

**PROPOSAL FOR A STANDARDIZED RATING SCALE FOR THE CLASSIFICATION
OF THE SEVERITY OF ADVERSE EVENTS, CHANGES IN
ELECTROCARDIOGRAMS, AND CLINICAL LABORATORY RESULTS**

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**ABSTRACT OF A PRESENTATION AT THE PUBLIC HEARING
RISK MANAGEMENT OF PRESCRIPTION DRUGS
Docket Number 02N-0115**

Background:

The FDA asked the following question in their announcement of this meeting in Section II. Scope of the Hearing, *B. Tools for Risk Management*:

Question:

What new tools can be created to better address specific drug risks?

Answer:

The CFR Section 201.57 states that the label should contain information on the categorization of adverse reactions by severity. In order to comply with this Section of the CFR, there needs to be consistency in the assessment of adverse events, changes in electrocardiograms, and clinical laboratory tests.

A standardized rating scale could be created to gauge the severity of adverse events, changes in electrocardiograms, and changes in clinical laboratory results. This standardized rating scale would be incorporated into all clinical protocols, so that the safety results are consistently categorized during the clinical research process for individual drugs and for all drugs that are in development. The same standardized rating scale would be applied to safety data that is collected during formal post-marketing surveillance studies and to any safety data that is collected during the post-marketing period.

The classification of severity needs to start at the clinical trials stage of drug development. Currently, the assessment of severity or the definition of severity is left to the sponsor. Definitions are usually provided in the clinical protocols but these definitions can differ within a drug development project, between drug development projects, during different stages of development, and from company to company. There needs to be a unified set of standards for rating the severity of adverse events, changes in electrocardiograms, and changes in the clinical laboratory results. This unified set of standards should be accepted and applied uniformly by all companies, investigators,

sponsor-investigators, and they should be incorporated into all clinical protocols and used consistently for all drugs in clinical development.

The adverse events included in the Package Insert are usually from controlled Phase II and Phase III studies. These studies would have been conducted over several years, by multiple investigators, in different geographic locations. There would probably be differences in the protocols, in the experience of the investigators, in study personnel, and the period of treatment would be variable depending on the type of drug, nature of the indication, and objectives of the study. It is likely that the nature of the drug development process would affect the consistency of the classification of severity.

There are two standardized scales available for rating the severity of adverse events, changes in electrocardiograms, and clinical laboratory results. They are the NCI (National Cancer Institute) Common Toxicity Criteria (CTC) and the NIH Division of AIDS Table for Grading Severity of Adult Adverse Experiences. These scales are used in cancer clinical trials and in clinical trials of drugs used to treat HIV infections. There are differences between these two rating scales but they provide an objective classification method. These rating scales could be combined and form the basis for a standardized severity rating scale.

The presentation will discuss the following:

- Lack of consistency in the rating of severity of safety information
- The effect of this lack of consistency on labeling
- Overview of the differences between the available severity rating scales
- The effect of consistency in the rating of the severity of safety information on the understanding of specific drug risks

Timing: about 10 minutes

Presentation is being sponsored by International Pharmaceutical Consultants, Inc., a private pharmaceutical development consulting company.

PUBLIC HEARING
RISK MANAGEMENT OF PRESCRIPTION DRUGS
DOCKET NUMBER 02N-0115

PROPOSAL FOR THE USE OF A
STANDARDIZED RATING SCALE
FOR THE CLASSIFICATION
OF THE SEVERITY OF
ADVERSE EVENTS, CHANGES IN
ELECTROCARDIOGRAMS, AND
CLINICAL LABORATORY RESULTS

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OVERVIEW

- Review severity determinations
- Review the current rating scales
- Review the results of PDR search
- Review selected PIs for use of Rating Scales
- Compare Rating Scales
- Proposal for Standardized or Universal Rating Scale for the determination of severity

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21 CFR 201.57

21CFR Section 201.57 states
that the label (Package Insert)
may contain information on
the categorization of adverse
reactions by severity.

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QUESTIONS

- How is severity determined?
- Is this determination consistent within classes of drugs, among drugs to treat an indication or a disease, among different classes of drugs, among sponsors?
- Are the definitions of severity harmonized within medical disciplines, within countries, between countries?

