
PROGRAM DESCRIPTION

OFFICE OF PHARMACEUTICAL QUALITY
Understanding CDER's Risk-Based Site Selection Model

Table of Contents

PURPOSE	1
BACKGROUND	1
POLICY	3
RESPONSIBILITIES	6
PROCEDURES	6
REFERENCES	8
DEFINITIONS	8
EFFECTIVE DATE	8
CHANGE CONTROL TABLE	9

PURPOSE

This MAPP outlines how the Office of Pharmaceutical Quality will manage the Site Selection Model (SSM) used by Center for Drug Evaluation and Research (CDER) staff to prioritize manufacturing sites for routine quality-related (i.e., current good manufacturing practice (CGMP)) surveillance inspections.

BACKGROUND

- FDA implemented the risk-based approach to prioritizing human drug manufacturing sites for routine CGMP surveillance inspection in FY 2005. It was one of many outcomes from the initiative Pharmaceutical Quality for the 21st Century — A Risk-Based Approach. The FY 2005 SSM replaced the previous approach, which was primarily based on the biennial inspection frequency for domestic sites as previously established in section 510(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360(h)).
- The Food and Drug Administration Safety and Innovation Act of 2012 amended section 510(h) of the FD&C Act, replacing the fixed minimum inspection interval for domestic establishments (i.e., sites)¹ with the requirement that FDA inspect domestic *and* foreign drug establishments “in accordance with a risk-based

¹ In this MAPP, the terms establishment, site, and facility are used interchangeably and cover physical locations subject to FDA drug manufacturing regulations and statutory authority.

schedule” that considers establishments’ “known safety risks.” This defined a risk-based inspection frequency for all sites, regardless of location, to promote parity in inspectional coverage and the effective and efficient use of FDA resources to address the most significant public health risks. The statutory change largely adopted the SSM criteria in use since FY 2005; however, it allowed FDA to place less emphasis on a set frequency of inspection.

- The October 2022 update of the *Compliance Program 7356.002 — Drug Manufacturing Inspections* added an objective to gain insight into the effectiveness of a drug manufacturer’s quality system in exceedance of CGMP requirements.
- The Food and Drug Omnibus Reform Act of 2022 amended section 510(h)(4) of the FD&C Act. It added a risk factor for establishments related to the compliance history of establishments in the country or region in which the establishment is located.
- The Office of Quality Surveillance (OQS), within CDER’s Office of Pharmaceutical Quality (OPQ), is responsible for producing CDER’s Site Surveillance Inspection List (SSIL) that prioritizes sites for surveillance inspections. This list is developed by inputting sites from CDER’s Catalog of Manufacturing Sites into the SSM. Subject sites are ranked by the CDER SSM so that the higher risk sites are assigned to the Office of Regulatory Affairs (ORA) for surveillance inspection.
- The number of sites assigned varies depending on FDA capacity as determined by multiyear resource planning with ORA.
- The SSM considers risk related to drug (drug substance and finished product) quality as may arise from violations of the CGMP requirements in the FD&C Act section 501(a)(2)(B) (21 U.S.C 351(a)(2)(B)) and related regulations (e.g., 21 CFR parts 210 and 211).
- The list of sites prioritized by the model includes sites in the CDER Catalog of Manufacturing Sites that are subject to routine surveillance inspections, as determined by section 510 of the FD&C Act. The CDER Catalog of Manufacturing Sites is composed of sites that commercially manufacture a finished pharmaceutical (drug product), an in-process material, or an active pharmaceutical ingredient (API; drug substance) for use in a drug intended for humans.
- The following types of sites are excluded from prioritization by the CDER SSM described in this MAPP:

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- Human drug compounding outsourcing facilities registered under section 503B of the FD&C Act (21 U.S.C. 353b), because the inspection schedule for these sites is established by a separate CDER selection process
 - Medical gas sites, which are managed by a separate selection process
 - Inactive ingredients (excipients) (may be inspected when deemed necessary)
 - Drugs intended for use only in clinical trials (may be inspected when deemed necessary)
 - The SSM and the databases it uses are the subject of continuous improvement programs. OQS solicits internal feedback from its FDA business partners yearly. In addition, at the time of the last significant revision, the SSM was subjected to external peer review from experts in academia. Finally, statistical analyses are used to assess the correlation between certain outcomes and current and prospective risk factors. All of this informs continuous improvement of the model. The current governance structure for the model includes a cross-functional, model improvement working group and a steering committee that reviews proposed changes to the model.
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POLICY

