Combination Products

Types and Handling of Product Complaints

John K Towns, PhD
Senior Research Fellow
Eli Lilly and Company
FDA/PQRI
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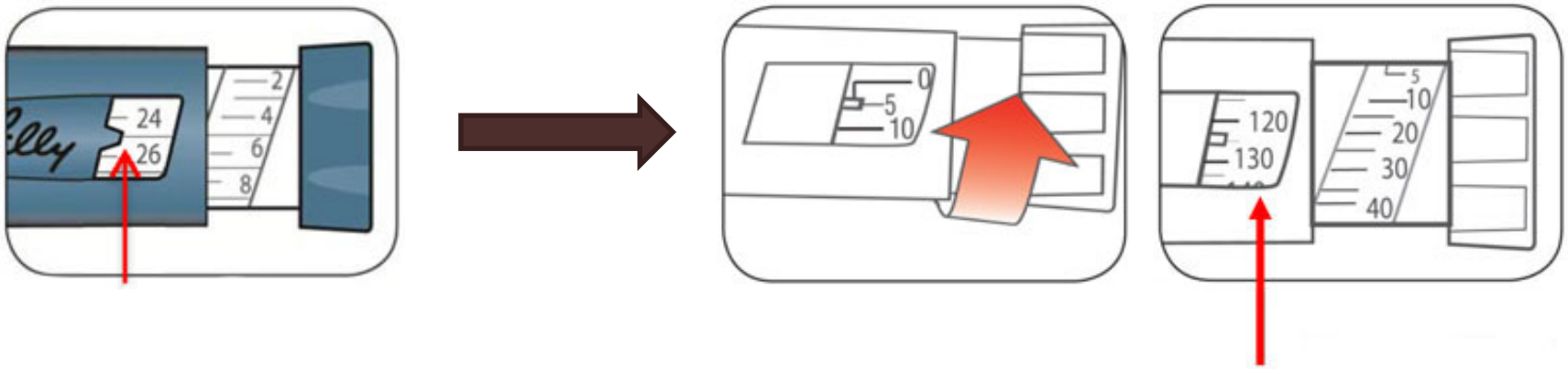
Combination Product
Reasons for Post Approval Changes

- Compliance Driven
  - Animal sourced material change
  - recombinant enzymes
- Supply Driven
  - Chromatography resins
  - Plunger composition
- Capacity Driven
  - Additional duplicate equipment or column scale-up
  - Device assembly automation
  - Additional manufacturing sites
- Patient Driven
  - Reformulation to address pain on injection
  - Clarify use tasks / Ease of use

Device Component Change
Human Factors Considerations

Example: Clarity of Units Dialed for Dose
Dial Markings Seen Through Dose Window
Insulin Pen Injector



Graphics for the Instructions for Use

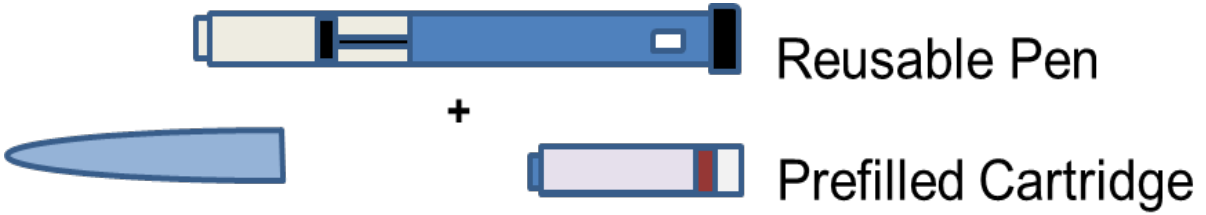
Agenda

- Combination Products and Comparison Products
  - Medical Devices
  - Drug Products
- Product Complaints – What Are They?
- Data Collection
  - Avenues for Receiving Complaints
  - Investigation Process
- Types of Combination Product Complaints
- Complaints and Social Media

Combination Product Examples

Single Entity Drug and Device
(e.g. semi-finished prefilled syringe within autoinjector)
Combination Products - 21 CFR 3.2(e)(1)

Separately Packaged Device and Drug
(e.g. reusable pen with replaceable prefilled cartridge)
Combination Products - 21 CFR 3.2.(e)(2)



vs. Drug Product 210.3(4)

Product Complaint

Complaint means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. 820.3(b)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. 312.32(a)

- *Life-threatening adverse event* or *life-threatening suspected adverse reaction.*
- *Serious adverse event* or *serious suspected adverse reaction.*
- *Suspected adverse reaction*.
- *Unexpected adverse event* or *unexpected suspected adverse reaction.*

[An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, combination product, or medical device, whether or not considered related to the product.]

