SNOMED International

A Division of College of American Pathologists

Written Comments to

Food and Drug Administration

Safety Reporting Requirements
for Human
Drug and Biological Products

April 14, 2003

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ORGANIZATION BACKGROUND

The CAP is a not-for-profit medical society serving nearly 16,000 physician members and the laboratory community throughout the world. The CAP is an advocate for high quality and cost-effective patient care. The College has approximately 40 years of experience in the development and ongoing maintenance of controlled clinical terminology and specifically SNOMED®, the Systematized Nomenclature of Medicine. It's experience in the development and ongoing maintenance of controlled clinical terminology extends well beyond just the interests of pathologists. SNOMED International and the CAP appreciate the opportunity to comment on the proposed rule.

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THE COLLECTION OF INFORMATION FOR DRUG SAFETY:

RECOMMENDATION

The Food and Drug Administration is proposing to amend its pre- and postmarketing safety reporting regulations for human drug and biological products. As reported in the Federal Register / Vol.68, No. 50, "the intended effect of these changes is to further worldwide consistency in the collection of safety reports and submission of safety reports, increase the quality of safety reports, expedite FDA's review of critical safety information, and enable the agency to protect and promote public health." The proposed changes are viewed as an "important step toward global harmonization of safety reporting" and a way to "harmonize the reporting requirements of U.S. Federal agencies...continuing to work together to address the best ways to streamline information sharing and harmonization."

We propose that the agency reconsider its approach by differentiating the requirements for the collection of safety data from the requirements for the aggregation and use of the data for specific analytical and reporting purposes. More specifically, we propose that the agency consider SNOMED CT® as a more appropriate terminology for the collection of safety data if harmonization and administrative simplification is indeed a goal.

THE RATIONALE

Patient safety issues will vary over time and across clinical investigators, sponsors and research organizations. The agency's own proposed rule spans a range of safety issues, sources and uses of safety data as well as urgency of reporting:

- Minimum data set and full data set for an individual case safety report prepared by manufacturer or applicant;
- Active query with the initial report of a suspected adverse drug reaction or medication error by a health care professional that includes the collection of patient history, physical exam, diagnostic results, and supportive lab tests;
- Supporting documentation for a report of a death or hospitalization (e.g., autopsy report, hospital discharge summary);
- Spontaneous reports from an individual health care professional or consumer;
- Company core data sheet prepared by applicants for a drug substance which contains material related to indications, dosing, pharmacology and other information in addition to safety information;
- Reports of actual or potential medication errors;
- U.S. Drug labeling for an approved drug or licensed biological.

Therefore, we believe safety reporting and health care delivery requires a terminology standard that is a broad integrated whole, not a collection of domain-specific or use specific terminology fragments. The terminology infrastructure must have breadth, scope and sustainable maintenance processes to ensure that it not

only meets the needs of today, but those of tomorrow. Finally, to foster efficiency and expedited reporting, the many different uses (e.g., safety documentation, research, public health, health care delivery and decision support) in addition to the FDA's safety reporting initiatives, should rely on the same detailed clinical information that is gathered at the point of care and aggregated, analyzed and ultimately reused for different purposes.

To meet these requirements, safety reporting and healthcare delivery needs a clinical terminology standard that:

- Creates internal consistency within and between the electronic patient record, study case report forms, and FDA safety reports;
- Facilitates information sharing with government agencies, sponsors and contractors of clinical research and investigators, in addition to caregivers from various clinical/functional groups, practicing across the continuum of care, with different computer platforms;
- Provide for consistent and complete retrieval required for public health and safety reporting as well as population based studies at a very detailed level using data collected by different sources and disparate methods;
- Enable aggregation and analysis at levels of abstractness that may differ from when the data was collected;
- Meet the essential elements of good terminology design as recognized by the medical informatics community and U.S. standards organizations.

