

RADARS® SYSTEM
DENVER HEALTH AND HOSPITAL AUTHORITY

Draft Guidance for Industry on Assessment of Abuse Potential of Drugs
Comments for Docket No. FDA-2010-D-0026

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March 26, 2010

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The RADARS[®] System appreciates the opportunity to comment on this draft guidance for industry on the *Assessment of Abuse Potential of Drugs* (Docket No. FDA-2010-D-0026). Particular comments are as follows:

Pre-marketing abuse liability testing is appropriate for scheduling decisions because labeling reflects the POTENTIAL abuse liability. However, labeling decisions about the nature of the drug have to be done using real-world data from post-marketing surveillance because labeling is intended to reflect the ACTUAL abuse of the drug.

The statement that information that is not “statistically significant can provide only anecdotal information” (Lines 764-5) is inherently incorrect. Any given study does not have to be statistically significant to be meaningful, nor does statistical significance indicate the quality of the data.

Further, the Agency routinely requests and uses data from “anecdotal” studies such as the RADARS System, National Poison Data System, and others. These studies should also be described using the correct terminology – “observational” studies.

The data sources listed in Lines 744-752 are noted to be Federally-mandated data sources. However, the Agency is noted to currently use both public and private data currently, including claims data from commercial vendors. The fact that a data collection system is not Federally-mandated does not preclude its use.

The Researched Abuse, Diversion and Addiction Related Surveillance (RADARS[®]) System was initiated in 2002 and is owned and operated independently by Denver Health and Hospital Authority, a not-for-profit safety net hospital. The System provides continuous surveillance of the abuse, misuse, and diversion of opioids and stimulants throughout the United States (www.RADARS.org). The RADARS System is composed of multiple Programs, each representing a different perspective on abuse, misuse, and diversion: Drug Diversion (DD), Poison Center (PC), Opioid Treatment (OT), Survey of Key Informants' Patients (SKIP), Impaired Health Care Workers (IHCW), and College Survey (CS) Programs.

As the RADARS System is owned and operated independently, the pharmaceutical company subscribers are not involved in the development of data collection methodology, data collection and reporting, or data interpretation. Subscribers are also prohibited from using RADARS System surveillance data for any purpose other than for risk management activities.

Further benefits of the RADARS System include:

- The availability of population-based programs (College Survey Program) as well event-based programs (all other RADARS System Programs)

- Product-specificity. This is crucial for reporting differences observed due to the presence of abuse deterrent or extended release mechanisms, and between generic and branded products, among others.
- Research questions can be tailored according to the nature of a product's abuse deterrent properties since tracking overall coarse indicators is insufficient.
- Data collected and reported at regular, frequent time intervals (each quarter) with a relatively short lag time (4 months after the end of the quarter of interest)

The agency states in this draft guidance that data sources such as "substance abuse clinics, poison control centers, state boards of pharmacy, medical examiners (ME), police diversion units, ..." contain "information...that is neither systematically acquired nor statistically significant" and can provide "only anecdotal information that a substance is being illicitly used, purchased, sold or diverted." Several of these data sources describe those found in the RADARS System Programs

However, the RADARS System collects data in a systematic fashion and has a rigorous quality assurance program in place to assure that valid, accurate data are reported. This type of rigorous quality assurance program is not described for the Federal data sources cited by the Agency as providing "data on abuse, misuse, overdose and diversion..."

The RADARS System Quality Assurance Program

The RADARS System has an established quality assurance program that incorporates a clear set of quality control steps throughout the data collection and reporting process. Quality assurance programs are a crucial component of any surveillance system. A good quality assurance program consists of planned and systematic actions that ensure the project is performed and data are generated, documented and reported in accordance with Standard Operating Procedures (SOPs) and applicable regulations. The entire quality assurance program ensures accurate data are sent to clients and meets regulatory requirements. This quality assurance program includes (refer to Appendix A):

- *Document Development and Change Control:* Establishment and maintenance of documents is essential to ensure process consistency and regulatory compliance. These documents include Standard Operating Procedures (SOPs), research tools (surveys and questionnaires), study reports, forms and any other crucial documents generated through the conduct of the project. The quality assurance function coordinates the development, implementation and maintenance of controlled documents, ensuring:
 - Documented review and approval prior to implementation
 - Modifications are properly incorporated and tracked (audit trail of changes)
 - Only current versions are used and are readily available to staff
 - Affected personnel are notified and trained as appropriate
 - Tracking of all documents being reviewed
- *Standard Operating Procedures:* Standard Operating Procedures ensure accuracy, uniformity and compliance with applicable regulations and standards. The quality assurance function coordinates SOP management, ensuring:
 - SOPs are written using established templates and guidelines
 - SOPs are readily available to personnel