U.S. FOOD & DRUG ADMINISTRATION

September 5, 2017

WARNING LETTER

Ref: CMS Case: 525881

2. Your firm failed to establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product (21 CFR 211.198(a))

For example, [date] you received a customer complaint for [CP] that failed to activate. You opened an investigation on [date], and confirmed that the product failed to activate. During your investigation, you disassembled the [CP] for this complaint sample and determined the root cause was a deformed [ ] component of the auto-injector. This was the same type of manufacturing defect in the [ ] component that you confirmed in [date]. … you had not examined all of your reserve samples to determine the extent of the defect within the same lot of finished products, nor did you expand your investigation to other lots. You did not determine whether the defective component identified in this complaint sample might have been linked to the lots of components you rejected in [date], even though your component supplier was still investigating the matter and you had released multiple lots of finished product to the market that had been manufactured using the same potentially defective component. You closed your investigation and determined that "no market action would be taken."

Difference between Combination Product and Device Investigations

Combination Product	Device
Drug and device constituent parts available for investigations	Typical only device available for investigation
Large number of retain samples available due to drug GMP requirements	Limited number of retain samples, not a regulatory requirement
Parallel assembly sites and drug manufacturing sites – multiple populations/permutations	Typical single manufacturing site, potentially parallel drug manufacturing sites
Limited performance testing possible to characterize device	Device performance characterized through testing during investigation
Post-marketing safety reporting enforcement delayed to July 31, 2019	Regulatory reporting follows device rules • MDR Reporting
Limited number of defect opportunities; defined by expiry date. Typically significantly lower complain rates than reusable devices	Large number of defect opportunities during life cycle; multiple interactions; life cycle not controlled through specified use life, but not always adhered to by patients.

Typical Top Complaint Categories - Autoinjector

- Injection incomplete
- Device not working
- Dose confirmation
- Device activated with base cap attached
- Device activated before placement on skin
- Lack of drug effect
- Needle bent

Complaint Process Steps

- Receive complaint. Data collection and documentation
- Enter complaint into global product complaint database
- Perform initial assessment. Determine level. Notify management if necessary
- Determine Need for Investigation→ Document rationale for no investigation
- Three documented attempts for sample return by Day X
- Forward complaint to appropriate investigating site
- Reassess complaint level. Notify management, if necessary
- Perform investigation and record results
- Approve investigation
- Assign complaint back to originating site
- Reply to complainant as appropriate
- Close complaint within Day X of notification

Complaint Process Overview
Streamlined Approach

Combination of centralized/decentralized approach for complaint infrastructure:

- Intake and customer interaction at the local affiliate level.
- Use of central IT-system mandatory.
- Initial triage and decision on investigation path at regional centers.
- Management of complaint triage procedures (product specific) and technical documents centrally managed.
- If detailed investigation required, triage centers forward complaint (with or without sample) to central device complaint unit, which decided on further path of investigation.
- All investigations for newly launched products (approx. during the first 1 – 2 years) are conducted at central unit.
- Investigations for mature products can be completed at regional centers for complaints that have been well characterized and have been documented in formally approved technical documents, following globally standardized and harmonized product specific procedures.

Complaint Process Overview (continued)

Different risk-based approaches to investigating complaints and leveling.

- Total time for investigation from original notification date to complaint closure is X days. Marketing affiliates need to make 3 attempts within X days to obtain sample, if needed.
- Using a risk based analysis, product complaints are triaged into 3 levels. These levels help to determine the priority and depth of the investigation.
- Investigations:
  - If root cause is known and documented in a technical report, complaint can be closed without a detailed investigation, using the rationale from the technical document.
  - If prior investigations have been performed for the same issue, an abbreviated investigation is possible, referencing prior investigation(s).
  - For new or unclear issues, a detailed investigation must be performed. Content of the detailed investigation is defined globally for all such investigations.

