THE WHAT AND WHY OF MedDRA

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MedDRA

Medical Dictionary for Regulatory Activities

- The drug and biologic Industry uses the terminology in its clinical trial data and safety databases for collection of adverse events.

- Clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry through the entire regulatory process, from pre-marketing to post-marketing; and for data entry, retrieval, evaluation and presentation.

Safety Reporting Regulations

- Postmarketing drugs
- Generic drugs
- Therapeutic biologics
- "Grandfather" drugs *(pre 1938)*
- IND Safety reports, NDA/BLA report

FDA Guidance for Industry Premarketing Risk Assessment

- *"Because individual investigators may use different terms to describe a particular adverse event, FDA recommends that sponsors ensure that each investigator's verbatim terms are coded to standardized, preferred terms specified in a coding convention or dictionary. Proper coding allows similar events that were reported using different verbatim language to be appropriately grouped. Consistent and accurate coding of adverse events allows large amounts of data regarding these events to be analyzed and summarized and maximizes the likelihood that safety signals will be detected…*

- *In general, FDA suggests that sponsors use one coding convention or dictionary (e.g.,* ***MedDRA****) throughout a clinical program…"*

FDA Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

- *"FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS)…, using thorough database search strategies based on updated coding terminology (e.g., **the Medical Dictionary for Regulatory Activities (MedDRA**). When available, FDA recommends that standardized case definitions …"*

MedDRA

If current trends are followed, this may also be mandated for the tobacco industry.

Proactively: Good terminology to compile and analyze health data.

Is medically validated and allows consistent, standardized application for capture of both health effects AND Product quality issues.

Implementation with internal coding guidelines will leave little room for “soft coding”.

Scope: MedDRA Covers...

- Signs and symptoms
- Disease
- Diagnosis
- Therapeutic indications
- Name and qualitative results of investigations and lab results
- Medical, social, family history, and risk factors
- Surgical and Medical procedures

Applications of MedDRA

- To report ADRs/AEs, to capture and present product indications, investigational results and patient history

- To aggregate reported terms in **medically meaningful** groupings for reviewing, analyzing, summarizing and communicating safety data

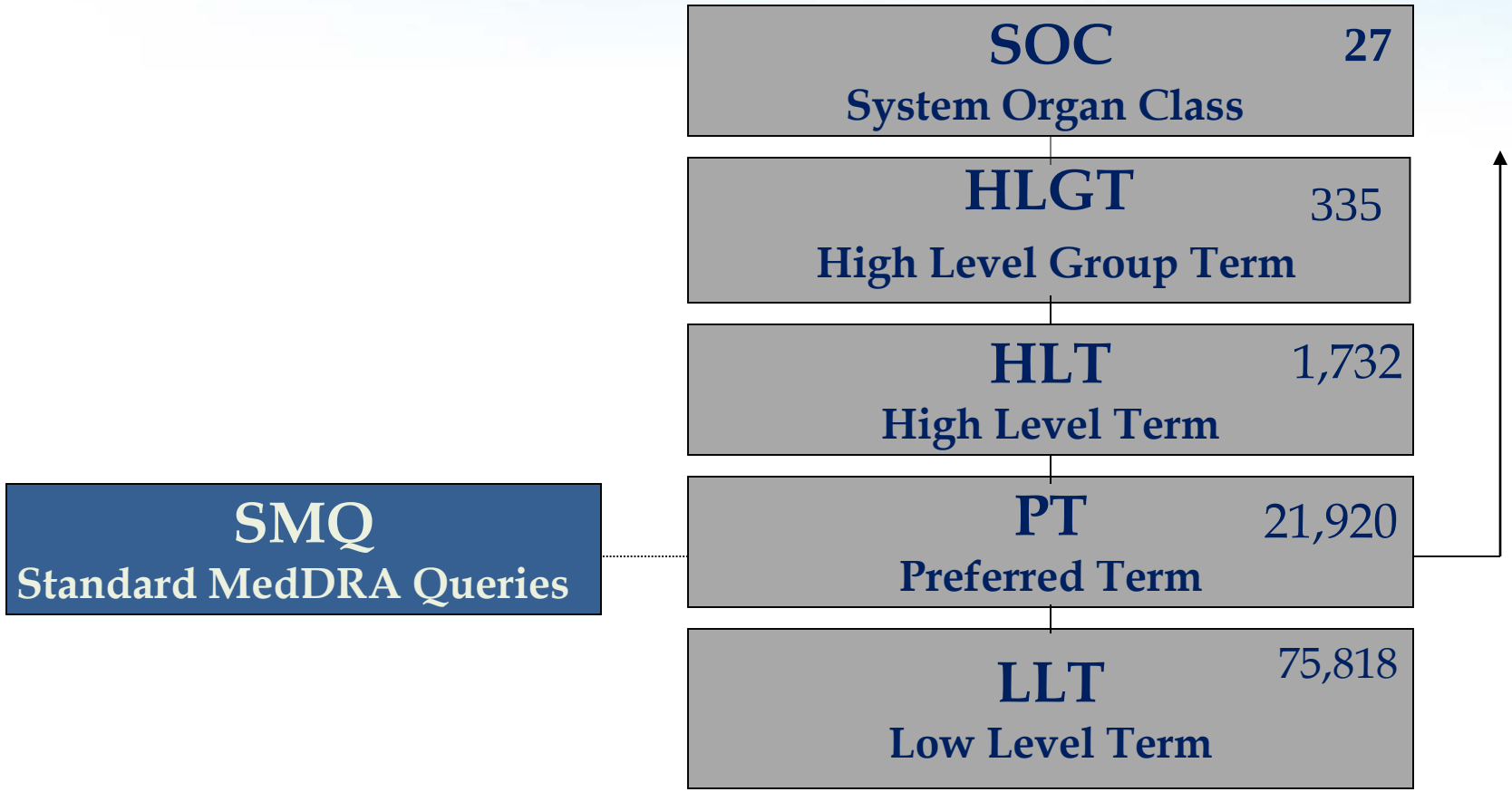
- To enable consistent retrieval of specific cases or medical conditions from a database and to identify their frequencies

