CHAPTER 56 – Drug Quality Assurance

SUBJECT: Drug Quality Reporting System (DQRS) (MedWatch Reports); NDA Field Alert Reports (FARs) Revision Note: Program revised 09/11/2015 to update implementation date, completion date, organizational/procedural changes and program contacts.	IMPLEMENTATION DATE September 11, 2015 COMPLETION DATE

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
Industry Codes: 54, 56, 60-66	56021A – DQRS, DRUG QUALITY REPORTING SYSTEM (MedWatch) 56021B – DQRS, NDA-FIELD ALERT REPORTING

FIELD REPORTING REQUIREMENTS:

A. DQRS (MedWatch Reports):

Districts must complete, in a timely manner, their investigations and follow-up to those DQRS (MedWatch) reports, furnished by the CDER Office of Pharmaceutical Quality (OPQ), Office of Quality Surveillance (OQS), Division of Quality Surveillance Assessment, (DQSA), Quality Deviation Assessment Branch (QDAB), that have significant product quality defects (i.e., suspect counterfeits, product contamination, poor packaging, product mix-up, labeling concerns, therapeutic failures). Send an e-mail notification to CDER DQRS Reports. For non-violative inspections generated under this program, when the Establishment Inspection Report is completed in Turbo EIR or replacement system , to the OPQ/OS/DQSA/QDAB. For all violative inspections, documentation should be submitted in MARCS-CMS in accordance with the Regulatory Procedures Manual (RPM).

B. NDA FARs (New Drug Application Field Alert Reports):

The Federal Food, Drug and Cosmetic Act, section 505(k) requires New Drug Application (NDA) holders to provide a Field Alert Report, on distributed drug product, to the Agency with any information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to another article, as well as information concerning any bacteriological contamination, significant chemical or physical changes, product deterioration, or failure of one or more distributed drug product batches to meet their respective specifications.
Notify QDAB when Establishment Inspection Reports (EIRs) are completed in Turbo EIR and send NDA-FARs received from manufacturers under 21 CFR 314.81(b)(1), and 21 CFR 314.98(c) for Abbreviated New Drug Applications (ANDAs), to QDAB by e-mail (cderdqrsreports@fda.hhs.gov) within five working days of district receipt. For all violative inspections, documentation should be submitted in MARCS-CMS in accordance with the Regulatory Procedures Manual.

PART I - BACKGROUND

A. **DQRS (MedWatch Reports):**

The MedWatch program plays a vital role in the post marketing phase of regulating all pharmaceutical products. It has a twofold purpose: 1) to rapidly identify significant health hazards associated with the manufacturing and packaging of pharmaceuticals, and 2) to establish a central reporting system for capturing and identifying drug quality problem areas or trends that may require regulatory action.

Since the early 1970's, the Food and Drug Administration (FDA) has operated a voluntary program specifically directed to health care professionals for the reporting of observed or suspected defects and problems associated with finished drug product in the pharmaceutical supply chain.

Over the years the name of the program has changed. From 1988 to 1993, the program was called the "Drug Quality Reporting System (DQRS)" and the form used for reporting was DQRS Form 3318.

In June 1993, the Food and Drug Administration (FDA) introduced the MedWatch reporting program. It was designed to simplify reporting to FDA by means of consolidating several FDA reporting programs involving drugs, biologics, devices, and medical foods through the use of a single reporting form (FDA 3500/3500A) (Attachment Part VI B) and a toll free telephone/fax number. Although the MedWatch form replaced the DQRS Form 3318, it did not replace the DQRS system and offices in the Center for Drug Evaluation and Research (CDER) that are responsible for evaluating and processing drug quality problems reported to FDA. FDA Form 3500 is used for voluntary reporting by both healthcare professionals and consumers and is the subject of the DQRS program.

Important Note: FDA Form 3500A is used for mandatory reporting of adverse drug events (e.g., 15 day reports for adverse event reporting covered by 21 CFR 314.80) by application holders and is not the subject of the DQRS program. See Compliance Program 7353.001 Postmarketing Surveillance (PMS) and Epidemiology: Human Drugs -Adverse Drug Effects. These reports can be submitted by toll free telephone (1-800-FDA-1088), fax number (1-800-FDA-0178), internet or mail.