Active queries and other database analyses to rule out the causal relationship between a product and an adverse event requires collecting, aggregating and

correlating data about the trigger event, and medical and surgical interventions used to treat the event. This means integrating data points. Emergency room data may have to be linked to laboratory data for a definitive diagnosis and integrated with radiologic findings and even prescribing information in a timely manner. Such efforts would be greatly facilitated by a standard clinical terminology that is used at the point of care.

Evidence indicates that SNOMED CT fulfills these basic requirements for the collection of safety data more effectively than MedDRA at this time.

Testimony to the Institute of Medicine (IOM) Committee on Patient Safety Data Standards earlier this year from Blackford Middleton and others suggested that the committee establish acceptable standard controlled vocabulary and codes for a minimum data set, and recognized SNOMED CT within an HL7 RIM message as a means to achieve the level of "semantic interoperability" (i.e., interoperability based on meaning) that is so critical to patient safety and health care delivery. We concur and further recommend that SNOMED CT be the central ingredient in any patient safety infrastructure.

In March of this year, the National Committee on Vital and Health Statistics (NCVHS) Subcommittee on Data Standards for the Patient Medical Record received a report from its consultant evaluating 38 clinical terminologies against specific criteria. Only ten terminologies were perceived to meet the essential criteria, SNOMED CT being the most comprehensive and rated the highest.

The National Library of Medicine and the College of American Pathologists are in the final stages of executing a contract for the distribution of SNOMED CT through the Library's UMLS Metathesaurus. This would make SNOMED CT widely available to the research and patient care community. Combined with the recognition of the SNOMED CT Structure as an ANSI standard and the current evaluation of SNOMED CT by the Consolidated Healthcare Informatics as part of the e-gov initiative, SNOMED CT is best positioned as a, if not the, clinical terminology standard for the U.S. The same cannot be said for MedDRA.

As part of its long-term strategy, the CAP recognizes the importance of consistency internationally to enable data transfer and accurate communication across the globe. To that end, the CAP has been working with the National Health Service in the United Kingdom, the developers of Clinical Terms V.3 formerly known as the READ codes, to further deploy SNOMED's value beyond national borders and maximize utilization of resources available to develop a truly comprehensive and internationally accepted clinical terminology. The U.K. Information Strategy for Health states that "Subject to successful testing for implementability, after 1 April 2003... Electronic patient records and Electronic Health Records should use the NHS preferred clinical terminology, SNOMED® Clinical Terms."[1]

[1] Building the Information Core-
Implementing the NHS Plan January 2001

SNOMED CT users currently exist in 28 countries. A number of the national governments of these countries are evaluating SNOMED CT as their clinical terminology standard as they modernize their respective health care infrastructures.

In addition, third party evaluations of earlier editions of SNOMED have shown that SNOMED was superior to other terminologies and classification schemes specifically for use in adverse event reporting. In a paper by Liu et al[2], an object-oriented representation of contraindications was proposed that would allow computerized checking of drug prescription safety. It distinguished four types of contraindications: pathological state, physiological state, findings of investigation procedures and diagnostic or therapeutic procedures. The vocabulary usable for expressing the contraindications appropriate for automated prescription checking was also investigated. SNOMED was shown to give "coverage of the largest number of categories and thus appears to fit best to the needs of a database on contraindications."

The experience with the UK and other countries will enable shared patient safety initiatives on a global basis.

[2] "Object-Oriented Modeling and Terminologies for Drug Contraindictions", Meth Inform Med. 1998; 37: 45-52.

