MedDRA | Medical Dictionary for Regulatory Activities

DIA Clinical Safety and Pharmacovigilance Community

Community Call

20 April 2017

Biological Product Concepts in MedDRA

Judy Harrison, MD

Chief Medical Officer, MedDRA MSSO

DIA DEVELOP INNOVATE ADVANCE

Topics

- Manufacturing quality terms
- Biological product exchange concepts

SOC *Product issues*

- 27th SOC implemented in MedDRA Version 19.0 on 1 March 2016
- Accommodates non-clinical/non-patient related concepts pertaining to products
- Important concepts as they may affect patient safety
- Goal of product quality terms in MedDRA is to support recording of product quality issues and any associated adverse events using a single terminology

Contents

- Includes terms relevant for issues with
  - Product quality
  - Devices
  - Manufacturing and quality systems
  - Supply and distribution
  - Counterfeit products

Contents and Structure

- SOC Product issues ⟵
  - HLGT Device issues
    - HLT Device computer issues
    - HLT Device electrical issues
    - HLT Device incompatibility issues
    - HLT Device information output issues
    - HLT Device issues NEC
    - HLT Device malfunction events NEC
    - HLT Device operational issues NEC
    - HLT Device physical property and chemical issues
  - HLGT Product quality, supply, distribution, manufacturing and quality system issues ⟵
    - HLT Counterfeit, falsified and substandard products ⟵
    - HLT Manufacturing facilities and equipment issues ⟵
    - HLT Manufacturing issues NEC ⟵
    - HLT Manufacturing laboratory controls issues ⟵
    - HLT Manufacturing materials issues ⟵
    - HLT Manufacturing production issues ⟵
    - HLT Product contamination and sterility issues
    - HLT Product distribution and storage issues ⟵
    - HLT Product label issues
    - HLT Product packaging issues
    - HLT Product physical issues
    - HLT Product quality issues NEC
    - HLT Product supply and availability issues ⟵