FDA currently employs a contractor to operate the MedWatch contract. The contractor receives all MedWatch reports, sends an acknowledgement letter to the reporter and distributes the reports to the various centers according to the product/problem on the report. All reports received concerning **drug quality problems** are forwarded to the OPQ/OQS/DQSA/QDAB.

QDAB is responsible for the review and evaluation of all such drug quality reports, the issuance of prioritized assignments, the monitoring of their status and the review of all DQRS related EIRs and laboratory worksheets. In addition, QDAB conducts trend analyses, and serves as a contact point for field inquiries regarding assignments, and any questions regarding reports from the DQRS data base.

The disclosure section in the FDA MedWatch Form 3500/3500A is of particular importance. If the reporter indicates their preference for anonymity by checking the do not disclose box, then FDA must comply and not disclose the identity of the reporter to the manufacturer.

B. NDA Field Alert Reports (FARs)

The NDA/ANDA Field Alert reporting requirements, 21 CFR 314.81(b)(1)(i) and (ii), became effective on May 23, 1985. The regulation requires holders of NDAs and ANDAs "to submit certain information about distributed drug products" to the jurisdictional FDA district offices within three working days. The 3 working days begins when the applicant becomes aware of a reported problem through either a complaint or internal testing. It does not begin the day the applicant confirms or invalidates a problem. FARs may be reported via telephone or other means of rapid communication with prompt written follow-up. The FAR and its mailing cover should be plainly marked: "NDA-Field Alert Report". Form FDA 3331 (References Part VI A) provides a standardized form for applicants to report.

FARs, in contrast to the "postmarketing reporting of adverse drug experiences" covered by 21 CFR § 314.80, contains a variety of drug quality issues and are of interest to both field and CDER offices.

Quality defect problems reported in FARs involve violative issues and concerns that pose a potential health hazard to the public. These problems include, but are not limited to, matters concerning dissolution failures, impurity levels, mislabeling and sub/super potency of distributed drug products and articles. If the applicant holder can invalidate the problem (e.g. problem was due to an analytical laboratory error) within 3 working days, a FAR is not required. For guidance on investigating out of specification (OOS) test results, see *Investigating Out-of-Specification Test Results for Pharmaceutical Production*. If the applicant holder determines that further investigation is required or a corrective action is initiated (e.g. formulation revision, labeling change, etc.), a FAR must be submitted.

Criteria for when a FAR must be submitted by the NDA/ANDA holder include but are not limited to:

- Any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article
- Bacterial contamination
- Significant chemical, physical or other changes

- Product deterioration
- Failure of one or more distributed batches of drug products to meet the specification established in the application.

Foreign NDA/ANDA holders must follow the same criteria for FAR reporting (as used for domestic sites) for drug products manufactured overseas according to the specifications of an NDA/ANDA and/or distributed in foreign markets. Foreign application holders are required to have a U.S. Office/Agent (21 CFR 314.50(a)(5) who is responsible for reporting to the FDA. The U.S. agent shall follow the same guidelines for FAR submission, reporting within 3 working days to the jurisdictional district office where a problem occurred. In the case of an involved foreign facility, the U.S. agent shall submit the FAR to the district office where the U.S. agent is located.

QDAB is the CDER focal point to receive, evaluate, and forward FAR reports to the appropriate CDER review divisions and other headquarters offices for follow-up and further evaluation. FARs are entered into the DQRS database for tracking and trending purposes.

C. Miscellaneous Reports

Certain selected reports of suspected product problems received at headquarters from various external sources (consumers, trade, professional, etc.) are being routed to QDAB for evaluation and may be included under this compliance program.

Reports which clearly do not fall under the purview of this program, i.e. veterinary products, are forwarded to the appropriate FDA units for their evaluation and follow-up. Reports involving food products or supplements and vitamins are referred to the jurisdictional district office for their information, and a copy of the report is provided to CFSAN. Reports involving biological products (which are not under CDER regulatory authority) or medical devices are provided to CBER or CDRH.