- To facilitate electronic data exchange

MedDRA: Basic Structure

- Standardized terminology:
  - 5-level Hierarchy
  - Multiaxiality
  - Granularity
- Retrieval groupings:
  - Standardized MedDRA Queries (SMQ)

Structure Overview MedDRA (version 19.0)



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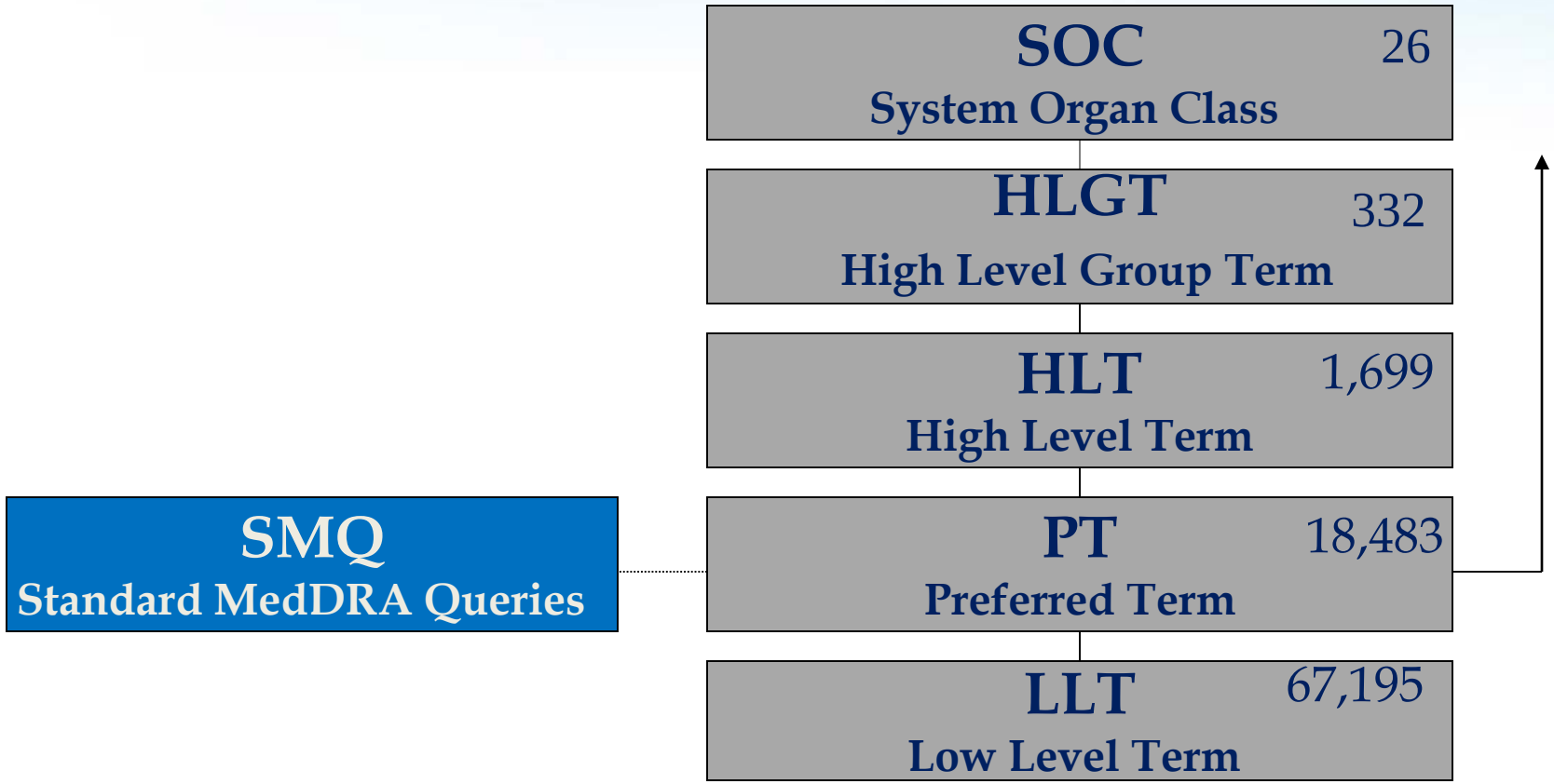
Structure Overview MedDRA (version 11.1)



System Organ Class (SOC)

- Top level of hierarchy, the broadest concept of standardized terminology, used for data grouping