ABOUT SNOMED CT

SNOMED CT, comprehensive clinical terminology used to code, retrieve and analyze clinical data is "best of breed." SNOMED CT content and structure are well positioned to fulfill the role of collecting safety data. The breath, scope and expressivity of SNOMED CT are unparalleled. Its quality has been consistently rated #1 by independent third parties. [3] [4]

The scope of SNOMED CT encompasses the entire medical record. The terminology can precisely represent clinical information across the scope of health care. The January 2003 version of SNOMED CT contains more than 333,000 medical concepts, over 900,000 descriptions or synonyms related to these concepts, and approximately 1,300,000 computer readable hierarchical and semantic relationships between concepts. (See Appendix 1&2) Represented are symptoms (e.g., rash and erythema); findings and diagnoses (such as ventricular fibrillation, liver necrosis, S3 Gallop, anthrax septicemia and widening of mediastinum); living organisms; medications (at the clinical and proprietary drug level with dosage forms, strengths, units, routes of administration); blood and blood components; chemical substances (including vaccines, toxins, and contrast agents); medical devices; laboratory tests and test results (e.g., serum potassium level); procedures (e.g., sigmoidoscopy); anatomic structures and standard assessment tools (such as Glasgow Coma Scale, Bethesda Codes).

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[3] "The Content Coverage of Clinical Classifications", JAMIA 1996; 3:224-233.

The ability to record detailed information on adverse drug reaction relies upon existence of terminology content in two areas. Drugs themselves, and the disorders, signs and symptoms that may be the result of an adverse reaction to the drug. SNOMED CT is very rich in both of these areas as exemplified by the example of U.S. drug labeling vs. SNOMED content for adverse effects associated with the drug Moricizine. (See Appendix 3)

Many of the common medical concepts are used across clinical domains, and, at varying levels of specificity:

- Symptoms, signs, disorders may be documented by nurses, physicians, allied health professionals and veterinarians.
- A laboratory test performed may be documented in the lab using a test name that indicates analyte, method and scale, (i.e. LOINC or local code) whereas the order is written at the more general level (e.g., serology rickettsial antibody test).

The SNOMED CT structure links equivalent expressions to the appropriate medical concept and aggregates concepts across multiple hierarchies. It defines each concept semantically. (See Appendix 4) Physicians, nurses, pharmacists and other clinicians can express concepts at the level of detail appropriate to them. It provides a single integrated terminology for the many different types of concepts that must be linked to each other for safety reporting and care delivery:

- Allergies to drugs

[4] "Phase II Evaluation of Clinical Coding Schemes: Completeness, Taxonomy, Mapping, Definitions and Clarity", JAMIA, 1997; 3:238-251.

- Procedures to devices
- Diseases to contraindications.

An example related to cytovene is presented in Appendix 5.

The computer-readable format enables the clinical concepts reported by one person in one software system to be interpreted and linked to terms with the same meaning in another system, providing enhanced compatibility across software applications. And, SNOMED makes it possible for patient safety reports other than drug safety reports (e.g., adverse events that occur during surgery) to use the same underlying infrastructure. It streamlines record keeping by facilitating better communication and reuse of coded information. Thus, by supporting the day-to-day work of clinicians, SNOMED CT addresses, at the same time, the special needs of investigators, such as safety reporting. For example:

- Its content is used to meet some of the most pressing patient safety needs related to electronic drug and laboratory order entry. University of Nebraska for example, initiated an electronic order entry system using SNOMED CT for its problem lists.
- Its breadth facilitates therapeutic decision support as is demonstrated by use of SNOMED CT within TheraDoc's expert system inference engine used at University of Utah Health Sciences Center. The new proprietary US drug extension of SNOMED CT released earlier this year brought into a single terminology framework codes for indications, contraindications, allergies, side effects, virtual drug and proprietary product information.

- SNOMED CT includes codes, hierarchies and semantic definitions for the National Quality Forum's (NQF's) never events, to support patient safety initiatives.
- All medical concepts needed to code and analyze autopsy reports, another important patient safety measure, are included and have been successfully used to establish a web-based autopsy database at Duke University.
- Other users like Micromedix are tagging content using SNOMED CT to facilitate just-in-time access to knowledge bases that can prevent errors from occurring.
- The CAP has been working with the Centers for Disease Control and the American College of Surgeons Commission on Cancer. As of January 2004, the Commission requires that data elements contained in CAP's cancer checklists be reported for each site and specimen as part of its accreditation program. These checklists will be available as SNOMED CT encoded templates to reduce errors of omission and to facilitate accurate electronic reporting.
- Life sciences researchers are using SNOMED CT for indexing and mining information from databases. Genelogic, a provider of genomics-based information products and services, stores and retrieves tissue samples that match the highly specific criteria of researchers.