[end of Part I]

PART II - IMPLEMENTATION

A. OBJECTIVE

To reduce public health risk by quickly identifying drug quality defects in the market place which may require corrective action.

- Assure the timely evaluation of drug quality defect reports -- NDA Field Alert and DQRS reports.
- Provide guidance to the field for processing and handling FAR, and DQRS reports.
- Provide guidance to the field regarding FAR and DQRS follow-up and for-cause inspections.

B. PROGRAM MANAGEMENT INSTRUCTIONS

DQRS (MedWatch Reports):

QDAB will issue assignments to the appropriate district by e-mail to obtain specific information about a reported problem. An information copy of the assignment will be sent to the analyzing laboratory when it is identified.

A computer generated report (in lieu of a copy of the original report e.g. a MedWatch report) is forwarded with the assignment, to the district offices. The computer generated DQRS report contains all of the information reported on the original MedWatch form, except for the reporting person's signature. Some reports will require immediate attention, e.g. suspected imminent health hazard.

Following the review and evaluation process of DQRS Reports, QDAB, assigns a priority classification for follow-up investigation by the responsible district office. The priority classification (P1, P2, P3) are listed below. All DQRS and miscellaneous reports are given a priority code, defect classification code and an MSB file reference number. MSB refers to the Manufacturing Surveillance Branch (MSB) which no longer exists. However, the use of "MSB" continues. The MSB file reference number consists of the last two digits of the fiscal year followed by a sequential number, e.g. 11-02046. The priority codes are assigned as follows.

DQRS reports that require immediate attention such as a death report (P1) or suspected imminent hazard will be communicated to the District Director or the Director, Investigations Branch.

DQRS Priority classification codes are assigned as follows:

a.) **Priority 1 (P1)** reports are defined as imminent or serious health hazards, or significant violations of current Good Manufacturing Practices (CGMP). Inspections or follow-up for P1s have a target completion date not to exceed 15 calendar days. Serious health hazards include (but not limited to):

- A death has or possibly could occur if the drug is used
- The product could cause harm to the patient this includes but is not limited to products that may cause serious harm due to super-potency, sub-potency, dissolution, labeling and/or packaging errors
- Suspected counterfeit
- Serious CGMP violations exist that could represent a risk to the public, if left uncorrected (e.g. possible product contamination, incorrect container).

b.) **Priority 2 (P2)** reports are defined as significant CGMP violations that do not represent a potential health hazard. P2 reports require inspectional follow-up or evaluation within 60 days

- Reported quality defects are potentially significant CGMP problems that do not represent a potential health hazard

c.) **Priority 3 (P3)** reports are defined as follows:

- Problem appears to be isolated, or of a cosmetic nature that does not involve a potential health hazard, or any significant violations, e.g. broken container, shortage of tablets or capsules in a container, faded tablets, container label print quality, or corrective actions have already been taken by the firm.
- P3 reports require follow-up by the appropriate district at the next regularly scheduled inspection.

NDA Field Alert Reports (FARs)
Since Field Alert Reports are initially submitted to the district office, these reports do not receive priority codes. FDA Forms 3331 are sent from the district to the cderdqrsreports@fda.hhs.gov mailbox for evaluation and follow-up, along with any district recommendations, and Health Hazard Evaluations from the firm. When additional information regarding FARs is needed, QDAB will contact the appropriate district office for additional investigation and inspectional follow-up.

This compliance program does NOT include instructions for drug quality complaints received directly by the district offices from consumers (consumer complaints), health professionals, etc. The districts should process and act upon those reports in accordance with established quality management systems and procedures within their organizational entities.

C. DISTRICT RESPONSIBILITIES

To designate a Drug Defect Reporting Monitor or Drug Field Alert Monitor who is responsible for either the DQRS program, FAR program, or both programs in order to maintain continuity in these programs. It is recommended that each district establish and maintain a district DQRS/FAR e-mail mailbox account for receipt of DQRS and FAR reports and related correspondence from QDAB.