- SOCs may reflect:
  - anatomical functional body systems
  - etiology (Infections and infestations SOC),
  - purpose (Surgical and medical procedures SOC)

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27 System Organ Classes (SOCs)

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital and familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepato-biliary disorders
- Infections and infestations
- Immune system disorders
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- **Product issues**
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Musculoskeletal and connective tissue disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

High Level Group Term (HLGT)

- HLGTs are broad levels of terminology directly under a SOC and composed of HLTs
- HLGTs group related HLTs by anatomy, pathology, physiology, etiology or function
- HLGTs are used for data retrieval, presentation and analysis

High Level Term (HLT)

- HLT is directly under the HLGT and above the PT
- An HLT groups related PTs by anatomy, pathology, physiology, etiology or function

  The HLT level represents medical entities which are detailed by the distinct, unique concepts expressed by the PTs
- HLTs are used for data retrieval, presentation and analysis

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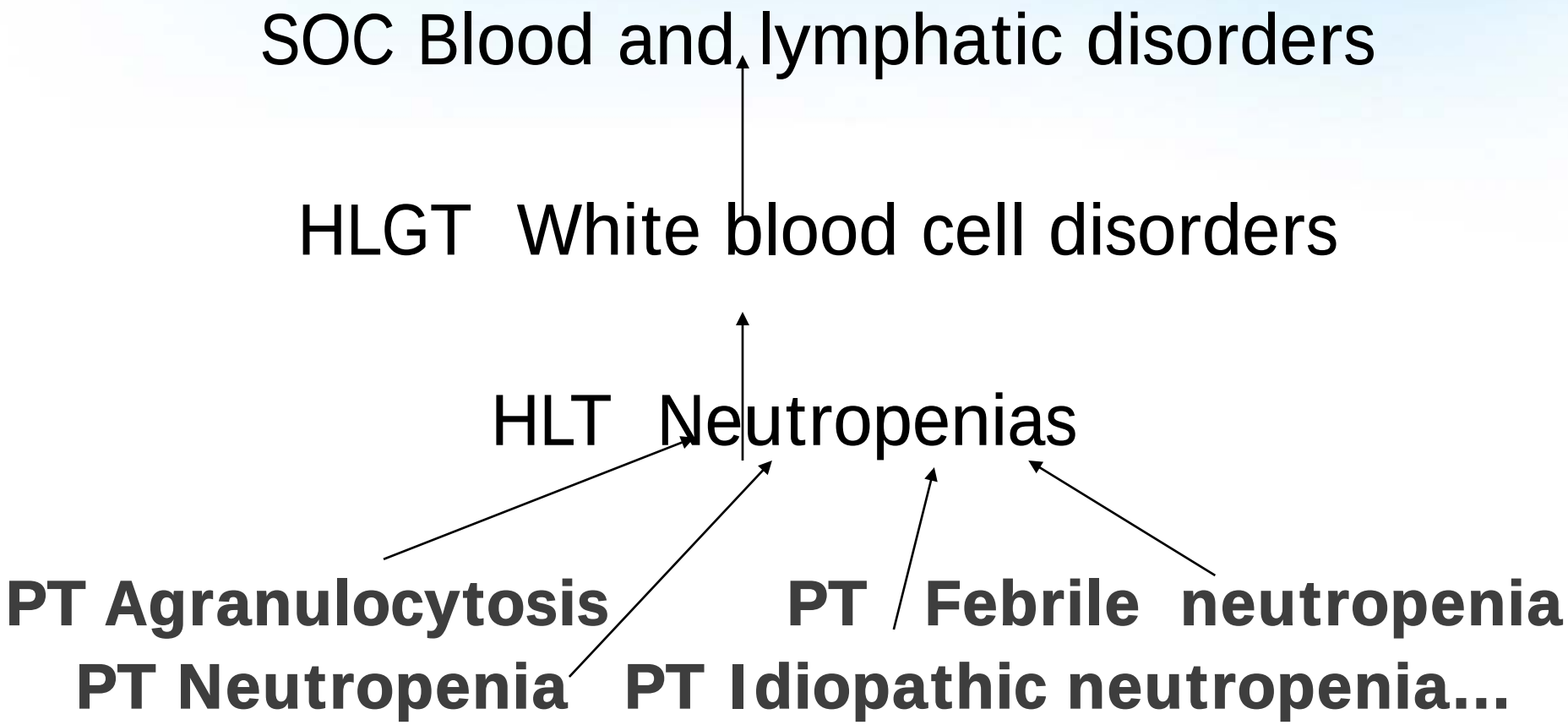
Preferred Term (PT)

- PT is a distinct, unique medical concept
- Regulatory authorities exchange information at the PT level
- PT is the reporting level to FDA and MHLW, LLT-PT to EMEA
- An identical current LLT exists for every PT
- PT (with its component LLTs) may be multiaxial, associated with more than one SOC

Hierarchy SOC-HLGT-HLT-PT



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Lowest Level Term (LLT)

- Verbatim is coded to the closest LLT
- An LLT is linked to a single PT (Preferred Term)
- LLTs linked to the same PT are:
  - Lexical variants
  - Synonyms
  - British and American spellings
  - May represent an aggravation of the concept
- LLT may be current or non-current
- Reporting to EMEA: LLT-PT