- SOPs are developed and maintained through a controlled process
- Only current versions are used
- Periodic review of SOPs is conducted to make certain they reflect actual processes
- Affected personnel are trained prior to SOP implementation
- SOP Master List and Master Binder are updated and obsolete versions are archived

In addition, RADARS System staff coordinates the implementation of Standard Operating Procedures for all Program sites and contractors.

- *Quality Control:* The quality assurance program incorporates the following quality control steps that assure the integrity and reliability of the data:
 - Data Entry Verification: provides a reliable start to the entire data collection process by guaranteeing that only accurate data are entered
 - Data Validation: while data entry verification ensures that reported data are entered correctly, additional checks for correctness and compliance with applicable standards, rules and conventions (i.e., data validation) are performed
 - Data Verification: Data submitted by the Programs are verified at different stages of the process (by each Program) prior to and after upload to central database and prior to inclusion in the final reports
 - Final Report Verification: The RADARS System conducts final report verifications to ensure that subscribers receive accurate data. Additional quality control checks are employed to check denominator data for inconsistencies and verify data outputs and statistical analyses.
- *Electronic Systems Control:*
 - Access is limited to authorized individuals
 - Each user has an individual account with a unique and secure User ID/PW combination
 - ID/PW combinations are changed frequently
 - Procedures and controls are in place to prevent the altering, browsing, querying, or reporting of data via external software applications that do not enter through the protective system software
 - Controls are in place to prevent unauthorized access to database servers
 - Controls are in place to prevent, detect, and mitigate effects of computer viruses, worms, or other potentially harmful software
 - Changes to the system (e.g., component replacement) are evaluated and validated according to risk and all changes are documented
 - Data transmission is performed through the use of encryption software, secure ftp site or dedicated fax machines.
- *Training Program:* The quality assurance function implemented a training program to ensure that employees and contractors of the RADARS System are qualified by education, training and experience to perform their assigned tasks. Implementation of the training program specifically involved:
 - Establishing a training plan delineating training requirements for each employee
 - Ensuring compliance with the training plan
 - Creating and maintaining a training database and maintaining supporting documentation

- Maintaining current copies of curriculum vitae / résumés
- *Quality Audits and Monitoring:*
 - Database Quality Audits: On a quarterly basis, the RADARS System Quality Assurance staff performs a Database Quality Audit, following statistically valid sampling schemes, to ensure that data on the final dataset match the source data (surveys or questionnaires) at the Program sites
 - Program Monitoring visits: Performed periodically to assess compliance with agreements and Standard Operating Procedures
 - Internal Audits: Performed periodically to assess compliance with Standard Operating Procedures, standards and regulations
 - Contractor Audits: Performed periodically to assess compliance with agreements and Standard Operating Procedures (if applicable)
- *Corrective Action:* The quality assurance program's Corrective Action component ensures the documentation and proper handling of identified nonconformances:
 - Discrepancies are documented, including a description of the event and how it was discovered
 - An investigation is conducted, focusing on identification of root cause, short term corrections, long term corrective actions and preventive actions
 - Documentation is reviewed and approved by management
 - Error impact analysis is performed
 - Affected parties are notified
- *Database Controls:*
 - Validation: Initial validation consisted of path testing to ensure the system worked as intended (i.e., valid data was accepted and invalid data was rejected).
 - Central Database Internal System Data Validation: The system runs various internal checks at different stages during the upload process to ensure that:
 - 1) data uploaded into tables on a SQL Server have the same format as the source data
 - 2) data are in a consumable format
 - 3) row counts match
 - Database Backup and Disaster Recovery processes: Implemented through the use of IBM's Tivoli Storage Manager Application. Database is backed up nightly to a file system located onsite, and then backup files are copied to a tape system located offsite.
 - Audit Trail: Each instance of an upload is logged into the Central Database logging tables which track the source, reason, the time and date of the attempted upload, and the case counts per drug.

Thank you again for the opportunity to comment on this draft guidance.

Sincerely,
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APPENDIX A

The RADARS[®] System Quality Assurance Program