DQRS (MedWatch Reports):

QDAB prioritizes DQRS reports of product quality defects and sends the reports by e-mail to the districts for further evaluation and inspectional follow-up based on the priority (see above Part II B. a., b., and c.). The district should notify QDAB (cderdqrsreports@fda.hhs.gov) if they have any information, such as a recent inspection, that could change the initial priority classification assigned by QDAB.

Districts should notify QDAB if a DQRS report is received for a manufacturer that is not located in their jurisdiction by returning the DQRS report to QDAB through the cderdqrsreports@fda.hhs.gov mailbox or forwarding the report to the appropriate district and copying the cderdqrsreports@fda.hhs.gov mailbox.

District should:

1. Contact QDAB by e-mail (cderdqrsreports@fda.hhs.gov) concerning any drug quality complaints received directly by the district from health care professionals and consumers.
2. Account for the receipt and disposition of all DQRS assignments with their respective DQRS report and exhibits received from QDAB.
3. Keep QDAB informed of the status of P1 and P2 DQRS assignments by communicating when an assignment is completed. Forward any new relevant information concerning the DQRS report to QDAB. This can be done via the cderdqrsreports@fda.hhs.gov mailbox and copying the initiator of the assignment. Any communication should include the MSB number assigned to the DQRS report.
4. Forward a copy of any follow-up DQRS investigations and summaries of analytical findings to QDAB for evaluation and inclusion into the DQRS database.

NDA Field Alert Reports:

1. The district coordinator is encouraged to set up a DQRS/FARs e-mail box dedicated to receiving field alert reports from the firms in their district. Firms should be instructed to send all FARs to this one mailbox. This would eliminate FARS going to other areas in the district office e.g. to the recall coordinator.
2. It is recommended that the district coordinator is to serve as the district's contact point to facilitate communications with an applicant holder on matters pertaining to the status of a field alert (i.e. initial and final status of FAR or FDA Form 3331) and with QDAB.
3. Send each FAR (initial, follow-up and final) to CDER DQRS Reports **within five working days after receipt from the firm**.
4. Contact applicants, if necessary, to obtain additional information to include any CAPAs, and request a time line for initiating or completing their investigation.

5. Perform assessments of all FARs (initial, follow-up, and final) and provide them to cderdqrsreports@fda.hhs.gov mailbox. For the assessments, determine if the firm's root cause analysis and corrective and preventive actions, as stated on the FARs and any subsequent District follow-up, are adequate to mitigate risk, and comply with FDA regulations.
6. For districts dealing with a U.S. agent submitted FAR, please submit the FAR to the cderdqrsreports@fda.hhs.gov mailbox with a copy to OMPTO at ORAHQFAR@fda.hhs.gov. On an as needed basis instruct U.S. agents in your district about the proper method for submission of FARs involving foreign facilities. (See NOTE Part I C.)

[end of Part II]

PART III – INSPECTIONAL

A. DQRS (MedWatch Reports):

Investigations should determine the validity of the problem reported and it may include a CGMP inspection based on the investigator's findings. Unless otherwise instructed in the assignment, follow-up inspections for DQRS reports should collect the following information:

- Validity and extent of the reported problem
- Product(s) (including lot numbers) affected
- Management's knowledge of and response to the problem prior to the investigation*
- Root cause(s) of problem(s)
- Action(s) taken by management to correct the problem
- Corrective action and preventive action plans (CAPA)

* QDAB furnishes a computer-generated report along with a letter to the manufacturer/marketer of the product(s) identified in the DQRS report (except when a report indicates a product is injudicious, e.g., fraudulent, counterfeit, etc.). The letter includes the MSB file reference number of the DQRS report and a statement that FDA considers the report as part of their complaint file under 21 CFR 211.198, and the report might also fall under the manufacturer's reporting obligations under 21 CFR 314.81(b)(1).