Hierarchy PT - LLT

PT Febrile neutropenia
LLT Febrile neutropenia
LLT Neutropenic fever

PT Neutropenia
LLT Neutropenia
LLT Neutropenia aggravated
LLT Chronic neutropenia

Hierarchy PT – LLT example from MedDRA 8.0

PT Dizziness

LLT Dizziness
LLT Dizziness aggravated
LLT N/C Dizziness (excl vertigo)
LLT N/C Dizziness and giddiness
LLT Dizzy
LLT Dizzy spells
LLT Felt faint
LLT Felt giddy
LLT Giddiness
LLT Light headedness
LLT Light-headed
LLT Light-headed feeling
LLT Lightheadedness
LLT Orthostatic presyncope
LLT Pre-syncope
LLT Presyncope
LLT Swaying feeling
LLT Wooziness
LLT Woozy

Hierarchy PT – LLT example from MedDRA 10.1

PT Dizziness

PT Presyncope

LLT Dizziness
LLT Dizziness aggravated
LLT N/C Dizziness (excl vertigo)
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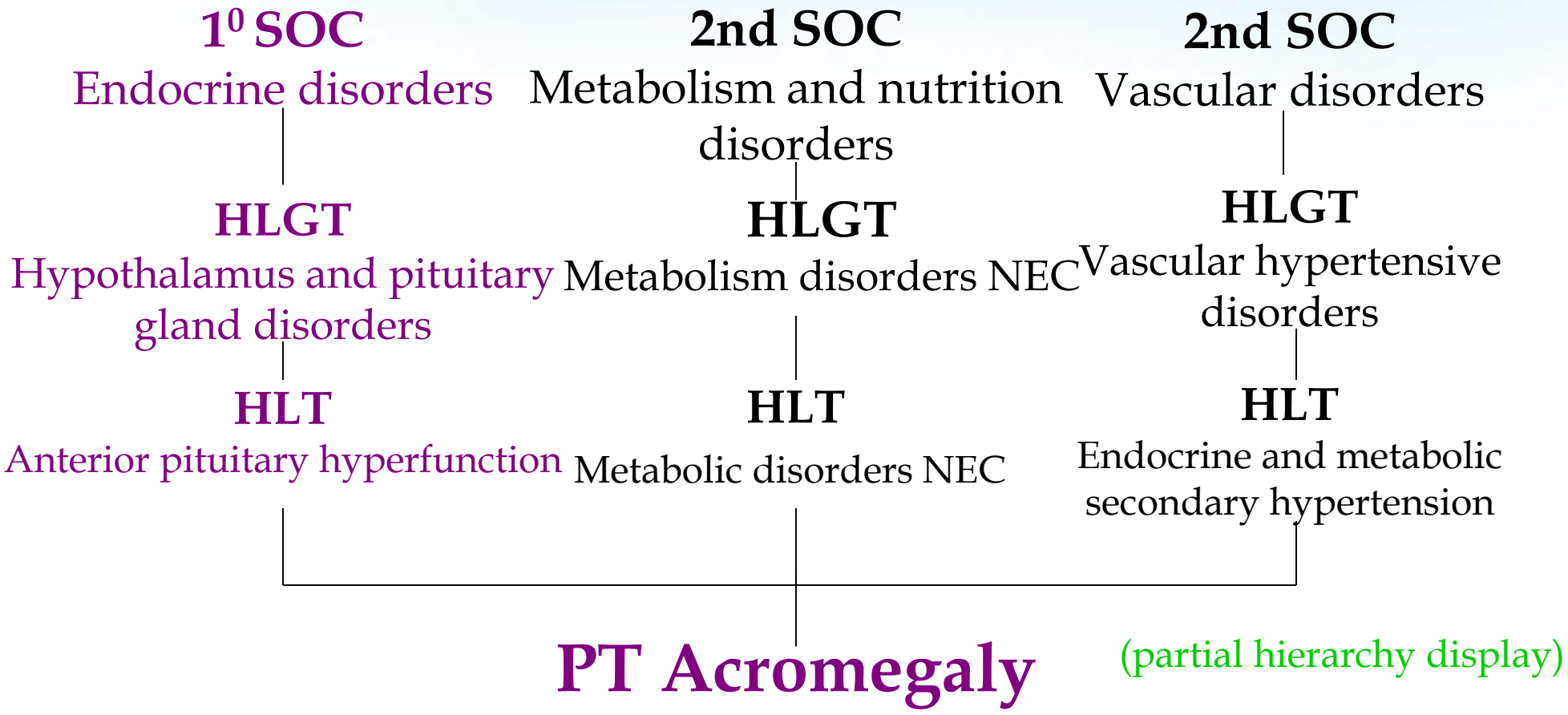
MedDRA Multi-axiality

- Multi-axiality: the representation of a medical concept in multiple SOCs, depending on its meaning
  - Allows grouping by different classifications
  - Allows retrieval and presentation via different data sets

- Purpose of Primary SOC
  - Determines which SOC represents multi-axial PTs in cumulative data outputs
  - A standard supporting/enabling consistent data presentation for reporting to regulators