The SNOMED CT semantic infrastructure also facilitates the complete and consistent retrieval of data for clinical research, postmarketing safety reporting, outcome analysis and other public health analyses, allowing aggregation at varying

levels of specificity and by a wide variety of defining characteristics (e.g., etiology, drug, morphology, etc.).

The design of SNOMED CT has been driven by the expressed needs of the market place for features that improve their ability to develop useful applications. In response to these needs, the design adds unique numeric identifiers, includes links to legacy codes, supports a sustainable migration and maintenance strategy, permits adaptability for national purposes, and fosters alignment with other standards such as HL7, XML, and DICOM.

As an American National Standards Institute (ANSI) approved standards developer, the College of American Pathologists has committed to a review process that incorporates ANSI's minimum due process requirements. The SNOMED CT structure has been balloted as an ANSI standard and at the close of the balloting process, CAP reported that 74% of the canvass list voted. Of those responding to the initial and recirculation ballot, 89% voted in favor of the SNOMED CT structure as an ANSI standard.

And, from the perspective of the FDA's need for harmonization with ICH and WHO, data collected using SNOMED CT can be mapped to classification systems such as MedDRA for regulatory reporting.

CONCLUSION

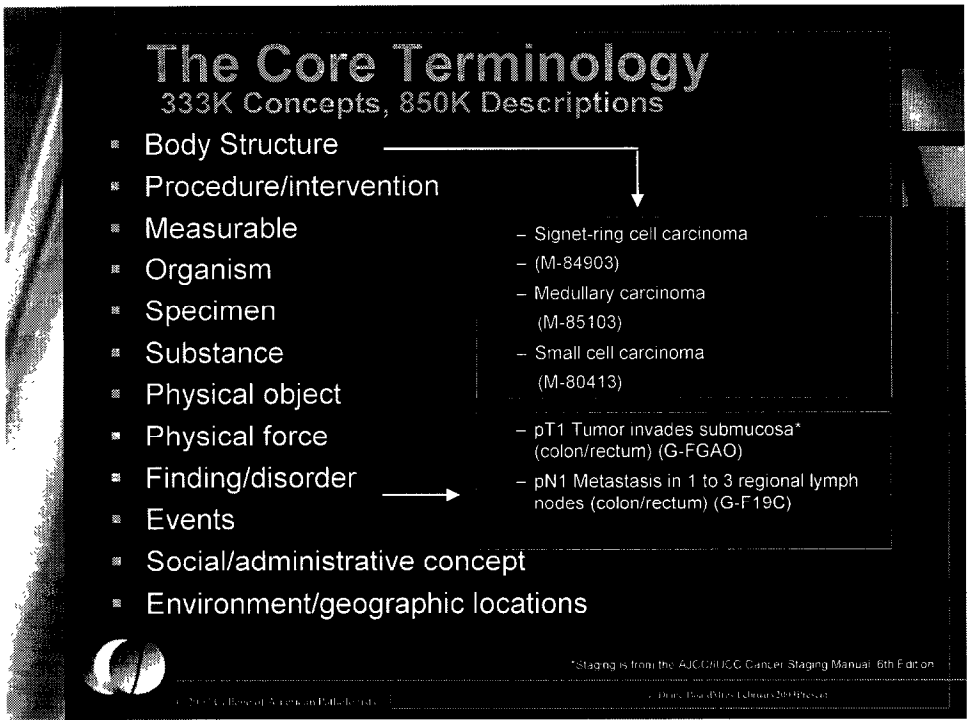
In summary, we urge the agency to recommend a terminology standard for the collection of safety data that is a broad integrated whole, such as SNOMED CT, not a narrow data set or domain specific terminology and classification scheme such as MedDRA. The decision of an appropriate terminology for statistical analysis and regulatory harmonization should be considered separately.