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QUESTIONS (Cont'd)

An example of a frequently used rating scale:

- MILD: Symptoms which do not interfere with patient's daily activities.
- MODERATE: Symptoms which may interfere with daily activities.
- SEVERE: Events which interrupt patient's usual daily activities.

Is this non-standard, rating scale useful?

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QUESTIONS (Cont'd)

- Can this rating scale be used for all types of drugs?
- Does it add to the understanding of safety results?
- In a multinational development program, will the results be consistent?
- Do these definitions mean the same to a French physician and to a physician in Rockville?

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QUESTIONS (Cont'd)

- Do these definitions mean the same to a cardiologist, to an oncologist, to an internist, to a dermatologist?
- How are these definitions applied to a patient who is hospitalized or has had recent surgery and doesn't have a daily activity?
- How do you apply these definitions to laboratory abnormalities?
- How do you apply these definitions to electrocardiogram abnormalities?

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RATING SCALES

Four rating scales available to describe the severity of adverse events

- NCI Common Toxicity Criteria (CTC) (used in oncology studies)
- NIH Division of AIDS Table for Grading Severity of Adult Adverse Experiences (ACTG Table for Grading the Severity of Adverse Experiences)
- WHO Rating Scale
- ECOG Toxicity Criteria (same as CTC)

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METHODS

- Searched the PDR (CD version Jan 2002) for CTC, NCI, ACTG, ECOG, mild, moderate, and severe.
- In the Package Inserts that contained these terms, the Adverse Events, EKG, and Abnormal Laboratory Sections were reviewed to determine how the different rating scales were used and if they were used consistently.

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RESULTS

- The Package Inserts (PI) that included NCI/CTC were drugs for the treatment of a carcinoma and the PI that included ACTG were drugs for the treatment of HIV infections
- For adverse events, ECOG was the same as NCI-CTC
- Mild, moderate, and severe were found, but in some PI, severe referred to the severity of the presenting disease.

PDR SEARCH RESULTS

PARAMETER	NUMBER OF MONOGRAPHS
Number of Rx Drugs	> 2800
Mild	887
Moderate	700
Severe	1284
ACTG	16
NCI	13
ECOG	8
CTC	5

NEW QUESTIONS

- Was the ACTG Severity Rating Scale used for all of the HIV drugs and was the NCI- CTC scale used for all of the oncology drugs?
- Within the specific therapeutic groups, was the usage consistent?

PURPOSE OF REVIEW

- The purpose was to review the process, not to be critical of any drug or any Package Insert.
- Determine how the severity or intensity of adverse events are displayed in the Package Inserts

Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
VISTIDE	NO	NO
ZIAGEN	Yes, Grades 1-4 lumped together	NO
COMBIVIR	NO	NO, abnormal levels listed, e.g., ALT (>5.0 x ULN)
CRIXIVAN	NO	NO, abnormalities of severe or life threatening intensity, e.g., increased ALT > 500% ULN

Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
EPIVIR	NO	NO, abnormal levels listed, e.g., ALT (>5.0 x ULN)
FORTAVASE	States that main table of adverse events correspond to ACTG Grade 3 and 4	The PI states that there may be exacerbation of chronic liver disease with Grade 4 elevated liver function tests Table displays Marked Laboratory Abnormalities and that this corresponds to ACTG Grade 3 or above
HIVID	Yes, Table displays Adverse Events that were ≥ Grade 3 in ≥ 1% of patients	Yes, Table displays Laboratory Abnormalities that were Grade 3/4

Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
INVIRASE	Main Table displays Adverse Experiences of Moderate, Severe, or Life-threatening Intensity	Yes, Table displays Marked Laboratory Abnormalities, defined as a shift from Grade 0 to at least Grade 3 or from Grade 1 to Grade 4 (ACTG Grading System)
KALETRA	NO, Main Table displays Adverse Events of Moderate, Severe, or Life-threatening Intensity	Yes, Table displays Laboratory Abnormalities that were Grade 3/4 Reported in $\geq 2\%$ of Adult Patients
AGENERASE	YES, incidence of Grade 3 or 4 rash	YES, information on Grade 3 or 4 AST, ALT, amylase, or bilirubin tests