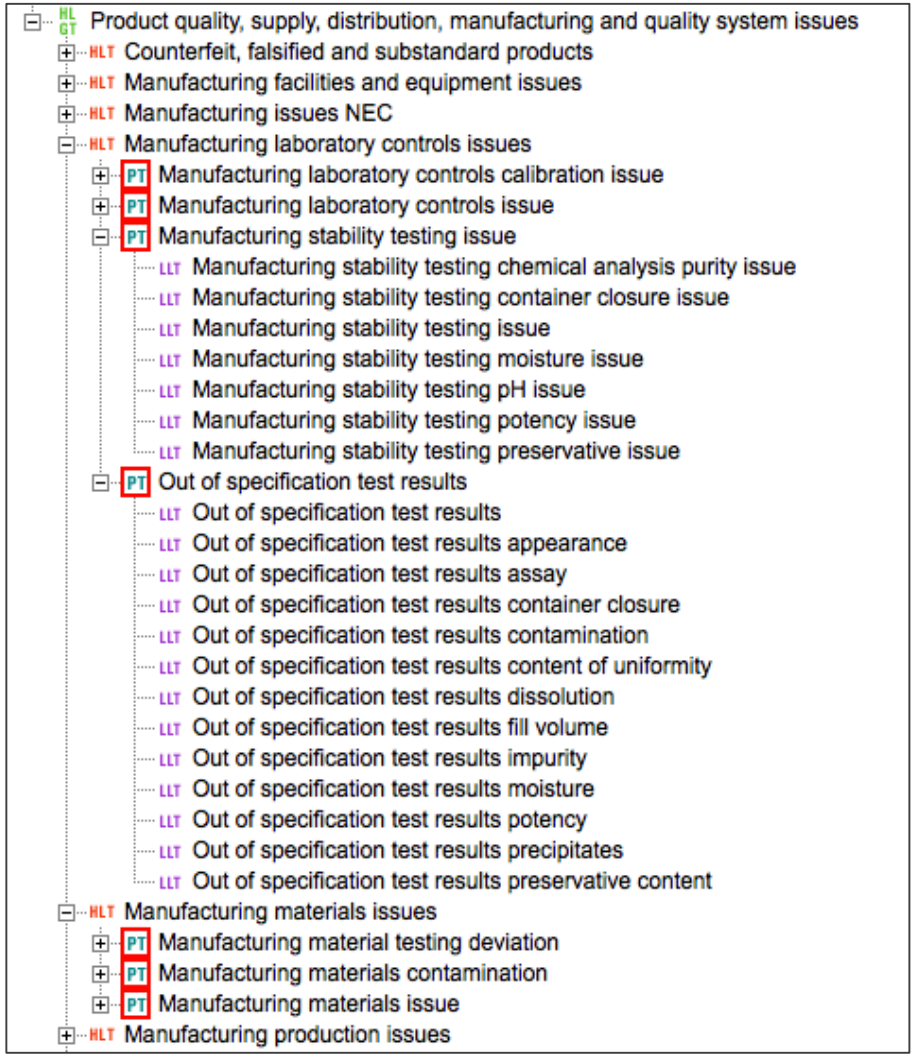
⟵ =New

Existing grouping terms (moved from General disorders SOC)

Intended Use

- Use of standardized terminology for product quality issues will facilitate data exchange
- Potential uses of product quality terms, including manufacturing and distribution issues
  - Reporting product defects to regulatory authorities
    - EMA's new Defective Product Report template is based on MedDRA
      - 5 HLTs, 29 PTs
  - Track and trend quality issues or deviations in organizations' internal databases
- Encourage use by quality departments in organizations

Manufacturing Terms



- Structure based on
  - FDA Guidance for Industry. Pharmaceutical Good Manufacturing Process Regulations September 2004
  - ICH Quality Guidelines including Q10 Pharmaceutical Quality System
- Covers drugs and biological products
- Current content mostly focused on small molecule drugs

Biological Product Manufacturing Terms

- Biological products are manufactured in living systems
- Complex process, highly susceptible to changes in environment
- Can affect safety and efficacy of product
- Need for manufacturing terms specific for biological products
- Users are encouraged to submit Change Requests to the MSSO
  - Online tool – WebCR
  - https://mssotools.com/webcr/default.aspx

Ask

Biological Product Exchange Concepts: Current Status

- Representation of substitution/exchange concepts in MedDRA is under discussion by ICH regulators
- Need for nomenclature and terms to be aligned
- Proposal developed for MedDRA
  - Concept description for product substitution
  - New terms for various exchange scenarios
- Presented at EudraVigilance Expert Working Group meeting in February 2017
- Additional feedback obtained from EU industry groups
- CSP Community feedback on the proposal is welcome

Background

- Danish regulator identified need for MedDRA terms to capture exchanges of biological products
  - Facilitate pharmacovigilance
  - Biological reference product and biosimilar
  - Similar to existing brand/generic substitution terms
- Feedback obtained on relevant concepts
  - EU Member States (Request for Non-Urgent Information)
  - ICH M1 Points to Consider Working Group
  - EMA, FDA, MHLW/PMDA

Biosimilar Definitions

Definitions are very similar

EMA	FDA
A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established. Guideline on similar biological medicinal products. 23 October 2014. CHMP/437/04 Rev 1.	A biological product submitted in a 351(k) application that has been shown to be highly similar to the reference product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product Nonproprietary Naming of Biological Products. Guidance for Industry. January 2017 CDER/CBER

Interchangeability

- Biosimilarity is not the same as interchangeability
- Differences in who is allowed to authorize interchange (prescriber vs. pharmacy level)

EMA	FDA
Evaluation of biosimilar medicines for authorisation purposes by the EMA does not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Substitution policies are within the remit of the EU member states.	To meet the additional standard of interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient
The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.	Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider

Substitution

- Propose to use general term “ Product substitution” at PT level in MedDRA
  - Types of products as LLTs
    - Brand/generic (small molecules)
    - Biological reference product/biosimilar
- Commonly used term
- “Product interchange” may be confused with “interchangeability”
- Coders may not know details of product type
  - Two separate PTs for small molecules vs. biologics may cause confusion
- Propose a Concept Description to aid in accurate and consistent coding and retrieval