1. Introduction

- 1.1 OQS will use the SSM, with defined risk factors, to generate the SSIL. The SSIL only prioritizes sites for scheduling routine surveillance inspections, not other inspection types.² Goals of the surveillance inspection program, as defined in *Compliance Program 7356.002 — Drug Manufacturing Inspections*, are to ensure that sites consistently manufacture drug products of acceptable quality and minimize consumers' exposure to adulterated drug products in accordance with requirements under sections 510 and 704 of the FD&C Act (21 U.S.C. 360 and 374). More specifically, the objectives of the program are:
- a) Determine whether inspected establishments are operating in compliance with applicable CGMP requirements and, if not, provide the evidence for actions to prevent adulterated products from entering the market. As appropriate, remove adulterated products

² Inspection types other than surveillance are (1) preapproval, (2) postapproval, and (3) for-cause (see concept of operations white paper *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*).

from the market, and take action against persons [(including firms)] responsible.

- b) Provide an assessment of establishments' conformance to CGMP requirements for Agency decisions.
 - c) Gain insight into the effectiveness of a drug manufacturer's quality system. In addition, it may inform understanding, to the extent possible, of practices at a facility that not only support meeting CGMP compliance requirements to establish and maintain a robust state of control but also promote a quality culture that allows for exceeding this standard.
 - d) Provide input to establishments during inspections to improve their compliance with regulations.
 - e) Better understand current practices in drug manufacturing for the purpose of updating the CGMP requirements, regulatory policy, and guidance documents.³
- 1.2 A goal of using the SSM is to achieve parity in inspection frequency for sites with equivalent risk scores, regardless of product type (e.g., whether originator, generic, over-the-counter monograph, or biosimilar).

2. Risk Factors

- 2.1 The SSM will use risk factors consistent with section 510(h)(4) of the FD&C Act. This provision identifies specific risk factors and allows FDA to determine additional ones, as follows:
- a) The compliance history of the establishment.
 - b) The record, history, and nature of recalls linked to the establishment.
 - c) The inherent risk of the drug or device manufactured, prepared, propagated, compounded, or processed at the establishment.
 - d) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 of this title [the FD&C Act (21 U.S.C. 374)] within the last 4 years.
 - e) Whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809 of this title [the FD&C Act (21 U.S.C. 384e)].

³ This list is a quote from *Compliance Program 7356.002 —Drug Manufacturing Inspections*.

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- f) The compliance history of establishments in the country or region in which the establishment is located that are subject to regulation under this Act [the FD&C Act], including the history of violations related to products exported from such country or region that are subject to such regulation.
 - g) Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources.⁴
- 2.2 OQS will use the SSM to generate a risk score for each site. Risk factors are based on either empirical evidence collected by FDA, subject matter experts' judgment, or a combination of both. The following are currently identified as risk factors for inclusion in the SSM:
- a) Site type (e.g., manufacturer, packager only, control lab only)
 - b) Time since last surveillance inspection (or if the site was never previously inspected)
 - c) FDA compliance history
 - d) Compliance history of the country or region
 - e) Foreign regulatory authority inspectional history (with an authority deemed capable under section 809 of the FD&C Act)
 - f) Patient exposure (using available information such as data submitted pursuant to section 510(j)(3) of the FD&C Act (21 U.S.C 360(j)(3)) as added by the Coronavirus Aid, Relief, and Economic Security Act (CARES Act))
 - g) Hazard signals (such as Field Alert Reports, Biological Product Deviation Reports, MedWatch reports,⁵ recalls, etc.)
 - h) Inherent product risk:
 - i. Dosage form
 - ii. Route of administration

⁴ This list is a quote from 510(h)(4) of the FD&C Act, as amended by section 3613 of the Food and Drug Omnibus Reform Act of 2022.

⁵ MedWatch collects adverse drug event reports from consumers, physicians, and pharmacists — the subset of these deemed potentially related to manufacturing quality are forwarded to OQS for individual evaluation and are also used in the model.

