

# INTERNATIONAL SOCIETY of PHARMACOVIGILANCE (ISoP)

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CIOMS Lecture, 13 November 2018, 11:00 h - 12:00 h

Session Title: **"New use of clinical concepts in MedDRA:  
Can MedDRA labelling groupings help to standardise  
safety labelling?"**

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# MedDRA

## Medical Dictionary for Regulatory Activities

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# Generalities

- MedDRA : Medical Dictionary for Regulatory Activities
- Created by the International Council for Harmonisation (ICH) in the 90's
- Purpose : Harmonization and standardization of the medical wording :
  - Between the different drug's stages of life
  - Between the different countries and non governmental organizations
- Mandatory for health authorities of ICH's founder countries (EMA,MHRA, FDA...) and the pharmaceutical industries...



# Organization

MedDRA was designed hierarchically to allow large-scale data analysis with different degrees of specificity

Each event is organized by the following way :

Dedicated to  
data analysis

- One SOC “System Organ Classes”  
SOCs group HLGTs by etiologies, event site or objective
- One HLGT “High Level Group Terms”  
HLGT is a descriptor grouping together one or more HLTs related by anatomy, pathology, physiology, etiology or function
- One HLT “High Level Terms”  
Represents an inclusive category linking the PTs associated with it by anatomy, pathology, physiology, etiology or function.

Dedicated to  
codage

- One PT “Preferred Terms”  
PT is a unique medical concept relating to a symptom, a sign, a disease, a diagnosis, a therapeutic indication, an investigation, a surgical or medical intervention, a medical, social or family history characteristic
- And optionally by one “Lowest Level Terms”  
= Synonym of different PT. It can include the whole name or its abbreviation and a direct or inverted word order

(For example , PT = acquired immunodeficiency syndrome -> LLT = AIDS, the acronym)

# Organization

Examples :

LLT	Barlow's syndrom	Hand-Foot skin reaction
PT	Mitral valve prolapse	Palmar-plantar erythrodysesthesia syndrome
HLT	Mitral valvular disorder	Dermatitis ascribed to specific agent
HLGT	Cardiac valve disorder	Epidermal and dermal conditions
SOC	Cardiac disorder	Skin and subcutaneous tissue disorders



# Advantages (1)

- Multilingual (English Chinese, Czech, Dutch, French, German, Hungarian, Italian, Japanese, Portuguese, and Spanish)
  - ➡ Facilitated translation of an ICSR from one country to another with a code assigned to each PT
  - ➡ Facilitating data flows between countries
- Transversal and continuous
  - ➡ During all the drug's lifetime : from clinical studies to pharmacovigilance
  - ➡ Facilitates the analysis of all data
- Multiaxial: a PT could be linked to more than one SOC, and SMQs could be made at different degrees of specificity

# Advantages (2)

- Easy to use : there is more than 70,000 LLTs grouped under 20,000 PTs
- Adapted to regulatory activities by coding the medical terms used for
  - ➡ The notification of AEs
  - ➡ The drafting of regulatory documents (SMPc)
  - ➡ The security (PBRER)
- Updated regularly (every 6 months)
- Restrictive for pharmaceutical industries : ICSR must be reported as 'Serious' when the PT belongs to the IME list

But, there are some limits...

# Limits

- No quantification of the severity of the effect nor hierarchisation of the seriousness of each effects within an ICSR  
Example : cutaneous eruption on face which is not serious but severe
- No distinction between an adverse effect and an event
  - ➡ Contribute to the bias when analyzing big data by PRR