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Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
NORVIR	NO, the Main Table displays Adverse Events of Moderate or Severe Intensity	NO, Table displays Marked Laboratory Abnormalities Reported in $\geq 3\%$ of Adult Patients, e.g., ALT > 215 IU/L
RESCRIPTOR	Majority of adverse events were of mild or moderate (ACTG Grade 1 or 2) intensity and a table of rashes that were of Grades 1, 2, 3, and 4. Also a table of adverse events that were of Moderate to Severe or Life-Threatening intensity	NO, Marked laboratory abnormalities, e.g., ALT > 5 x ULN

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Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
RETROVIR	NO	YES, Table of Frequencies of Selected Grade 3/4 Laboratory Abnormalities, e.g., ALT > 5 x ULN
SUSTIVA	YES and NO, one table with tabulation of Number of Mild, Moderate, and Severe Nervous System Symptoms One table with tabulation of treatment-emergent rashes, with severity expressed in Grade 1, 2, 3, and 4. Grading system used was NCI Grading System One additional table with adverse events of moderate or severe intensity	NO

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Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
TRIZIVIR	YES, Clinical adverse events in Grades 1-4 ($\geq 5\%$ frequency)	NO, selected tests with laboratory abnormalities, e.g., ALT $> 5 \times$ ULN
VIDEX	NO	YES and NO, selected tests with laboratory abnormalities, e.g., ALT $> 5 \times$ ULN and Table of Frequencies of Selected Laboratory Abnormalities (Grade 3/4)
VIRACEPT	NO	Yes, Table displays Marked Laboratory Abnormalities, defined as a shift from Grade 0 to at least Grade 3 or from Grade 1 to Grade 4 (ACTG Grading System)

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Drugs for HIV Infections

Drug Name	Adverse Events	Laboratory Abnormalities
VIRAMUNE	YES and NO, One table with tabulation of rashes, with a comparison of all Grades and Grades 3 and 4 (severe or life-threatening) One table of adverse events without severity information	NO, Marked laboratory abnormalities, e.g., ALT > 250 U/L
ZERIT	NO, listing of adverse events without an indication of severity	YES, Table of Frequencies of Selected (Grade 3/4 Laboratory Abnormalities), e.g., ALT $> 5 \times$ ULN
ZIAGEN	YES, Table of Selected Clinical Adverse Events Grades 1-4 ($\geq 5\%$ frequency)	NO

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ONCOLOGY DRUGS

Drug Name	Adverse Events	Laboratory Abnormalities
GEMZAR	YES, WHO Grade of severity used for adverse events, for combination study adverse events displayed with NCI -CTC-Grades	Yes, WHO Grades of severity used for laboratory abnormalities, for combination study adverse events displayed with NCI -CTC-Grades
NAVELBINE	YES, NCI Grades used, note states that modified NCI Grades used but how modified not mentioned	YES, for selected abnormal laboratory results
HYCAMTIN	YES, NCI Grades used	NCI Grades used for hematology
MUSTARGEN	NO	NO

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ONCOLOGY DRUGS

Drug Name	Adverse Events	Laboratory Abnormalities
PARAPLATIN	NO	NO
DOXIL	Grades used for selected adverse events	Hematology results provided with limits of changes
THIOPLEX	NO	NO
EULEXIN	NO	NO
CASODEX	NO	NO
NILANDRON	NO	NO
PROLEUKIN	YES AND NO. Table of Grade 4 adverse events plus table of adverse events without Grades	NO

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ONCOLOGY DRUGS

Drug Name	Adverse Events	Laboratory Abnormalities
IFEX	NO	NO
COSMEGEN	NO	NO
MITHRACIN	NO	NO
ARIMIDEX	NO	NO
AROMASIN	No, list of adverse events of all CTC grades	YES, for selected tests
TAXOL	YES, Any symptoms and then Severe symptoms, Severe defined as Grade III toxicity or greater	YES and NO
XELODA	YES	NO