NDA Field Alert Reports

1. Districts must ensure that applicant holders are submitting FARs as required by 21 CFR 314.81(b)(1)(i) and (ii).
2. As part of the district's preparation for inspections, review any FARS (and relevant DQRS reports) to be covered while on inspection. Two weeks prior to the inspection, the district should request through CDER DQRS Reports the FAR history associated for a specified firm and drug product from QDAB.
3. For investigations which involve Out of Specification results for finished marketed products, the district should ask if the firm submitted any FARs to the Agency.
4. For FARs that affect more than one product, firms should submit one FAR per NDA/ANDA of distributed product. Multiple lots of the same product may be submitted on one form.
5. When reviewing Standard Operating Procedures (SOPs) during inspections, note the firm's handling and reporting of NDA FARs to ensure their compliance with 21 CFR 314.81(b)(1)(i) and (ii).
6. Failure of a firm to submit an NDA/ANDA FAR for distributed violative product is reportable as an FDA-483 observation.
7. Investigators, in conjunction with Field Alert Monitors, should attempt to determine if the firm's root cause analysis, as stated in any FAR has been thoroughly investigated. The

firm's investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. They should also determine if the corrective and preventive actions (CAPA) are adequate to mitigate risk.

[end of Part III]

PART IV - ANALYTICAL

Analytical chemical and microbial sample analysis in the NDA FAR and DQRS report under 7356.021A/B programs may be requested on an ad hoc basis. All sampling and collection assignments should be entered into FACTS.

A. ANALYZING LABORATORIES

1. ORA Field Laboratories are designated to conduct regulatory sample analysis under 7356.021A/B. When samples are sent to the ORA Field Labs for analysis, the investigator should communicate with the Office of Regulatory Science prior to sample collection as well as to the Field laboratory to determine the exact sample size needed for analysis. The following laboratories have been provided for:

   a. Chemical Testing Laboratories: NRL, PHI-DO, SRL, SJN-DO DET-DO, PRL-SW

   b. Radioactive Drugs: WEAC

   c. General Microbiology: NRL, SRL, PRL-SW, SAN-DO and DEN-DO

   d. Sterility: NRL, SRL, SAN-DO, DEN-DO

   e. Endotoxin Testing: NRL, SRL, SAN. DEN

   f. Nutrient Testing: Atlanta Center Nutrient Analysis (ACNA)

2. CDER Servicing Laboratories

   Office of Pharmaceutical Quality, Office of Pharmaceutical Science, Office of Testing and Research, Division of Pharmaceutical Analysis, 645 Newstead Ave., St. Louis, MO 63110

B. Methodology

Drug samples will be analyzed as regulatory samples for drug quality or microbial contamination by either the USP methodology or by the (NDA/ANDA) firm's method if it is more stability indicating. Specified methodology used in analysis will depend on factors, such as limit of detection, limit of quantitation, as well as the specificity and nature of the problem for which the product is being tested.

For questions about methodology or which tests to conduct, contact ORA/Office of Regulatory Science or the CDER/OPQ/OQS/DQSA/QDAB.

C. Sample Collections

QDAB will issue an ad hoc sample assignment in FACTS to the districts to collect samples for testing under 56021A DQRS Reports or 56021 B for NDA Field Alerts.
Sample sizes will depend upon the nature of the product to be analyzed and the tests selected for analyses. For questions on specific sample sizes, the districts should contact the appropriate ORA servicing laboratory. (See the IOM chapter 4.1.4 and 21 CFR 2.10 for additional information on official samples)

D. **Reporting Instructions**

Samples collected under NDA Field Alert should be reported under 56021A for DQRS and 56021B NDA FARs.

Ad hoc samples are to be entered into FACTS and flagged with the appropriate MSB file reference number. All worksheets generated by this program should be routed through your supervisor. A copy of the sample summary and worksheets should be forwarded to QDAB CDERDQRSREPORTS@fda.hhs.gov.

[end of Part IV]

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Unless an inspection results in the documentation of an egregious high risk violation where the agency was not notified of the incident as required by the regulations, generally an advisory action would be the first choice of regulatory action for violations covered under this compliance program.

However, it is recommended that for NDA/ANDA FAR, significant violations (under or lack of reporting) should be included in recommendations for advisory actions due to other violations of the Act (CGMP, ADE, or unapproved drugs) and should be sent in MARC-CMS to CDER'S OPQ/OQS/DQSA. Consult additional compliance programs related to the violation in determining if a regulatory action is appropriate.