# Limits<sub>(2)</sub>

- Risk of minimizing and concealing an event

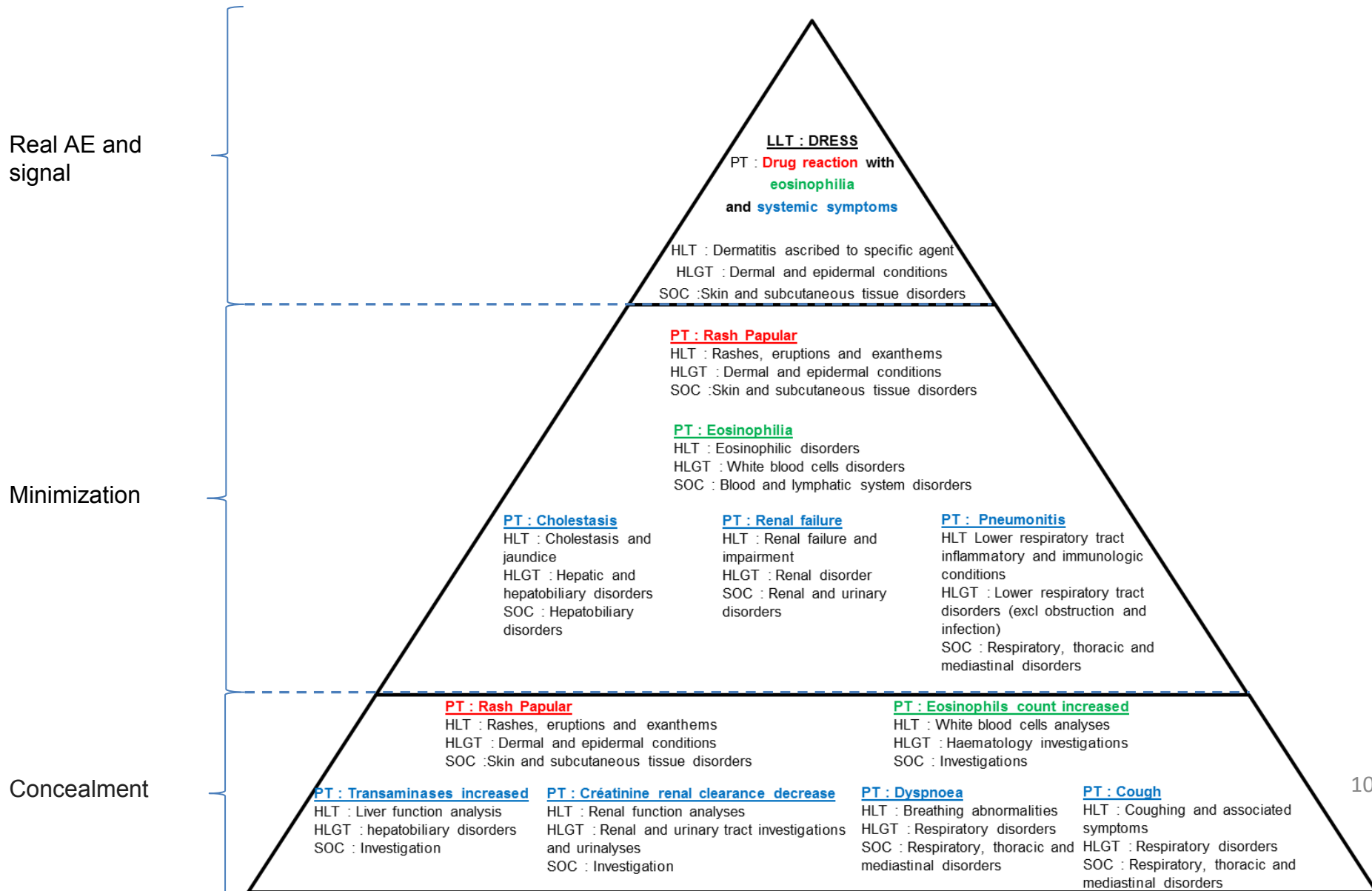
## ➡ Minimization

DRESS example (Drug reaction with eosinophilia and systemic symptoms). By reporting each of the AEs separately, there will not have the same weight in terms of signal compared to PT DRESS

## ➡ Concealment

PT Hypoglycemia refers to the metabolic and nutritional disorder, but  
PT Serum glucose decrease refers to SOC Investigation

# The ways of dissimulation



Thank you for your attention,



# **MedDRA Labeling Groupings (MLGs): A Harmonised Approach to Safety Communication**

CIOMS MLG Exploratory Team  
International Society of Pharmacovigilance 18<sup>th</sup> Annual Meeting  
Geneva  
13 November 2018