SNOMED CT would enable the collection and analysis of comparative data from the diverse groups reporting events as part of the framework for building a comprehensive risk assessment and management system for drug safety. The data collected using SNOMED CT could be repurposed by mapping to MedDRA when needed for statistical purposes and regulatory harmonization.

The strengths and benefits of SNOMED as a recognized leader in clinical terminology have been demonstrated over the span of 40 years. The CAP is clearly a strong advocate for high quality, cost effective patient care as shown through its long term commitment to the on-going development of SNOMED as a comprehensive, broad based terminology. As an organization the CAP envisioned the importance of standardized terminology to support quality care and patient safety. Therefore, it has continued to enhance the structure and expand the scope and global use of SNOMED to ensure that it is scientifically accurate and representative of the practice of medicine worldwide.

We would welcome the opportunity to work with the agency toward this end.

Appendix 1


The Core Terminology
333K Concepts, 850K Descriptions
Body Structure
Procedure/intervention
Measurable
Organism
Specimen
Substance
Physical object
Physical force
Finding/disorder
Events
Social/administrative concept
Environment/geographic locations
– Signet-ring cell carcinoma
– (M-84903)
– Medullary carcinoma
(M-85103)
– Small cell carcinoma
(M-80413)
– pT1 Tumor invades submucosa*
(colon/rectum) (G-FGAO)
– pN1 Metastasis in 1 to 3 regional lymph
nodes (colon/rectum) (G-F19C)
*Staging is from the AJCC/UICC Cancer Staging Manual 6th Edition

Appendix 2: SNOMED CT Content

Domain Area	Example Concepts/Terms	Approx. Number Concepts	Approx. Number Terms*
Clinical disorders (diagnoses)	Rheumatoid Arthritis Coronary Artery Disease Spiral Fracture of the Humerus Paranoid Schizophrenia	71,000 (All diseases)	188,000
Subjective symptoms	Fatigue Lower Back Pain Radiating to Foot Vertigo Numbness	837 The number represents the set of findings that can either be reported by the patient or observed by an external observer, and where it could be either, we categorize these simply as findings (see below).	2057
Observed findings	S3 Gallop Tenderness in Right Lower Quadrant Maculopapular Rash Papilledema	38,000 (All findings)	91,000
Procedures performed by clinicians (preventive, diagnostic, and therapeutic)	Sigmoidoscopy Urinary Catheterization Hip Arthroplasty FEV-1 Test	38,000 (Total procedures minus lab and imaging)	95,000
Laboratory tests and test results, including specimen types, testing methods, and micro-organisms	Serum Potassium Level CSF Culture Hepatitis B Surface Antigen RIA	25,000 (Lab procedures plus lab test findings, specimens and microoganisms)	64,000