Product Substitution Concept Description

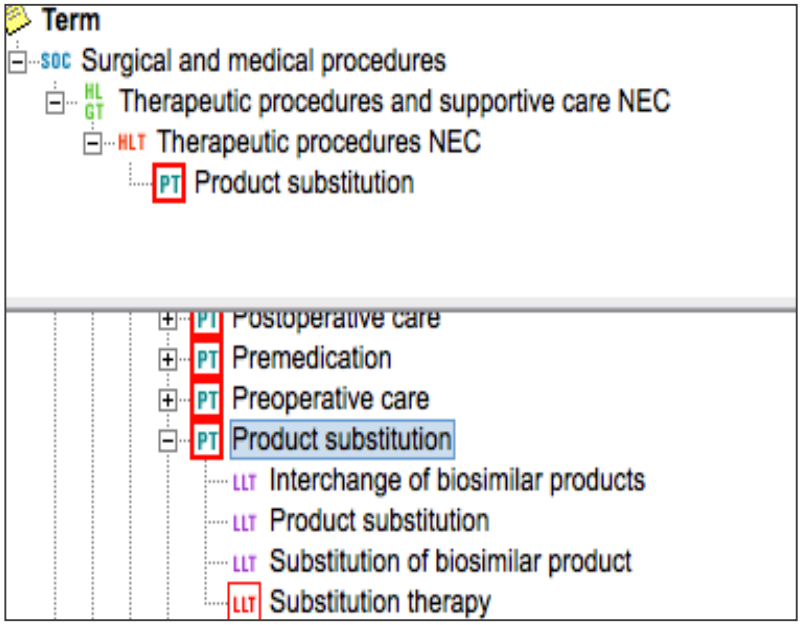
In the context of MedDRA, product substitution refers to 1), the act of exchanging therapeutically equivalent chemical substances/small molecules that contain the same active substance such as brand to generic or generic to generic substitution, and 2), exchanging biological products such as a biological reference product with a biosimilar product. Product substitution does not define whether products can be substituted or are considered interchangeable from a legal perspective, or the level at which the substitution or interchange can be authorized, e.g., by the prescriber or at the pharmacy level.

Proposed Changes in MedDRA

- Terms for the act of substitution
- Terms for substitution issues (reported as related to an ADR)
- Terms for substitution errors