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# Outline



- **Problem statement from a CIOMS exploratory team**
  - Perspectives from regulatory guidances
- **A further explanation of MedDRA**
- **Reference Safety Information (RSI) as a communication tool**
  - The MedDRA hierarchy terms
  - New groupings of MedDRA terms
- **Preliminary roadmap to MedDRA Labeling Groupings (MLGs)**
  - Current landscape
  - Principles and considerations for harmonization of MLG development and voluntary application
- **Summary, next steps, Q&A**

# Problem Statement



- Clinicians and the healthcare community need clear, consistent, and understandable information in RSI for biopharmaceuticals
  - Need to distill safety evidence für use in RSI
  - Using existing regulatory guidance
  - Presenting some data is straightforward whereas certain other data may be more challenging
- When existing terminology, e.g., MedDRA, is not appropriate, little guidance is available on how to achieve the desired representations in RSI and outcomes in healthcare
  - Harmonized, consensus principles for grouping of terms and simplification of RSI are needed
  - Independent “one-off” approaches are emerging

# CIOMS MLG Exploratory Team



Organization	Representative
Bayer	Ilona Große-Michaelis
European Medicines Agency	Aniello Santoro
Food and Drug Administration (US)	Sonja Brajovic
Health Canada	Lynn Macdonald
Pfizer	William W. Gregory
Pharmalex	Judith K. Jones

# Current Guidance: US FDA



- “In general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided .... Such lists are not informative and tend to obscure the more clinically meaningful information.” (p 2)
  - Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, January 2006 (16 pp)
  - Requirements are in 21 CFR 201.57(c)(7)

# Current Guidance: European Commission



- “The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.” (p 2)
- “Consistent medical terminology should be used throughout the SmPC. For example, the use of MedDRA as described in the annex for section 4.8 should be applied though [sic] the SmPC, in particular for sections 4.3 and 4.4 and 4.8.” (p 3)
- Undesirable effects (Section 4.8), “It is important that the whole section is worded in concise and specific language ...” (p 15)
- “**Frequencies** of cited adverse reactions should be stated as accurately as possible.” (p 16)
  - European Commission Notice to Applicants (Rev 2): A guideline on Summary of Product Characteristics (SmPC), September 2009 (29 pp)