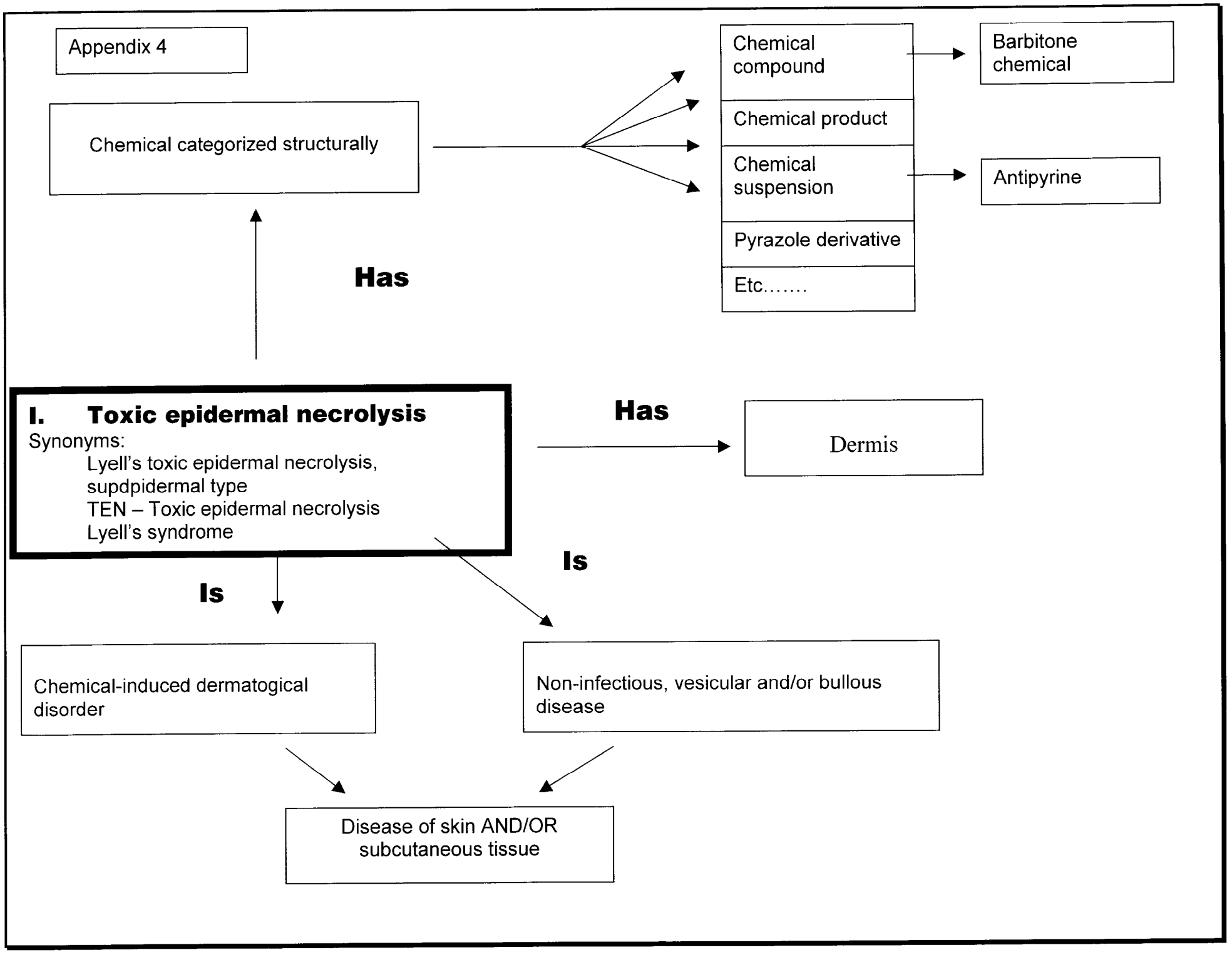
Radiology tests and test results/findings	Abdominal CT Scan Chest X-Ray Mammogram Thyroid Scan	3000 (Imaging procedures plus radiologic findings)	7000
Anatomical structures	Fibula Cerebellum Facial Nerve Vertebral Artery	26,000	75,000
Medications	Glucophage lisinopril Benadryl	16,500 in the SNOMED CT core 13,531 in the US Drug extension 40,722 in the UK Drug extension	53,409 in the SNOMED CT core 32,846 in the US Drug Extension 82,808 in the UK Drug Extension
Chemical substances other than medications	Vaccines Toxins Contrast Agents	23,000	59,000
Medical devices and supplies relevant to the documentation of clinical care	Pacemaker Heart Valve Prosthesis Greenfield Filter Indwelling Catheter Ventilator	2000	5000
Social and care-management concepts	Marital Status Values Occupations Healthcare Facility Types	5000	11,000
Standardized assessment tools	Glasgow Coma Scale Components APGAR Score Components Hamilton Depression Inventory Questions	2000	4000