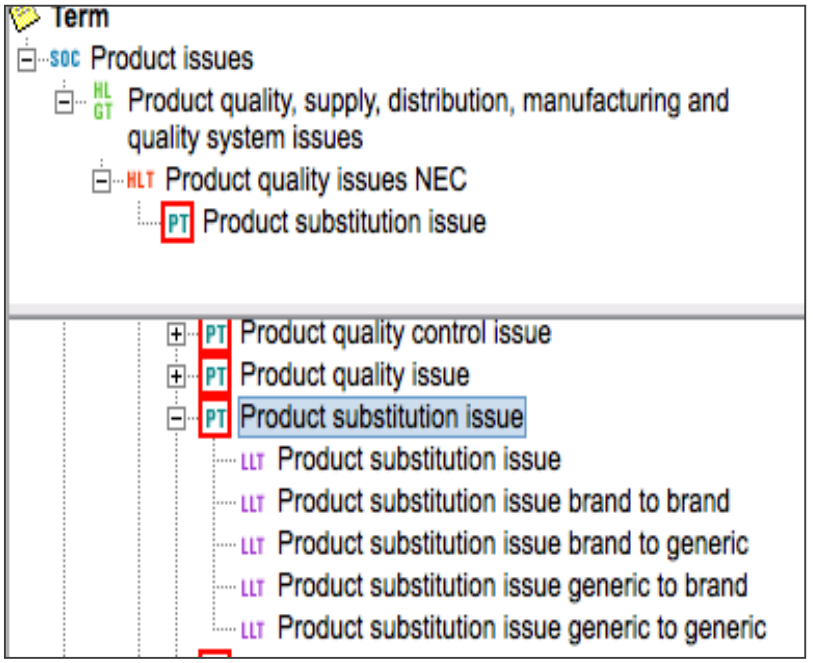
Product Substitution Terms

1. Make LLT *Interchange of biosimilar products* and LLT *Substitution of biosimilar product* non-current
2. Add LLTs
   - Product substitution brand to brand
   - Product substitution brand to generic
   - Product substitution generic to brand
   - Product substitution generic to generic
   - Biological product substitution biosimilar to biosimilar
   - Biological product substitution biosimilar to reference
   - Biological product substitution reference to biosimilar
   - Biological product substitution reference to reference



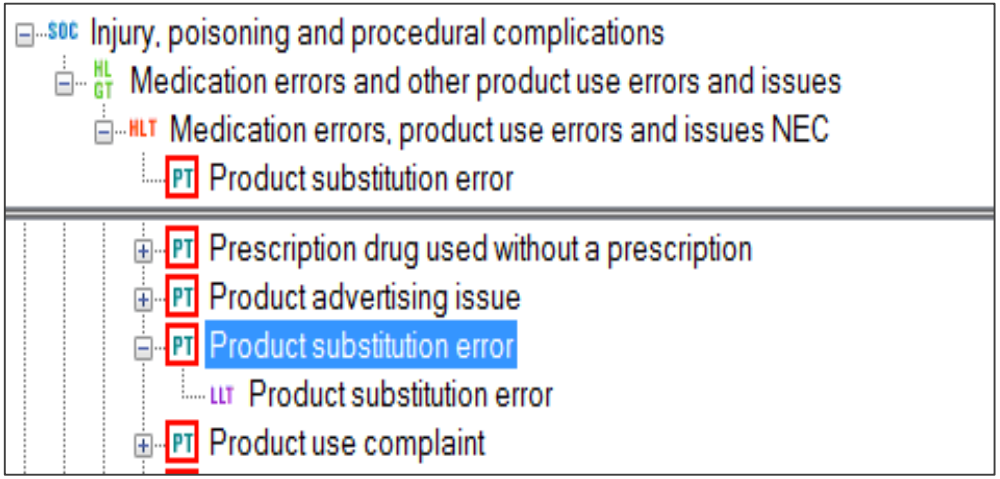
Product Substitution Issue Terms

1. Add LLTs
   - Biological product substitution issue biosimilar to biosimilar
   - Biological product substitution issue biosimilar to reference
   - Biological product substitution issue reference to biosimilar
   - Biological product substitution issue reference to reference



Product Substitution Error

1. Add LLT
   - Wrong product substituted



Preliminary Feedback

- Prefer to use “Exchange” or “Switch” instead of “Substitution”
- All proposed exchange scenarios are possible
  - Reference to reference, e.g., Neulasta (Pegfilgrastim) - Lonquex (Lipegfilgrastim), Recombinant Factor VIII products
  - Biosimilar to biosimilar, e.g., Tevagrastim (Teva) - Zarzio (Sandoz) –biosimilars of Neupogen (filgrastim)
- Other types of exchanges also to be considered
  - Originators (not all originators serve as reference products for biosimilars, e.g., somatotropin, human insulin)
  - Related biological products (same or closely related product but not authorized as biosimilar, e.g., interferon beta-1a, human immunoglobulin)

Discussion

- "Exchange" or "Switch" vs. "Substitution"
- What is best way to capture multiple permutations of exchange scenarios?
  - MedDRA
    - Could only capture general categories not specific drug names
    - Would coders know the specific regulatory status of a product?
  - Drug names
    - International Nonproprietary Name (INN), ATC codes, WHODrug, IDMP
    - Issue: Multiple products may share same INN
    - FDA's 2017 Guidance – 4 letter suffix for originator, related, biosimilar products
- How to capture inappropriate switches
  - E.g., switching reference to biosimilar of same class but using different reference product
  - Error vs. intentional

Ask