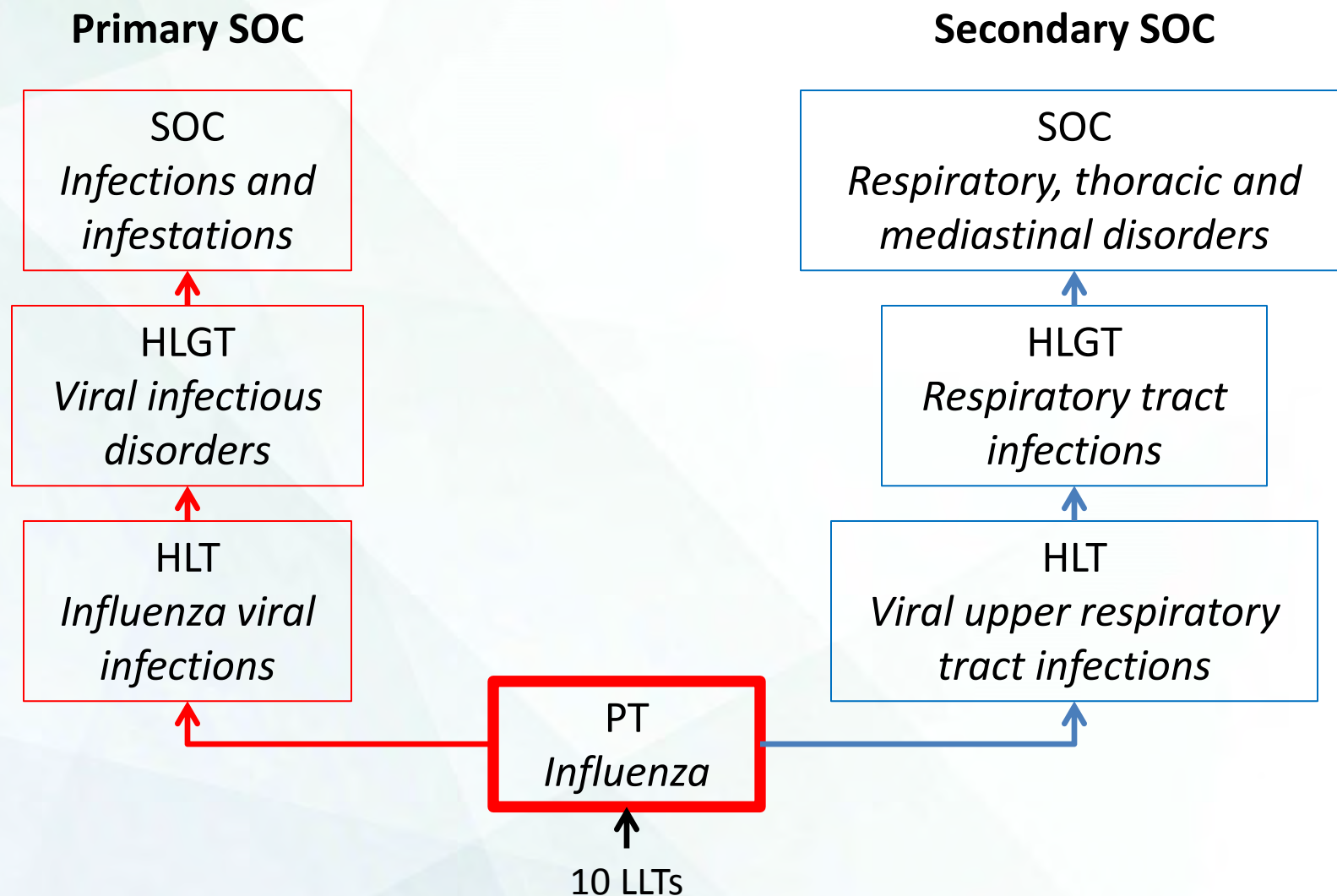
# Current Guidance: Health Canada



- “Adverse reactions that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) or disease pathophysiology in more than one body system (e.g., congestive heart failure: nocturnal dyspnoea, angina, pedal oedema) should be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect.” (p 22)
  - Health Canada Guidance Document: Product Monograph, June 2016

- PTs are the central focus of the terminology
  - high granularity
- Each PT is intended to represent an “unique medical concept”
  - LLTs are intended to be synonyms or lexical/spelling variants of the PTs
  - All higher levels of the hierarchy (HLTs, HLGs, and SOCs) are aggregates of PTs with various degrees of relationships to each other

# MedDRA Multi-axial Structure <sup>(1)</sup>



# MedDRA Multi-axial Structure (2)



- There are exceptions to multi-axiality
- Although most PTs can have “secondary allocations,” not all do
- PTs with allocations to these three SOC are NOT multi-axial:
  - SOC *Investigations*
  - SOC *Social circumstances*
  - SOC *Surgical and medical procedures*

# First RSI Option: The Existing MedDRA

- **Regulated adverse event data are coded with MedDRA**
  - Is a single PT appropriate? A grouping of PTs at a higher level may be suitable for direct representation of a clinically-meaningful concept in RSI
- **High Level Term (HLT) *Renal lithiasis* (10038478)**
  - Three PTs (v 21.1):
    - PT *Nephrocalcinosis* (10029146)
    - PT *Nephrolithiasis* (10029148)
    - PT *Stag horn calculus* (10041900)

# Semi-Straightforward Example for RSI



- Clinical trial data

Suspected adverse reaction	Frequency <sup>a</sup>
<i>Postural dizziness</i>	2%
<i>Exertional dizziness</i>	2%
<i>Unspecified dizziness</i>	2%

<sup>a</sup> Assume only one report of dizziness applies to each subject

- What RSI is meaningful for a clinician?

Suspected adverse reaction	Frequency <sup>a</sup>
<i>Dizziness</i>	6%

<sup>a</sup> Assume only one report of dizziness applies to each subject

# Another Semi-Straightforward Example



- Post-marketing safety data from spontaneous sources

Suspected adverse reaction	MedDRA PT	MedDRA SOC
<i>Wheezing</i>	Wheezing 10047924	Respiratory, thoracic and mediastinal disorders
<i>Rash</i>	Rash 10037844	Skin and subcutaneous tissue disorders
<i>Urticaria</i>	Urticaria 10046735	Skin and subcutaneous tissue disorders

What RSI is meaningful for a clinician and retains specificity?

