The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

London, 14 October 2003
Doc. Ref.: EMEA/H/24194/03/Final

Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm 1061
Rockville MD 20852
USA

Subject: ***EMEA Comments on the use of MedDRA and the Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule Part II Department of Health and Human Services (Docket No. 00N-1484).***
Food and Drug Administration, 21 CFR Parts 310, 312, et al.

Dear Madame/Sir,

With regard to the proposed rule for the 'Safety Reporting Requirements for Human Drug and Biological Products', please allow me to provide with you with the comments of the European Agency for the Evaluation of Medicinal Products (EMEA) on FDA's proposal to introduce MedDRA as single medical terminology for coding in post-marketing safety reports.

The EMEA welcomes this proposed rule on safety reporting and the requirement that post-marketing individual case safety reports have to be coded using MedDRA prior to submission to the FDA[1]. Detailed technical comments regarding the proposed use of MedDRA are outlined in Annex 1.

The announcement in July 2003 that the Department of Health and Human Services (DHHS) entered into a licensing agreement to make a clinical terminology database, SNOMED, available without charge to the health industry, has raised concerns of regulators and industry in the ICH regions. Although such initiative has to be welcomed from a public health perspective, pharmaceutical industry is seriously concerned about the impact of the use of a different medical terminology on the reporting in both the pre- and post-authorisation phase. The EMEA is of the opinion that the parallel use of alternative terminologies will seriously endanger the international harmonization efforts and add substantially to costs and workload in cross-terminology mappings, which will arise from such initiative. Detailed technical comments with regard to the use of SNOMED are outlined in Annex 2.

I hope the above comments will provide you with a useful input with regard to the above matter.

In case you have any further questions, please do not hesitate to contact me.

Yours sincerely,

PP Noël Wathion
Head of Post-Authorisation Unit

00N-1484

C41

[1] **12410 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules

London E14 4HB UK

Annex 1

Technical Comments regarding the use of MedDRA

As indicated in the Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule Part II Department of Health and Human Services (Docket No. 00N-1484 Food and Drug Administration, 21 CFR Parts 310, 312, et al.) many of the amendments that are being suggested are intended to harmonize FDA's safety reporting requirements with international standards developed by CIOMS and ICH[2].

Based on the experience gained in the European Economic Area (EEA), where the use of MedDRA came into effect for post-marketing activities in January 2003, EMEA can strongly endorse FDA's stance that the changes recommended by ICH will result in more effective and efficient safety reporting to regulatory authorities worldwide[3].

Further, EMEA fully supports the viewpoint of FDA, that it is essential to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of the three ICH regions[4].

As indicated in this draft rulemaking, companies and regulators used various medical terminologies for safety reporting purposes (e.g., WHO's Adverse Reaction Terminology (WHOART), Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), Japan's Adverse Reaction Terminology (J-ART)). The established terminologies have been criticized for a number of reasons, including: lack of specificity, limited data retrieval options, and an inability to effectively handle complex combinations of signs and symptoms (syndromes). In addition, use of different terminologies at different stages in the development and use of products complicates data retrieval and analysis of information and makes it difficult to effectively cross-reference data through the lifetime of a product. Internationally communication is impaired between regulatory authorities because of the delays and distortions caused by the translation of data from one terminology to another[5].

This is underlined by the fact, that all regulatory and industry ICH partners considered the adoption of a single international terminology. This would be advantageous for regulatory communications for the following reasons[6]:

- Improvements in the effectiveness and transparency of medicinal product regulation,
- Improvements in the ease, quality, and timeliness of data for analysis, exchange and decision making,
- Facilitation of the electronic exchange of data relating to medicinal products,
- Long-term savings in resources.

As correctly pointed out in the proposed rule, the use of different terminologies also has significant consequences for pharmaceutical firms. Companies operating in more than one jurisdiction have had to adjust to subsidiaries or clinical research organizations that use different terminologies because of variations in data submission requirements. The difficulty of analyzing data comprehensively may be compounded by use of incompatible terminologies and could lead to delays in recognizing potential public health problems[7].

---

[2] **12412 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules
[3] **12412 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules
[4] **12412 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules
[5] **12412 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules
[6] **M1 Call for Tender**

Taking into account that the ICH M1 terminology[8] and E2BM and M2 guidelines[9] were designed for the use of both the pre- and post-approval period, the use of a common standard, once implemented by all stakeholders involved, will substantially benefit the overall monitoring and evaluation of the safety of investigational and authorized medicinal products.