Appendix 3:
Example U.S. Drug Labeling Content vs. SNOMED

Event type: **Adverse reaction to drug (SCT ID 62014003)**
Causitive agent: **Moricizine (SCTID 108488000)**
Associated findings:

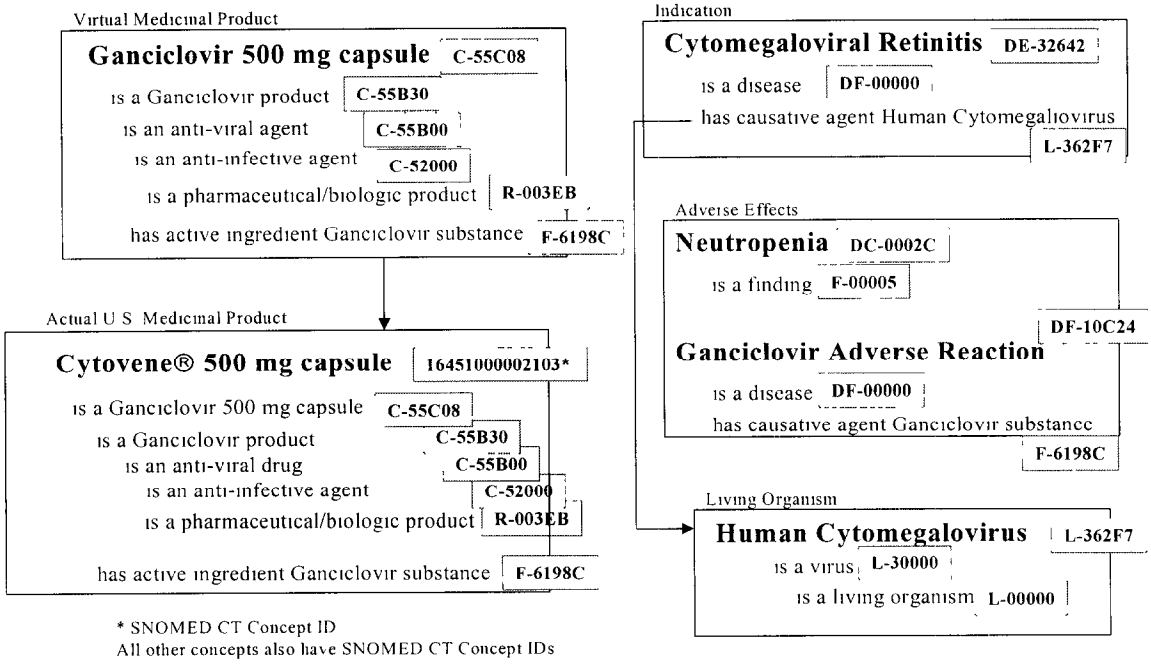
ID	Field1	Field2	Field3
1	CARDIOVASCULAR	**SNOMED CT terms**	Variation
2	palpitation	Palpitations	
3	sustained ventricular tachycardia	Ventricular tachycardia	Y
4	cardiac chest pain	Cardiac chest pain	
5	CHF	Congestive heart failure	
6	cardiac death	Death	Y
7	hypotension	Hypotension	
8	hypertension	Hypertensive disease	Y
9	syncope	Syncope	
10	supraventricular arrhythmias	Supraventricular arrhythmias	
11	atrial fibrillation	Atrial fibrillation	
12	atrial flutter	Atrial flutter	
13	cardiac arrest	Cardiac arrest	
14	bradycardia	Bradycardia	
15	pulmonary embolism	Pulmonary embolism	
16	myocardial infarction	Myocardial infarction	
17	vasodilation	Peripheral vascular dilation	Y
18	cerebrovascular events	Cerebrovascular accident	Y
19	thrombophlebitis	Thrombophlebitis	
20	CNS		
21	dizziness	Dizziness	
22	headache	Headache	
23	fatigue	Fatigue	
24	hypesthesias	Hypesthesia	
25	asthenia	Asthenia	
26	nervousness	Nervousness	
27	paresthesias	Paresthesia	
28	sleep disorder	Sleep disorder	
29	tremor	Tremor	
30	anxiety	Anxiety	
31	depression	Depression	
32	euphoria	Euphoria	
33	confusion	Confusion	
34	somnolence	Somnolence	
35	agitation	Agitation	
36	seizure	Seizure	
37	coma	Coma	
38	abnormal gait	Abnormal gait	
39	hallucinations	Hallucination	
40	nystagmus	Nystagmus	
41	diplopia	Diplopia	
42	speech disorder	Speech and language	Y