Complaint Volume

- Unique situation:
  - Device/combination products tend to have higher complaint rates than drug products
  - All devices:

[High opportunity to observe defects] X [High detectability of defects]

= Higher Complaint Rates

Example with Reusable Devices:

- Rate calculations difficult due to lifecycle/multi-use; classic rate calculations (number of units sold/number of complaints) can yield higher results when compared to drug or single use products
  - e.g. 3 year life cycle x 2 injections/day = 2190 Opportunities for product complaint for one device

Complaint Volume

- Key mitigations
  - Product design optimization
    - Implement learning into next generation of platform devices
    - Changes to current marketed combination products
      - Need to be cognizant of unintended consequence of patient familiarization
      - Might result in more complaints/use errors than trying to solve
  - Patient training: drive focus & provide tools
  - Right-size complaint handling process capability

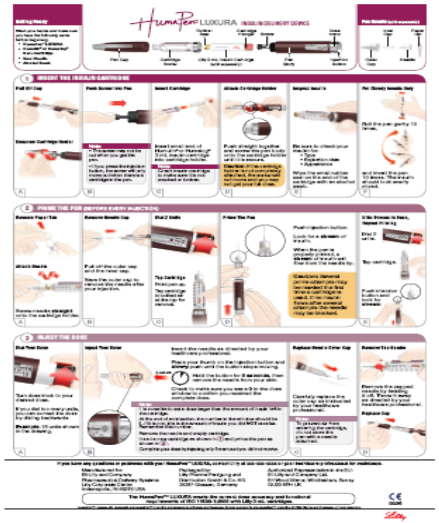
Complaint Volume

Reality:

- Despite strong efforts to reduce rates, absolute device /combination product complaint numbers tend to increase as products grow and new products are introduced, despite low complaint rates on par with industry.
- Need to focus on user experience and use related issues through “listening to patients”.
- New product launches increasingly utilize patient support programs, which are a great opportunity to further educate and train patients; however, any identified use issue through our active outreach must be captured as product complaint due to regulatory requirements, thus increasing overall complaint numbers and rates.

Patient Education

- Regional Level
  - Call Center
    - Core Documentation
    - (FAQ's, Troubleshooting Guides)
    - Agent Troubleshooting and Caller Education Processes
    - Marketing Materials
    - Doctor and Educator Educational Materials and Programs
    - Pharmacy Educational Materials
    - Patient Newsletter
  - Launch / Sales Training
    - Launch Training CD's
    - On-site training using technical staff
- User Level
  - Strong Human Factors program
  - Improved User Manuals



Future Consideration - Social Media

Follow

Mandy K. Smith

@realMandySmith

I can’t get the %$#@ cap off my drug this morning to take my Hubrelicty. These shots already hurt like crazy and now I am fighting with the pen! I hate Mondays!

RETWEETS	LIKES
53	**17**

06:25AM – 25 Mar 2019

Challenges in Mining Social Media

- Consumers do not normally use technical terms found in medical lexicons. Instead, they use creative phrases, descriptive symptom explanations, and idiomatic expressions. For example the phrase "*messed up my sleeping patterns*" was used to report "*sleep disturbances.*"
- Even when correctly identified, matched terms are not necessarily adverse effects. Terms used to describe ADRs can also be used for indications (reason to use the drug; e.g., "infection"), beneficial effects, or other mention types.
- User postings are informal, and deviate from grammatical rules. Include misspellings, abbreviations, and phrase construction irregularities that make extraction more difficult (compared to news or biomedical literature).

Pharmacovigilance from social media: mining adverse drug reaction mentions using sequence labeling with word embedding cluster features
Azadeh Nikfarjam Abeed Sarker Karen O'Connor Rachel Ginn Graciela Gonzalez
Journal of the American Medical Informatics Association, Volume 22, Issue 3, 1 May 2015, Pages 671–681, https://doi.org/10.1093/jamia/ocu041

Summary

- Combination product complaints differ from those for strictly drug or device
- Combination product complaint investigations require a thorough and expedient process
- Complaint volume trends are unique due to initial introduction of device platform, frequency of use and changes to user interface.
  - Changes in form likely will lead to short spike in product complaints to call center as change is perceived as being counterfeit product
- Multiple training and patient education programs to reduce product complaints for combination products
- Potential and ramifications of data mining of product complaints in social media