MedDRA[10] is indeed the best choice because it was developed with input from regulatory authorities and industry and the problems associated with the other terminologies were taken into consideration during development of MedDRA.

The advantages of MedDRA from a scientific point of view are that the terminology, as indicated above, is applicable to all phases of drug development (including biologicals) and to the health effects of devices. As such it is applicable for clinical studies, reports of spontaneous adverse reactions and events, regulatory submissions and medicinal product information[11]. The categories of terms classified as 'medical' for these purposes are as follows:

- Symptoms
- Signs
- Diseases
- Diagnoses
- Therapeutic indications –including symptoms, signs, diseases, diagnoses, diagnosis or prophylaxis of disease and modification of physiological function
- Names and qualitative results of investigations (including pharmacokinetics)
- Descriptive terms i.e. increased, decreased, normal, abnormal, present, absent, positive, negative
- Surgical and medical procedures
- Medical/social/family history

Although social circumstances are not usually regarded as medical terms, they fall within the scope if they are relevant for the evaluation of regulatory data e.g. in the assessment of clinical outcome of treatment in the light of exposure to risk factors. Examples are travel history, exposure to environmental hazards, tobacco use, etc.

A MedDRA maintenance process has been established in a way, that in addition to the routine maintenance of the terminology, mechanisms have been put in place that allow the terminology a continuous evolution in response to advances in scientific and medical knowledge and changes in the regulatory environment [12]. As such, the EMEA is of the opinion that the use of MedDRA should be endorsed in the health care area and in case of any deficiencies of the current terminology, changes or updates should be proposed to the MedDRA Maintenance and Support Service Organization (MSSO), which can respond in an efficient and timely manner to the needs of the users worldwide.

Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would require that each SADR in an individual case safety report be coded on FDA Form 3500A, CIOMS I Form, or VAERS Form using the appropriate ''preferred term'' in the latest version of MedDRA in use at the time the manufacturer or applicant becomes aware of the individual case safety report. FDA is proposing to require use of MedDRA to be consistent with ICH M1[13].

In this context EMEA would like to draw the attention to the fact that the use of MedDRA as defined in E2BM is not limited to the coding of SADRs. In the frame of the harmonized individual case safety reporting standards, the use of MedDRA was agreed as being applicable for all data elements as presented in table 1. As such, the EMEA strongly recommends to FDA to introduce the MedDRA coding to all data elements in order to achieve the overall goal of a substantial upgrading of the quality of safety analysis by incorporating uniformity of terms. As such the envisaged standardization of all

---

[8] **Medical Dictionary For Regulatory Activities Terminology (MedDRA) Introduction Guide**
[9] **ICH E2B(M)-Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports and ICH M2 Electronic Transmission of Individual Case Safety Reports Message Specification**
[10] **Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules
[11] **Medical Dictionary For Regulatory Activities Terminology (MedDRA) Introduction Guide**
[12] **M1 Call for Tender**

applicable terms using MedDRA would improve the quality of the roughly 250,000 safety reports submitted annually to FDA and would lead to better and more timely safety assessments and to improved communication of risk information by drug safety reporters and reviewers.

Table 1: ICH E2B(M) Data Elements and the use of MedDRA

Number	Description	DTD Descriptor
B.1.7.1a.2	Disease / surgical procedure / etc.	Patientepisodename
B.1.8f.2	Indication	Patientdrugindication
B.1.8g.2	Reaction	Patientdrugreaction
B.1.9.2.b	Reported cause(s) of death	Patientdeathreport
B.1.9.4b	Autopsy-determined cause(s) of death	Patientdetermineautopsy
B.1.10.7.1a.2	Disease / surgical procedure/ etc.	Parentmedicalepisodename
B.1.10.8f.2	Indication	Parentdrugindication
B.1.10.8g.2	Reactions	Parentdrugreaction
B.2.i.1.b	Reaction/event in MedDRA terminology (LLT)	Reactionmeddrallt
B.2.i.2.b	Reaction/event MedDRA term (PT)	Reactionmeddrapt
B.4.k.17.2b	If yes, which reaction(s)/event(s) recurred?	Drugrecuraction
B.4.k.11b	Indication for use in the case	Drugindication
B.4.k.18.1b	Reaction assessed	Drugreactionasses
B.5.3	Sender's diagnosis/syndrome and/or reclassification of reaction/event	Senderdiagnosis

In addition, EMEA is of the opinion that it is important to standardise and code test names (B.3.1c) in safety reports using MedDRA, and as such has requested companies to code test names in MedDRA, which includes names and qualitative results of investigations.

Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would also require that each individual case safety report of a medication error be coded both as a medication error and, if applicable, with the preferred term for any SADRs associated with the medication error. The proposal clarifies how actual and potential medication errors would be coded[14].

In the context of the reporting of medication errors the EMEA and National Competent Authorities in the EEA fully supported the request of FDA's Division of Medication Errors and Technical Support (DMETS) to include medication error terms in MedDRA to improve both FDA's and the pharmaceutical industry's system of analyzing medication errors detected through post-marketing surveillance.
Such medication error terms were requested by FDA at System Organ Class level (SOC) (injury, poisoning and procedural complications, at High Level Group Term (HLGT) (medication error and accidental exposure overdoses, High Level Term (HLT) (medication error) and specific Preferred Terms (PTs) and Lower Level Terms (LLTs)[15].

It is true that despite the general recognition that manufacturers could realize substantial gains if safety reporting and terminologies were standardized globally, companies currently have limited incentives to invest capital and resources in standardized reporting systems (e.g. MedDRA) unless the standards are required by regulation. This shortfall in industry incentives occurs because the economic gains of

[14] **12445 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules

harmonization cannot be attained by individual firms acting alone. Although achieving the desired international standardization and its corresponding economic and health benefits, industry would benefit from FDA action to reduce uncertainties associated with investments in harmonization and from the ability to more efficiently allocate resources associated with safety reporting[16].

Similar experience was obtained in the European Economic Area (EEA), where the European Commission in collaboration with the EMEA and National Competent Authorities addressed the harmonization aspect in safety reporting through legislation[17]. Directive 2001/83/EC aims to ensure the continued safety of medicinal products in use whereby it is necessary to make sure that pharmacovigilance systems in the Community are continually adapted to take into account of scientific and technical progress including changes arising as a result of international harmonization of definitions, terminology and technical developments in the field of pharmacovigilance.

As such the EMEA fully supports FDA's viewpoint, that by eliminating the use of multiple dictionaries, MedDRA would facilitate the retrieval, presentation, and summarization of SADR data and enhance the global communication and acceptance of safety information and reports. The use of a single dictionary will substantially upgrade the quality of safety analysis by incorporating uniformity of terms. MedDRA will aid in more expeditious and broader international drug use comparisons within a class, and prescribing and use decisions. Providing more complete information and more timely safety assessments would enhance the ability of the manufacturers to more quickly identify, monitor, and communicate the potential risks and benefits of marketed drugs and biologics[18].

With regard to FDA's proposal to require the use of the preferred term for reporting on the basis that each preferred term is representing a unique medical concept accepted internationally, the EMEA would like to point out that the Lowest Level Terms (LLT) are always linked to a Preferred Term (PT).

There are currently differences at coding level between the US and the EEA, whereby in the EEA coding for safety reporting is required at LLT level[19]. It is correct that preferred terms provide medically validated representations of colloquial terms, which will result in fewer misrepresentations and misunderstandings of colloquial reports from various parts of the world. However, the five level hierarchy of MedDRA provide options for retrieving data by specific or broad groupings as appropriate to the level of specificity required, with the option of returning to the LLT for maximum specificity. The EMEA regards the coding at PT level as required by FDA versus the coding at LLT level in the EEA as an issue that can be resolved easily based on the multi hierarchical structure of MedDRA.

The 'Current Flag Status' of LLTs and the facility to flag LLTs as non current means that such terms are retained within the terminology to allow preservation of historical data for retrieval and analysis, whilst allowing the 'current status' of terms to be used for data entry.

As such EMEA believes, that data coding and reporting should take place at the LLT level for which it was designed, and that the scientific evaluation should take place at the PT level[20]. With this approach the granularity and specificity of the LLT will always be maintained.

The EMEA shares the concerns of FDA that the use of MedDRA may result in a significant economic hardship for some manufacturers and applicants. However this is already addressed by proposals for a 'fee waiver' system. This fee waiver system for small and medium size enterprises was presented by the EMEA and approved by the MedDRA Management Board in July 2003. It will be implemented in September 2003 by the EMEA for a trial period of one and the results will be presented regularly to the MedDRA Management Board. As indicated in the draft rulemaking, applicants may request, under §§ 314.90 or 600.90, that FDA waive the requirement that each SADR in an individual case safety

[16] **12450 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules

[17] **Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use**

[18] **12451 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules

[19] **E2BM Implementation Working Group Question &Answers 18 July 2003**

report be coded using MedDRA. If FDA finds that this requirement is economically burdensome for a small company, the agency intends to grant the company a waiver. A large company may also be granted a waiver if, for instance, it only markets a single product that generates a few safety reports a year. FDA intends to grant all reasonable waiver requests. This determination will be made on a case-by-case basis[21].