Suspected adverse reaction in RSI	Frequency
<i>Hypersensitivity</i> <sup>a</sup>	Unknown

<sup>a</sup> Includes wheezing, rash, and urticaria



# **MedDRA Labeling Groupings (MLGs)**

**International Society of Pharmacovigilance  
18<sup>th</sup> Annual Meeting, Geneva**

Sonja Brajovic, MD  
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# FDA Required Drug Label

- **Defined by Code of Federal Regulations (21CFR201.57)**

“Prescription drug labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.”
- **FDA Guidances for industry on labeling**  
(<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm065010.htm>)
- **Labeling content is proposed by the manufacturer, reviewed by FDA, and negotiated into the FDA required drug label**

# FDA Guidance, Adverse Reaction Section of Labeling\*



Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect.

Similarly, adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction. For example, an allergic-type adverse event that has respiratory (wheezing) and dermatologic (rash, urticaria) manifestations should be classified as a single adverse reaction (e.g., hypersensitivity).

\*<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075057.pdf>

# EU: A guideline on Summary of Product Characteristics (SmPC)\*

Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect.

Similarly, reactions that represent a syndrome complex should ordinarily be grouped together under an appropriate heading to avoid obscuring the full range of respective symptoms.

\*[https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpec\\_guideline\\_rev2\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpec_guideline_rev2_en.pdf)

# Grouping highly similar ADRs in a label

**MedDRA® Labeling Groupings (MLGs):** aggregates of clinically highly similar MedDRA Preferred terms which signify a unique medical concept / adverse reaction for use in Reference Safety Information (RSI)

Regulatory guidance recommend grouping terms which represent a single adverse reaction

However, there are no agreed conventions or specific guidelines for appropriately grouping terms in the RSI in order to clearly and accurately represent a unique medical concept

# Highly Similar ADRs In A Label: Current Approaches



**No groupings applied, all PTs listed individually**  
highly similar PTs for the same adverse reaction are listed separately

- analyses of MedDRA PTs in isolation can lead to uninterpretable results
  - Cardiac failure; Cardiac failure, acute; Cardiac failure, chronic; Cardiac failure, congestive; Cardiopulmonary failure; Left ventricular failure; Ventricular failure; Acute pulmonary oedema, Pulmonary oedema
  - Hyperkalaemia; Blood potassium increased
- “For your own analyses, if you haven’t combined like terms, FDA cannot interpret your study reports, Integrated Summary of Safety (ISS), or Benefit-risk assessment (Section 2.5.6 of the Common Technical document, CTD)” – Dr. Ellis Unger, Director, Office of Drug Evaluation-I, CDER, US FDA

# Highly Similar ADRs In A Label: Current Approaches (2)

## Groupings developed and applied by a sponsor

- **label-specific groupings:** PT terms grouped per safety data for each specific product
- **label-independent groupings:** pre-defined PT groupings applicable to any product safety data; one PT belongs to a single MLG irrespective of the label

# MLG Examples From FDA Label X

Term includes cases reported within the clustered terms:

Leukopenia (*Leukopenia, White blood cell count decreased*)

Anemia (*Anaemia, Haemoglobin count decreased*)

Thrombocytopenia (*Platelet count decreased, Thrombocytopenia*)

Neutropenia (***Agranulocytosis**, Febrile neutropenia, Neutropenia, Neutrophil count decreased*)

# MLG Examples From FDA Label Y

Term includes cases reported within the clustered terms:

Bradycardia (*Bradycardia, Sinus bradycardia*)

Vision Disorder (*Diplopia, Photophobia, Photopsia, Reduced visual acuity, Blurred vision, Vitreous floaters, Visual impairment*)

Abdominal pain (*Abdominal discomfort, Abdominal pain, Lower abdominal pain, Upper abdominal pain, Abdominal tenderness*)

Esophagitis (*Esophagitis, Esophageal ulcer*)

Edema (*Edema, Peripheral edema, **Face edema**, Generalized edema, Local swelling, **Periorbital edema***)

Upper respiratory infection (*Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection*).