Multiaxiality – PT Level



MedDRA Structure Groupings

- Primary SOC: Congenital, familial and genetic disorders

  HLGT – Cardiac and vascular disorders congenital

  HLT – Cardiac septal defects congenital
  PT – Univentricular heart

- Secondary SOC: Cardiac disorders

  HLGT: Myocardial disorders

  HLT: Myocardial disorders NEC
  PT – Univentricular heart

Multiaxiality - HLT Level

Primary SOC
Congenital, familial and genetic disorders

HLGT
Metabolic and nutritional disorders congenital

2nd SOC
Metabolism and nutrition disorders

HLGT
Inborn errors of metabolism

HLT
Inborn errors of amino acid metabolism

PT Alkaptonuria

(partial hierarchy display)

Standardized MedDRA Queries

- Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest

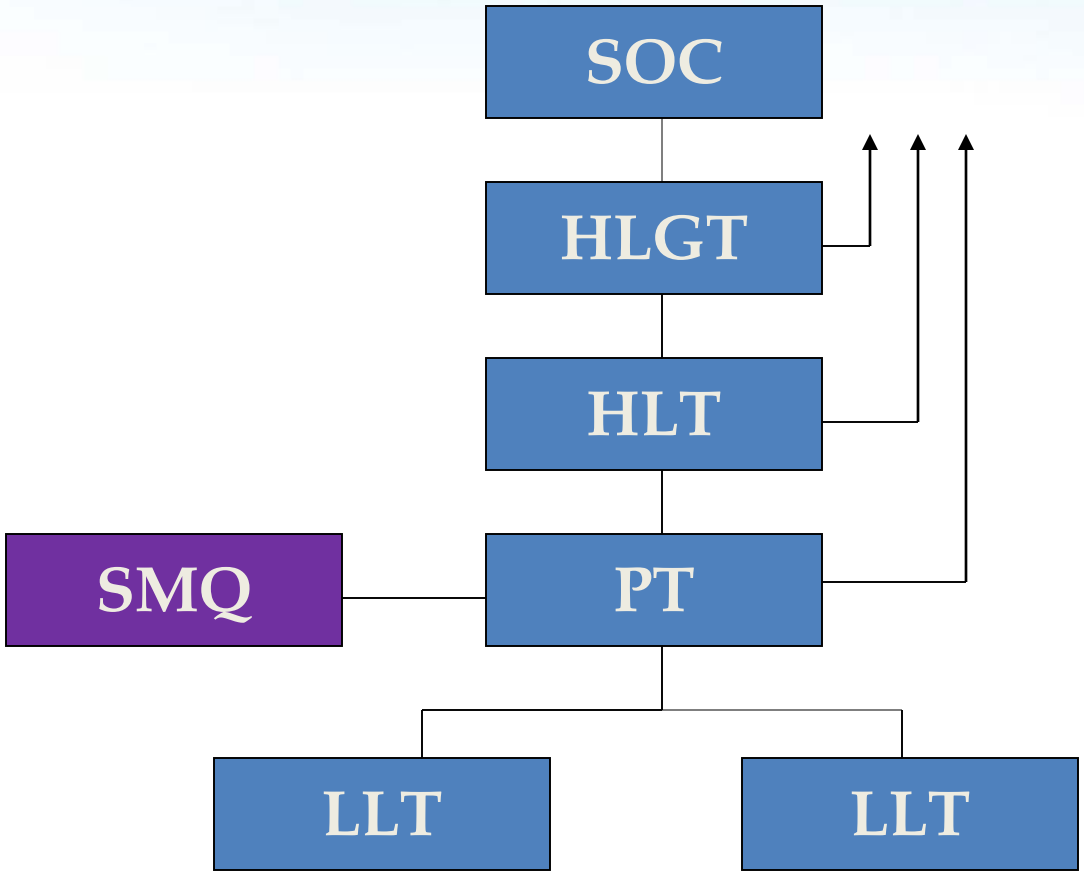
- SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports

- Currently in v19.0 there are 101 SMQ's

Examples of SMQs

- Acute pancreatitis
- Acute renal failure
- Agranulocytosis
- Anaphylactic reaction
- Angioedema
- Anticholinergic syndrome
- Asthma/bronchospasm
- Cardiac arrhythmias
- Cerebrovascular disorders
- Depression and suicide/self-injury
- Dyslipidaemia
- Haematopoietic cytopenias
- Haemolytic disorders
- Haemorrhages
- Hepatic disorders
- Hyperglycaemia/new onset diabetes mellitus
- Interstitial lung disease
- Ischaemic heart disease
- Lack of efficacy/effect
- Lactic acidosis
- Neuroleptic malignant syndrome
- Peripheral neuropathy
- Retroperitoneal fibrosis
- Rhabdomyolysis/myopathy
- Severe cutaneous adverse reactions
- Shock
- Systemic lupus erythematosus
- Taste and smell disorders
- Torsade de pointes/QT prolongation