43	akathisia	akathisia	
44	memory loss	Memory loss	
45	ataxia	Ataxia	
46	GU		
47	abnormal coordination	Coordination problem	Y
48	dyskinesia	Dyskinesia	
49	vertigo	Vertigo	
50	tinnitus	Tinnitus	
51	GI		
52	nausea	Nausea	
53	abdominal pain	Abdominal pain	
54	dyspepsia	Dyspepsia	
55	vomiting	Vomiting	
56	diarrhea	Diarrhea	
57	anorexia	Anorexia	
58	bitter taste	Primary bitter taste disorder	Y
59	dysphagia	Dysphagia	
60	flatulence	Flatulence	
61	ileus	Ileus	
62	urinary retention	Urinary retention	
63	urinary frequency	Urinary frequency	
64	dysuria	Dysuria	
65	urinary incontinence	Urinary incontinence	
66	kidney pain	Kidney pain	
67	impotence	Impotence	
68	decreased libido	Decreased libido	
69	RESPIRATORY		
70	dyspnea	Dyspnea	
71	hyperventilation	Hyperventilation	
72	apnea	Apnea	
73	asthma	Asthma	
74	pharyngitis	Pharyngitis	
75	cough	Cough	
76	sinusitis	Sinusities	
77	MISCELLANEOUS		
78	sweating	Sweating	
79	musculoskeletal pain	Musculoskeletal pain	
80	dry mouth	Dry mouth	
81	blurred vision	Blurred vision	
82	drug fever	Drug fever	
83	hypothermia	Hypothermia	
84	temperture intolerance	Body temperature finding	Y
85	eye pain	Pain in eye/ Pain around eye	Y
86	rash	Rash	
87	pruritus	Pruritus	
88	dry skin	Dry skin	
89	urticaria	Urticaria	


Appendix 4
Chemical categorized structurally
Chemical compound
Chemical product
Chemical suspension
Pyrazole derivative
Etc.....
Barbitone chemical
Antipyrine
Has
I. Toxic epidermal necrolysis
Synonyms:
Lyell's toxic epidermal necrolysis, supdpidermal type
TEN – Toxic epidermal necrolysis
Lyell's syndrome
Has
Dermis
Is
Is
Chemical-induced dermatogical disorder
Non-infectious, vesicular and/or bullous disease
Disease of skin AND/OR subcutaneous tissue

Appendix 5

SNOMED CT ®



* SNOMED CT Concept ID
All other concepts also have SNOMED CT Concept IDs

Beverly Pullen (s)

From: Diane Aschman (s)
Sent: Monday, April 14, 2003 3:44 PM
To: 'FDADockets@fda.gov'
Subject: Comments on Safety Reporting Requirements for Human Drug and Biological Products

Importance: High

On behalf of Paul A. Raslavicus, MD, President, College of American Pathologists and Franklin R. Elevitch, MD, Chair, SNOMED International Authority and myself, attached are written comments regarding FDA's proposal rule on "Safety Reporting Requirements for Human Drug and Biological Products" 21 CRF 310, 312 et al.

A written copy will follow by mail. Please know that we are willing to work with the FDA on these and related issues.

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FDA Safety
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