Dizziness (***Balance disorder**, Dizziness, Postural dizziness, **Presyncope***).

# MLG Examples From FDA Label Z

*Respiratory, thoracic and mediastinal disorders:*

**dyspnea** (includes *acute respiratory failure*, dyspnea, dyspnea exertional, *respiratory failure*, *respiratory distress*, *bronchospasm*, *bronchial hyperreactivity*, tachypnea, and *wheezing*)

*Vascular disorders:*

**hypotension** (includes *blood pressure decreased*, hypotension, *hypovolemic shock*, and *circulatory collapse*)

*Psychiatric disorders:*

**depression** (includes *depressed mood*, depression, *suicidal ideation*, and *completed suicide*)

# MLG Examples Across a Few Labels

	ADR in table	Included PT terms in a footnote
Drug B	Abdominal pain	abdominal pain, upper abdominal pain, lower abdominal pain, abdominal tenderness, gastrointestinal pain, abdominal discomfort
Drug C	Abdominal pain	abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
Drug D	Abdominal pain	abdominal pain, abdominal pain lower, abdominal pain upper, <b>abdominal rigidity</b> , abdominal tenderness, <b>acute abdomen</b> , esophageal pain
Drug E	Abdominal pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness
Drug A	Cardiac failure	Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, <b>Cardiomyopathy</b> , and Ejection fraction decreased
Drug A	Edema	Edema, Edema peripheral, Pitting edema, and Generalized edema
Drug E	Edema	<b>Face edema</b> , Generalized edema, Local swelling, Localized edema, Edema, Edema peripheral, <b>Periorbital edema</b>
Drug B	Edema	edema, peripheral edema, localized edema, <b>face edema</b>
Drug B	Rash	rash, macular rash, pruritic rash, generalized rash, papular rash, maculopapular rash

# Highly Similar ADRs In A Label: Current Approaches (3)

## Groupings developed and applied by a sponsor

- **label-specific groupings:** PT terms grouped per safety data for each specific product
- **label-independent groupings:** pre-defined PT groupings applicable to any product safety data; one PT belongs to a single MLG irrespective of the label

**Next presentation....**

## Example MLG Abdominal pain

### **PT inclusion (alphabetical order):**

- 1) PT Abdominal discomfort**
- 2) PT Abdominal pain**
- 3) PT Abdominal pain lower**
- 4) PT Abdominal pain upper**
- 5) PT Abdominal tenderness**
- 6) PT Gastrointestinal pain**

## Example MLG Abdominal pain

PT exclusion:

- 1) **PTs for abdominal pain forms of great severity,**  
e.g. PT Abdominal rebound tenderness, PT Abdominal rigidity
- 2) **PTs for colic terms,**  
e.g. PT Infantile colic, PT Biliary colic
- 3) **PT Flatulence with LLT Gas pain**
- 4) **PT Visceral pain**
- 5) **PTs represented in MLG Dyspepsia,**  
e.g. PT Epigastric discomfort, PT Dyspepsia
- 6) **PTs for oral, pharyngeal, oesophageal, rectal pain**
- 7) **PTs representing pain in specific abdominal organs,**  
e.g. PT Hepatic pain, PT Gallbladder pain
- 8) **PTs represented in MLG Pelvic pain,**  
e.g. PT Pelvic discomfort, PT Pelvic pain

## MLG creation

**Caveat:**

**Demonstration is based on  
one option used in one institution**

**Creation of an MLG example will be demonstrated**

**AIM:**

**transfer the medical concept into  
MedDRA language,**

**catch all relevant PTs  
(do not expect a 1:1 translation)**

## Stepwise procedure

- **Interdisciplinary approach/ builds on consensus**
- **Creation only if needed**
- **Product independent**
- **Voluntary usage**
- **Principles in a guidance paper available**
  - **e.g. important principles:**
    - one PT can be in one MLG only**  
**(frequency calculation)**
    - only PTs with identical (or very similar)**  
**degree of severity are grouped together**

## MLG Creation - Example

- **The following example for the unique medical concept “headache” illustrates usage of the MedDRA terminology and hierarchy and some of the associated limitations.**