MedDRA Structure Summary

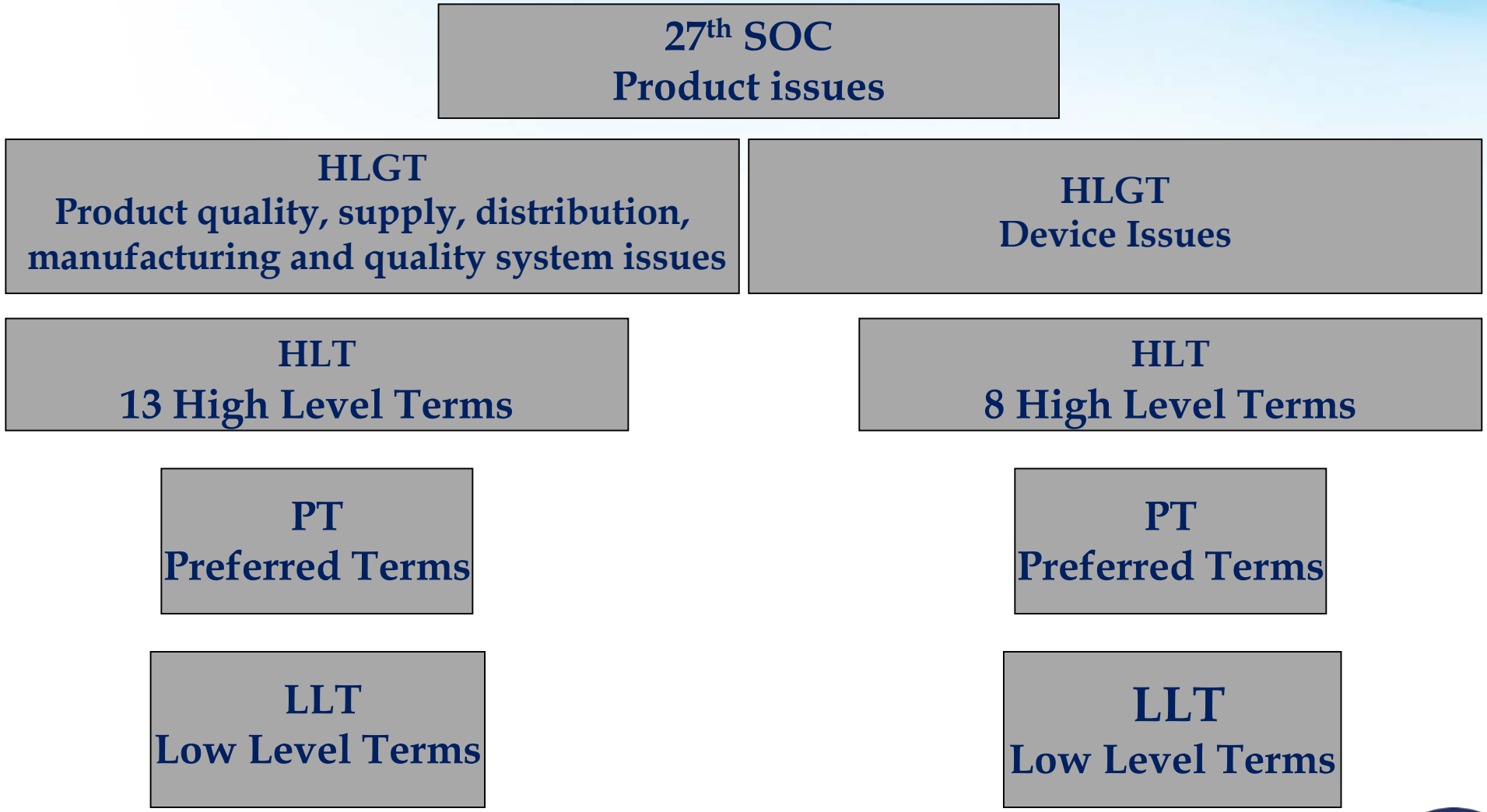


MedDRA
PRODUCT QUALITY COMPLAINTS

SOC Product issues

- New (27th) SOC for implementation in MedDRA Version 19.0 (March 2016)
- Includes terms relevant for issues with
  - Product quality
  - Devices
  - Manufacturing and quality systems
  - Supply and distribution
  - Counterfeit products
- Expert Working Group provided input on structure and contents
- PSI is part of WG
- Change requests for new terms

Structure Overview



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HLGT: Product quality, supply, distribution, manufacturing and quality system issues

HLT's

- Counterfeit, falsified and substandard products
- Manufacturing facilities and equipment issues
- Manufacturing issues NEC
- Manufacturing laboratory controls issues
- Manufacturing materials issues
- Manufacturing production issues
- Product contamination and sterility issues
- Product distribution and storage issues
- Product label issues
- Product packaging issues
- **Product physical issues**
- **Product quality issues NEC**
- Product supply and availability issues

HLGT: Device issues

HLT's

- Device computer issues
- Device electrical issues
- Device incompatibility issues
- Device information output issues
- Device issues NEC
- Device malfunction events NEC
- Device operational issues NEC
- Device physical property and chemical issues

HLT: Product physical issues

PT's

- Liquid product physical issue
- Product coating issue
- Product colour issue
- Product deposit
- Product dosage form issue
- Product friable
- Product gel formation
- Product odour abnormal
- Product physical consistency issue
- Product physical issue
- Product reconstitution issue
- Product shape issue
- Product size issue
- Product solubility abnormal
- Product taste abnormal