The following NDA/ANDA Field Alert Reporting violations should be considered for inclusion in a CGMP, ADE, or other recommendation for an advisory action:

The following citations should be used for violations related to this Compliance Program:

a) In cases where the evidence relates to a labeling violation:

Failure to submit an NDA Field Alert Report in compliance with 21 CFR 314.81(b)(1)(i). Applicants must submit information about distributed products within three days of learning about any incident that causes the drug product or its labeling to be mistaken for, or applied to another article.

b) In cases where the evidence relates to any bacteriological contamination, or any significant chemical, physical, or other change in distributed product, or any failure to meet specifications:

Failure to submit an NDA Field Alert Report in compliance with 21 CFR 314.81(b)(ii). Applicants must submit information about distributed products within three days of learning about bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application.

Under 21 CFR 314.50(a)(5), the applicant's attorney, US Agent, or authorized official must submit an NDA FAR for their client (applicant), who is importing to the United States, to the District Office where the Corporate Headquarters is situated.

[end of Part V]

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES
NDA Field Alert Reporting – 21 CFR 314.81(b)(1)(i) and (ii)
ANDA Field Alert Reporting – 21 CFR 314.98(c)
FDA Form 3331 – New Drug Application Field Alert Report
Investigating Out-of-Specification Test Results for Pharmaceutical Production

B, LINKS: MedWatch 3500 and MedWatch 3500A
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm2007307.htm

C. CONTACTS:

Office of Regulatory Affairs (ORA)

- **(ORA/Office of Operations (OO)/Office of Medical Products and Tobacco Operations (OMPTO)**

ORAHQDrugInspectionPOC@fda.hhs.gov

- **ORA/OO/Office of Regulatory Science**

Ian Paul Mayers – General Chemistry
Telephone: (301) 796-6552
Angele Smith – General Microbiology & Sterility
Telephone (301) 796-6133

CDER

CDER Office of Pharmaceutical Quality (OPQ), Office of Quality Surveillance (OQS), Division of Quality Surveillance Assessment (DQSA), Quality Deviation Assessment Branch (QDAB)
E-mail: cderdqrsreports@fda.hhs.gov

[end of Part VI]

PART VII - CENTER RESPONSIBILITIES

DQRS (MedWatch Reports):

The CDER Office of Pharmaceutical Quality (OPQ), Office of Quality Surveillance (OQS), Division of Quality Surveillance Assessment, (DQSA), Quality Deviation Assessment Branch (QDAB) will:

1. Receive, evaluate and code DQRS Reports for significant product quality defects and provide them to the Field for further evaluation and inspectional follow-up.
2. Issue an e-mail and FACTS assignment along with the DQRS report, to the district offices. Upon request from the district, CDER will issue a computer generated report containing all of the information reported on the original MedWatch form except for the reporter's signature.
3. Provide assurance that assignments will contain sufficient data for the field to evaluate the nature and extent of the problem/product being investigated; monitor the status of all assignments; and serve as a point of contact for field inquiries.
4. Request e-mail updates and phone numbers of DQRS coordinators for each district and their designated alternate's emails and phone numbers on an annual basis.
5. Notify Division of Medical Products and Tobacco Inspections (DMPTI) District Directors (DD) and the Directors of Investigations Branch (DIBs) of DQRS Reports that require immediate attention, such as a death report (P1) or suspected imminent hazard.

NDA Field Alert Reports:

1. When requested, QDAB will provide district offices with a summary listing of NDA/ANDA FAR reports of specific manufacturers and drug products to facilitate the drug inspection process.
2. Collaborate with ORA headquarters and district offices on Field Alert investigations and inspectional follow-ups.
3. Prepare and issue sampling assignment in FACTS (for ad hoc or directed samples).
4. Work with the ORA Field, Headquarters, district offices, and different FDA Centers to facilitate resolution of product quality defect issues.

Note: For both Field Alert Reports and DQRS, QDAB will notify the district if it is determined that a directed or for cause inspection assignment is warranted.

[end of Part VII]

[end of Program]