- ❖ **Starts with  
Definition of medical condition:**

***Headache* is defined as “pain in the head” [1]. It is synonymously called cephalgia, cephalalgia or cephalodynia [1].**

**As “pain” is defined as a more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings [1], also head discomfort is included in this MLG.**

[1] Dorland's Illustrated Medical Dictionary for Healthcare Consumers, 32nd edition, 2012, Philadelphia, Saunders

- ❖ Followed by translation into MedDRA and identification of relevant PTs according to the MLG principles

**Search for relevant MedDRA PTs to identify inclusion (and exclusion) of PTs for headache**

**Caveat:**

**do not limit by hierarchical MedDRA structure**

Hits for this MedDRA search:  
approx. 25 different hits/ MedDRA PT terms for headache in different hierarchical structures (different HLTs, HLGTs, SOCs)

# MLG Creation

## ❖ Identification of relevant PTs according to the principles

No.	PT	HLT (p)	HLGT (p)	SOC
1	Drug withdrawal headache	Headaches NEC	Headaches	Nervous system disorders
2	Exertional headache	Headaches NEC	Headaches	Nervous system disorders
3	Head discomfort	Neurological signs and symptoms NEC	Neurological disorders NEC	Nervous system disorders
4	Headache	Headaches NEC	Headaches	Nervous system disorders
5	Medication overuse headache	Headaches NEC	Headaches	Nervous system disorders
...				

# MLG creation - outcome



PT inclusion (alphabetical order):

- 1) PT Drug withdrawal headache**
- 2) PT Exertional headache**
- 3) PT Headache**
- 4) PT Head discomfort**
- 5) PT Medication overuse headache**
- 6) PT New daily persistent headache**
- 7) PT Primary headache associated with sexual activity**
- 8) PT Sinus headache**
- 9) PT Tension headache**
- 10) PT Vascular headache**

# MLG creation - outcome



PT exclusion:

- 1) PTs representing migraine,**  
e.g., PT Ophthalmoplegic migraine, PTs under HLT Migraine headaches
- 2) PTs representing syndromes with the potential symptom of headache,**  
e.g., PTs Craniocervical syndrome, Eagle's syndrome, SUNCT syndrome
- 3) PTs representing diagnoses with the potential symptom of headache,**  
e.g., PTs Temporal arteritis, Paranasal sinus discomfort, Sinus pain
- 4) PTs representing headache with specific underlying causes or diseases, of different etiology,**  
e.g., PTs Cold-stimulus headache, Postictal headache, Post-traumatic headache, Post lumbar puncture syndrome, Procedural headache, Premenstrual headache, Primary cough headache, Cervicogenic headache
- 5) PTs representing different degree of severity,**  
e.g., PTs Thunderclap headache, PT Cluster headache

## MLG creation - Summary

- **Identify all possible PTs fitting to the medical concept, independently of MedDRA hierarchy (limitations due to different concepts)**
- **Define inclusion and exclusion criteria for PTs precisely according to the principles**
- **Create and use transparent documentation**

# Summary



- **Reference Safety Information (RSI) for biopharmaceutical products encompasses tools to communicate clinically-important medical concepts, particularly to healthcare providers**
- **The approach to developing and simplifying RSI is not harmonized, despite existing regulatory guidance**
- **MedDRA Labeling Groupings (MLGs) may facilitate simplification of RSI by grouping similar MedDRA terms to communicate meaningful and important medical concepts when not appropriately supported by the established MedDRA hierarchy**
  - **MLGs would also facilitate calculation of frequencies of suspected ADRs from clinical trials and for comparison of frequencies between products (and, perhaps, across indications, populations, or posology).**
- **Feasibility of consensus principles is being assessed by CIOMS**

# CIOMS Proposed Approach

## Phase I

It is proposed that globally harmonized principles, points to consider, and pragmatic recommendations for development of MedDRA Labeling Groupings be developed by a Council for International Organizations of Medical Sciences (CIOMS) working group. The desired outcome is an international approach which would be available for voluntary consideration.

## **CIOMS Proposed Approach (2)**

**Depending on outcome of Phase I, Phase II:**

MLG design and development with examples

MLG sustainability

- **Q&A and panel discussion**