HLT: Product quality issues NEC

PT's

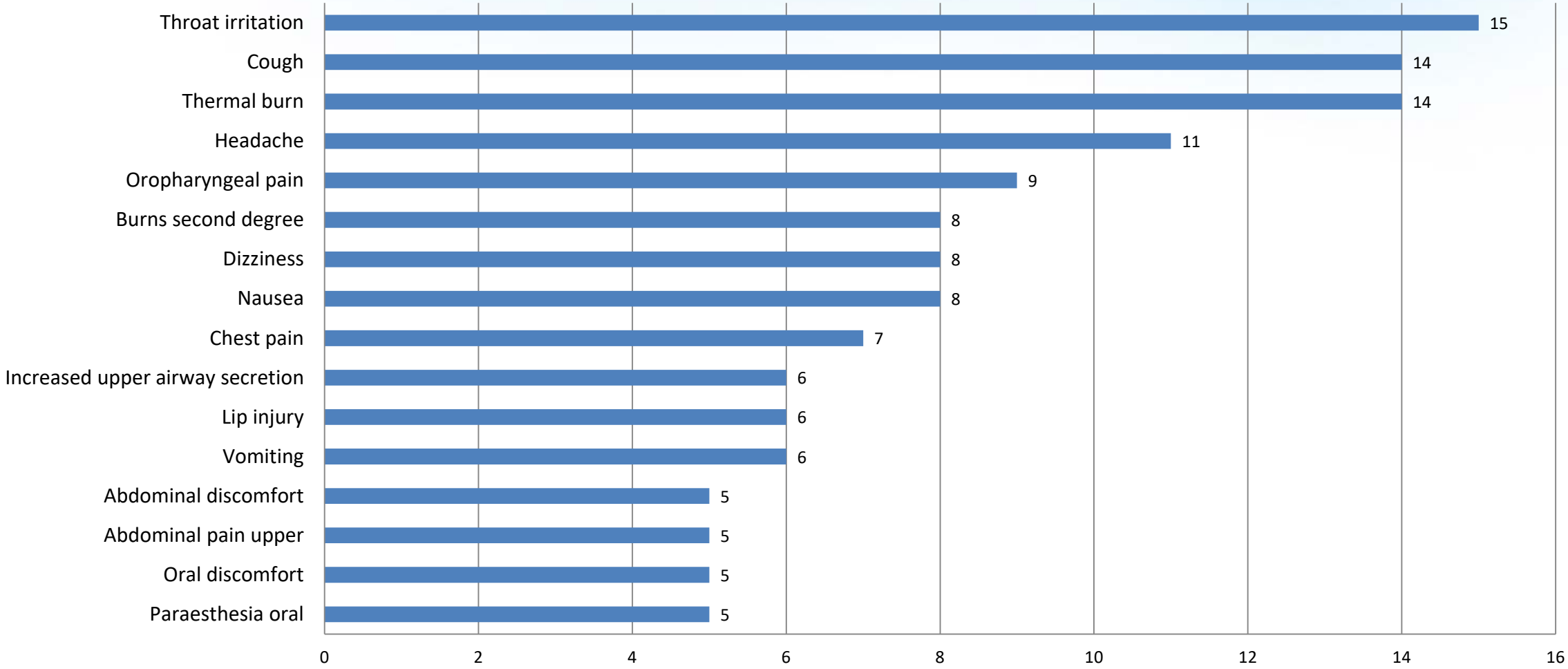
- Product adhesion issue
- Product compounding quality issue
- Product difficult to remove
- Product difficult to swallow
- Product formulation issue
- Product impurity
- Product measured potency issue
- Product origin unknown
- Product origin unknown
- Product process control issue
- Product quality control issue
- Product quality issue
- Product substitution issue
- Product tampering

Advantages

- 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
- Track and trend quality issues or deviations in own internal databases
- Potential cost savings to utilize same terminology

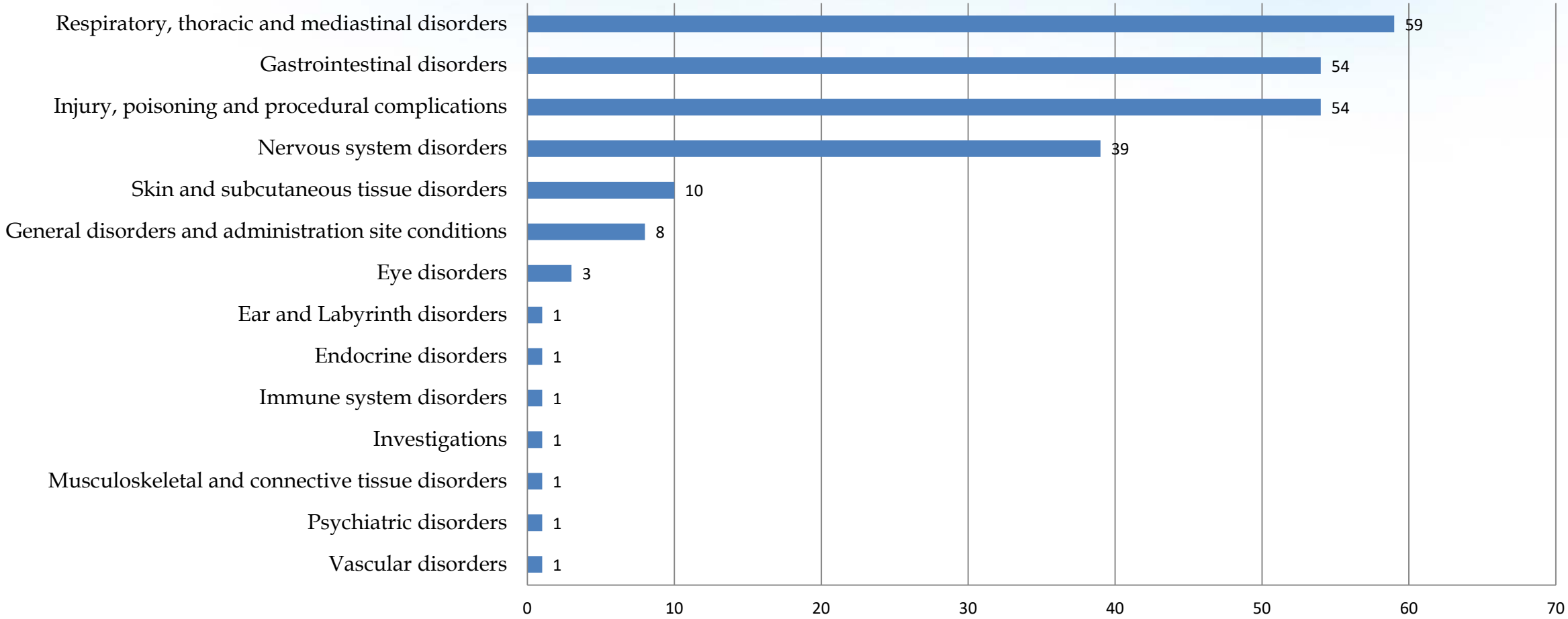
Trending Capability of Product health data at Preferred Term (PT) level