The EMEA sees this as a valuable incentive to encourage and support companies in safety reporting. In addition, EMEA suggests that the MedDRA licensing policies should be adapted to accommodate an acceptable pricing policy for low volume MedDRA users in the pharmaceutical industry to encourage the use of this international standard terminology and to reduce the coding burden for regulators, where resources are also limited.

The implementation time frame to require that SADRs in individual case safety reports be coded using MedDRA becomes effective 1 year after its date of publication in the Federal Register is reasonable, especially since MedDRA is now a stable terminology and available for implementation since 1997 (agreement on version 2.0 at ICH-4)[22].

The EMEA also appreciates the detailed summary of the costs and benefits of the proposed rule, which clearly outlines the expected health benefits resulting from the improved quality of the safety reports and subsequent analyses.

In conclusion and with reference to the proposed rule, the EMEA welcomes the required use of MedDRA, a medical dictionary developed by the ICH, in coding SADR terms. As pointed out correctly by FDA, MedDRA will provide a uniform, consistent and specific presentation of medical terms.

[21] 12478 Federal Register / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules

Annex 2

Technical Comments on the use of SNOMED

Even though FDA is proposing to use MedDRA as the standard medical terminology for reporting purposes under this rule, FDA recognizes that alternative standard classification systems for clinical information exist in the United States and supports the national health data standardization initiatives underway in the United States under the Health Insurance Portability and Accountability Act. Although this proposed rule does not impose reporting requirements on health care providers, FDA recognizes that clinicians, medical centers, hospitals and others may report safety information to pharmaceutical companies. These third parties may employ clinical terminology standards that differ from those proposed in the draft rule[23].

The announcement in July 2003 that the Department of Health and Human Services (DHHS) entered into a licensing agreement to make a clinical terminology database, SNOMED, available without charge to the health industry, has raised concerns of regulators and industry in the ICH regions. Although such initiative has to be welcomed from a public health perspective, concerns have been raised mainly by pharmaceutical industry about the impact on the use of a different medical terminology and the impact on the reporting in both the pre- and post-authorisation phase.

The EMEA is of the opinion that the parallel use of alternative terminologies will seriously endanger the international harmonization efforts and add substantially to costs and workload in cross-terminology mappings especially for pharmaceutical industry.

In this context, the EMEA would also like to express serious concerns about the impact of the potential use of different terminologies in the health care area. Health care providers are the primary source capturing and reporting adverse drug reactions in patients although FDA's safety reporting requirements do not apply as such to those parties. MedDRA was clearly designed as terminology for human health care purposes[24] and could also be used by health care providers.

In addition, the potential use of SNOMED by health care providers raises the following issues:

- A different standard will be applied to data captured by health care professionals and those captured by regulators;
- Studies performed on drug utilisation or in pharmacoepidemiology will use data as captured by health care professionals;
- Evaluation of such studies in comparison with data from spontaneous reporting systems will be impaired since data have been coded in different terminologies (e.g. SNOMED, MedDRA) and may need to be recoded or remapped;
- The overall pharmacovigilance process will be affected in particular the signal detection activities if different terminologies are going to be applied (e.g. a detailed analysis of epidemiological data coded in SNOMED and ICSR data coded in MedDRA will be difficult; it will not be possible to apply the specifically developed standardised MedDRA queries due to the diverse data sets).

Consequently EMEA would like to endorse the viewpoint of FDA that by eliminating the use of multiple dictionaries, MedDRA would facilitate the retrieval, presentation, and summarization of SADR data and enhance the global communication and acceptance of safety information and reports.

---

[23] **12413 Federal Register** / Vol. 68, No. 50 / Friday, March 14, 2003 / Proposed Rules

EMEA also shares FDA's opinion that the use of a single dictionary will aid in more expeditious and broader international drug use comparisons within a class, and prescribing and use decisions.

As such EMEA also hopes that the use of MedDRA can be endorsed at the level of health care providers in order to avoid disharmony in coding practices and substantial additional workload and costs for recoding and cross terminology mapping efforts especially as the appropriate maintenance mechanisms are put in place that allow a continuous evolution of the terminology according to the specific user needs.