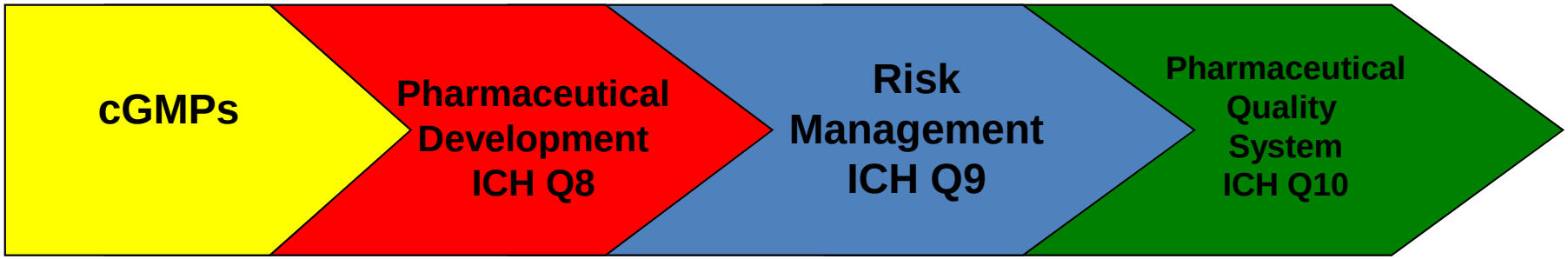
CGMP for Combination Products

- A QS regulation based **Streamlining Approach** 21CFR4.4(b)(2)
  - 21CFR211.84 Testing and approval or rejection of components, drug product containers and closures
  - 21CFR211.103 Calculation of yield
  - 21CFR211.137 Expiration dating
  - 21CFR211.165 Testing and release for distribution
  - 21CFR211.166 Stability testing
  - 21CFR211.167 Special testing requirements
  - 21CFR211.170 Reserve samples

Convergence in Regulatory Approach

Medical Devices (delivery device)

Drugs/ Biologics



Device Development – follow Design Control Process

Stage 1: Initiation	Stage 2: Planning	Stage 3: Development	Stage 4: Production	Stage 5: Commercialization
Market Assessment	Create Device Team	Create /evaluate Prototypes	Transfer Design	Launch Product
Assess Device value	Initiate Design History File	Design Review & Risk Analysis	Commission Facility	Manage Supply Chain
Technical Assessment	Define Design Inputs	Design Verification	Design & Process Validation	Conduct Post-Market Surveillance
Propose Device Attributes	Initiate partner/ CMO selection	Create Device Master Record	Complete Device Master Record	Manage CAPA & Complaints
Assess Regulatory Landscape	Conduct CMO Risk Assessments	Finalize Quality & Supply Agreements	Submit Regulatory Package	Identify Process Improvements
Develop Marketing Required Document	Create Device Development Plan	Human factors Usability study	Draft Complaints & CAPA Plan	Final Review
Review Process	Review Process	Review Process	Review Process	

FDA Regulations Relevant to Human Factors

- Quality System regulation: 21 CFR 820.30,

Design Controls – need for human factors is implied:

- **Design input** – includes "**needs of the user and patient**"
- **Design verification** – performance criteria met
- **Design validation** – "… devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis…." [incl. **use-related risks**]

*Molly Follette Story, PhD FDA /CDRH / ODE, RAPS Webinar June 7, 2012

Primary container compatibility issues

- J & J Eprex: leachables from uncoated syringe plungers
- Silicone oil causing protein aggregation
- Uneven coated silicone oil causing incomplete injection
- Leachable substances from staked needle causing drug degradation
- Sterility issue due to seal integrity problem

Thanks for your attention

- Dr. Anthony Andre will discuss Human factors and usability
- Dr. Wei Liu will discuss Primary container closure compatibility issue