Figure 3.1 January 2014 AE PT Data in Order of Frequency for Brand X cigarettes



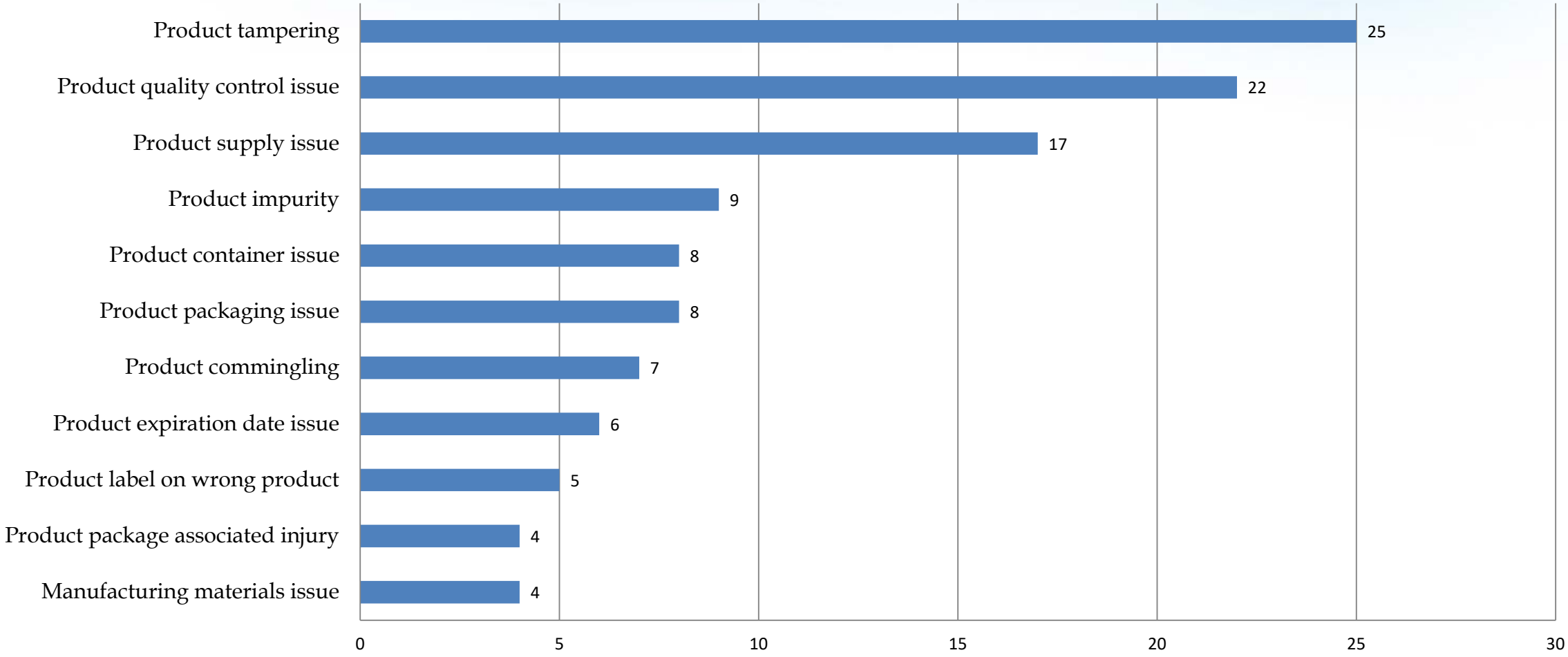
Trending Capability of Product health data at System Organ Class (SOC) level

Figure 3.2 January 2014 AE SOC data in Order of Frequency for Brand Y e-cigarettes



Trending Capability of Product quality data at Preferred Term (PT) level

Figure 3.3 July 2016 Product Quality PT Data in Order of Frequency for Brand A Cigarettes



MedDRA

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Thank you

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