- iii. Products intended to be sterile
- iv. API load (i.e., concentration of API in dosage form or unit dose)
- v. Biologic drug substance or drug product
- vi. Therapeutic class
- vii. Therapeutic index or range (e.g., narrow therapeutic index drugs)
- viii. Emergency use drugs (e.g., epinephrine)

3. Continuous Improvement of the Model

- 3.1 The SSM governance process requires that CDER and ORA annually review and approve changes to the SSM. This process encourages continual improvement by assessing the SSM's risk factors, weights, and methodology and then identifying areas for improvement and modification. Changes are supported scientifically by input from expert teams and may include updated data, new data sources, and/or revised methodology. When appropriate, this annual review includes research and additional studies to better assess the current model and impacts of change.

RESPONSIBILITIES

- OQS provides site and product data for input into the SSM. OQS also implements the SSM, supports the subsequent program of inspections, and manages review and continual improvement of the model. In addition, OQS issues the SSIL assignment within its Surveillance Action Plan (SAP), tracks inspection accomplishments, and issues quarterly SAP progress reports. Throughout the year, OQS processes site removal requests from ORA.
- ORA plans, tracks, and conducts inspections.⁶

PROCEDURES

- 1. Running the SSM and Generating the SSIL

⁶ This MAPP is intended for CDER staff; ORA is included for completeness only.

- 1.1 OQS identifies data discrepancies by reviewing and preparing the SSM. These are forwarded to the respective data set owners for resolution.
- 1.2 OQS runs the SSM for sites in the CDER Catalog of Manufacturing Sites. The SSM generates risk scores for each site that are used to prioritize the sites.
- 1.3 OQS performs a quality control assessment of the list.
 - a) Sites are identified in which the last inspection was classified as final official action indicated (OAI). The list of OAI sites is reviewed by ORA, OQS, and CDER's Office of Compliance for concurrence and the confirmed OAI sites are removed from routine surveillance inspection planning (i.e., OAI site reinspection is determined as part of the enforcement effort).
 - b) Sites currently on import alert are removed from routine surveillance inspection planning.
 - c) Any site that is newly registered, or otherwise without any prior routine surveillance inspection, is assigned and prioritized for inspection regardless of risk score. OQS may collaborate with ORA to verify that a new site is, in fact, subject to routine surveillance inspection.
- 1.4 The SSIL is shared with ORA through the SAP.
2. Tracking the Process of Planning and Conducting of Inspections
 - 2.1 ORA plans and conducts inspections assigned based on the SSIL.
 - 2.2 OQS tracks the accomplished inspections and provides quarterly updates through the SAP.
3. Site Removals: ORA can request removal of a site from the SSIL.
 - 3.1 OQS will investigate the reasons for the removal request.
 - 3.2 If the request is a result of a recent inspection that was performed after the SSIL was generated, the removal will be implemented upon confirmation that the CGMP inspection has been completed.
 - 3.3 If the removal is requested because of a change in a site's operational status (e.g., the site has gone out of business) or discrepancies between FDA's understanding of the site and the site's claims (e.g., the site claims

to no longer produce drugs for the U.S. market), then the removal can only take place if the OQS investigation confirms that FDA's information needs to be revised and the discrepancy between FDA and the site is corrected.

REFERENCES

- Compliance program *Compliance Program 7356.002 — Drug Manufacturing Inspections* (October 2022)
 - Concept of operations white paper *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations* (June 2017)
 - Final report *Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach* (September 2004)
 - Progress report *Pharmaceutical Quality for the 21st Century — A Risk-Based Approach* (May 2007)
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DEFINITIONS

- **Site Selection Model (SSM):** a risk management tool that supports a consistent, science-based approach for allocating inspectional resources for routine surveillance CGMP inspections.
 - **Site Surveillance Inspection List (SSIL):** the output list of prioritized sites from the SSM that are selected for inspection as part of the routine surveillance human drug *Compliance Program 7356.002 — Drug Manufacturing Inspections*.
 - **Surveillance Action Plan (SAP):** the Office of Quality Surveillance product that includes the SSIL and has quarterly progress reports.
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EFFECTIVE DATE

- This MAPP is effective upon date of publication.
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CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/26/18	Initial	N/A
6/26/23	Rev. 1	Updated to include FDORA 2022, CARES Act, and quality system effectiveness; updated OS to OQS; made nonsubstantive, editorial changes