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ONCOLOGY DRUGS

Drug Name	Adverse Events	Laboratory Abnormalities
NOLVADEX	NO	NO
HERCEPTIN	Used for Cardiototoxicity, any cardiac dysfunction and Class III-IV	Description of Grade III toxicities for WBC, platelets, and hemoglobin
TAXOTERE	YES	YES, with selected tests
MYLOTARG	YES	YES
GLEEVEC	YES	YES
RITUXAN	YES	YES
TEMODAR	YES	YES, for hematology tests
CAMPATH	YES	YES, for hematology tests
ONCASPAR	YES, for hypersensitivity reactions	NO

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ONCOLOGY DRUGS

Drug Name	Adverse Events	Laboratory Abnormalities
ELLEENCE	YES, for selected events	YES, for selected tests
LEUKINE	YES, for selected events	YES, for selected tests
TRISENOX	YES	YES, for hematology tests
IDAMYCIN PFS	YES, for selected events (WHO Scale used)	YES, for hepatic and renal function (WHO Scale used)
NOVANTRONE	NO	YES, for neutropenia
DAUNORUBICIN	NO	NO
INTERFERON ALFA-2b	YES, uses ECOG Toxicity Criteria, WHO Rating Scale	NO

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RATING SCALES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
NCI-CTC	None or within normal limits	Mild	Moderate	Severe	Life Threatening
ACTG	Not included	Mild	Moderate	Severe	Life Threatening

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Comparison of Rating Scales (AE)

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea CTC	Able to eat	Oral intake significantly decreased	No significant intake, requiring IV fluids	-----
Nausea ACTG	Mild discomfort, maintains reasonable intake	Moderate discomfort, intake decreased significantly, some activity limited	Severe discomfort, no significant intake, activities limited	Minimal fluid intake

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Comparison of Rating Scales (Labs)

	Grade 1	Grade 2	Grade 3	Grade 4
GGT CTC	> 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	> 20.0 x ULN
GGT ACTG	1.25-2.5 x UNL	2.5-5 x UNL	5-10 x UNL	> 10 x UNL
Amylase CTC	1.1-1.5 x UNL	1.5 - 2.0 x UNL	2 - 5.0 x UNL	> 5.0 x UNL or clinical pancreatitis
Amylase ACTG	1.5 x UNL	> 1.5-2.0 x UNL	> 2.0 - 5.0 x UNL	> 10.0 x UNL

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Comparison of Rating Scales (EKG)

	Grade 1	Grade 2	Grade 3	Grade 4
Example of Rating Scale for Electrocardiogram Abnormality				
Prolonged QTc interval (QTc > 0.48 seconds) CTC	Asymptomatic, not requiring treatment	Symptomatic, but not requiring treatment	Symptomatic and requiring treatment	Life- threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
ACTG	Not included	Not included	Not included	Not included

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PROPOSAL

Create a standard or universal rating scale to gauge the severity of adverse events, changes in electrocardiograms, and changes in clinical laboratory results.

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PROPOSAL (Cont'd)

Three rating scales available

- Need to expand and unify the rating scales into one standard or universal rating scale.
- Use the NCI Common Toxicity Criteria (CTC) Scale as a model
- The resulting standard or universal scale should be used consistently in all clinical studies

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PROPOSAL (Cont'd)

This standardized rating scale would be incorporated into all clinical protocols, so that the safety results are consistently categorized during the clinical research process for individual drugs and for all drugs that are in development

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PROPOSAL (Cont'd)

The same standardized or universal rating scale would also be applied to safety data that is collected during formal post-marketing surveillance studies and to any safety data that is collected during the post-marketing period.

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**EFFECT ON
UNDERSTANDING RISKS**

- Databases from clinical trials conducted in different countries, by different investigators could be combined.
- Comparison of safety results among drugs in a class and among classes would be possible
- Comparison of safety results among drugs used to treat a disease or an indication would be possible
- The same rating scale would be used during the development process and during the marketing period

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CONCLUSIONS

- There would be many steps needed to implement this proposal
- Would need to generate and agree on the standardized or universal rating scale and it would need to be accepted.
- At the present time, the data or information doesn't exist
- It would be a prospective project, a point in time would need to be established to start the collection of data so the results could be added to the Package Inserts.

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CONCLUSIONS (Cont'd)

- As MedDRA provides the industry the ability to communicate across borders in describing or coding adverse events, a standardized or universal rating scale for determining severity would further this communication.
- The ability to have consistent safety information would be possible and worth the effort.

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