

PROGRAM DESCRIPTION

Office of Pharmaceutical Quality

Understanding CDER’s Risk-Based Site Selection Model

Table of Contents

PURPOSE.....1
BACKGROUND1
POLICY.....3
RESPONSIBILITIES5
PROCEDURES5
REFERENCES.....6
DEFINITIONS6
EFFECTIVE DATE.....7
CHANGE CONTROL TABLE.....7

PURPOSE

This MAPP outlines the policies and procedures for the Site Selection Model (SSM) used by CDER staff to prioritize manufacturing sites for routine quality-related (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 FY2005. It was one of many outcomes from the initiative *Pharmaceutical Quality for the 21st Century — A Risk-Based Approach*. The FY2005 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).
- The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 amended section 510(h) of the FD&C Act, replacing the fixed minimum inspection interval for domestic establishments (i.e., sites) with the requirement that FDA inspect domestic *and* foreign drug establishments “in accordance with a risk-based 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

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- largely adopted the SSM criteria in use since 2005; however, it allowed FDA to place less emphasis on a set frequency of inspection.
- The Office of Surveillance (OS), within the 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)) 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:
 - Human drug compounding outsourcing sites registered under section 503B of the FD&C Act, 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. OS solicits internal feedback from its FDA business partners yearly. In addition, 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 to review proposed changes to the model.
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POLICY

1. Introduction

OPQ will use an SSM, with defined risk factors, to generate the SSIL. The SSIL only prioritizes sites for scheduling routine surveillance inspections, not other inspection types.¹ Goals of the surveillance inspection program, as defined in Compliance Program 7356.002, 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. More specifically, the objectives of the program are:

- To determine whether inspected firms (i.e., sites) are operating in compliance with applicable CGMP requirements, and if not, to provide the evidence for actions to prevent adulterated products from entering the market; as appropriate, to remove adulterated products from the market, and to take action against persons (including firms) responsible;
- To provide an assessment of firms' conformance to CGMP requirements for Agency decisions;
- To provide input to firms during inspections to improve their compliance with regulations; and
- To better understand current practices in drug manufacturing for the purpose of updating the CGMP requirements, regulatory policy, and guidance documents.

Within the context of the Compliance Program, one goal of the SSM is to achieve parity in inspection frequency, meaning equal frequency for sites with equivalent risk, regardless of geography (foreign versus domestic), or product type (e.g., whether originator, generic, or OTC monograph).

2. Risk Factors

2.1 Introduction

The SSM will use risk factors consistent with section 510 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 manufactured, prepared, propagated, compounded, or processed at the establishment.

¹ Inspection types other than surveillance are (1) preapproval, (2) postapproval, and (3) for-cause (see FDA 2017b).

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- d) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 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.
 - f) Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources.

OS will use the SSM to generate a risk score for each site. Scoring of risk components is 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) Foreign regulatory authority inspectional history (with an authority deemed capable under section 809 of the FD&C Act).
- e) Patient exposure.
- f) Hazard signals (such as FARs, BPDRs, MedWatch reports,² recalls, etc.).
- g) Inherent product risk:
 - i. Dosage form.
 - ii. Route of administration.
 - iii. Products intended to be sterile.
 - iv. API load (concentration of API in dosage form or unit dose).
 - v. Biologic drug substance or drug product.
 - vi. Therapeutic class.
 - vii. Narrow Therapeutic Index (NTI) drugs.
 - viii. Emergency use drugs.

3. Continuous Improvement of the Model

² FAR stands for "Field Alert Report;" BPDR stands for "Biological Product Deviation Report." MedWatch collects adverse drug event reports from consumers, physicians and pharmacists — the subset of these deemed potentially related to manufacturing quality are forwarded to OS for individual evaluation and are also used in the model.

The SSM governance requires an annual review and approval process wherein CDER and ORA jointly assess the model. There is continual improvement such that the risk factors, weights, and methodology of the recently executed SSM are assessed and areas for improvement, modification, and enhancement are identified. This involves reviewing the methodology, risk factors, and weights used in the model, assessing the current version of the model, recommending modifications (if any) to the model (including updated data, new data sources, and/or revised methodology), forming necessary expert teams, and conducting necessary research and studies (where applicable) in order to scientifically support proposed SSM modifications.

RESPONSIBILITIES

- **OPQ/OS.** The Office of Surveillance provides site and product data for input into the SSM and processes site removal requests from ORA throughout the year. OS also implements the SSM, supports the subsequent program of inspections, and manages continual review and improvement of the model. In addition, OS issues the assignment as an SSIL within its Surveillance Action Plan (SAP), tracks inspection progress, and issues quarterly SAP reports.
 - **ORA.** The Office of Regulatory Affairs plans, tracks, and conducts inspections.³
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PROCEDURES

1. Running the SSM and Generating the SSIL

- 1.1 OS takes the current catalog of sites, uses the approved risk factors and weights to generate scores at the site level, and addresses any problems with the input data. OS then ranks the sites by score.
- 1.2 OS performs a quality control assessment of the list.
 - a) Data discrepancies identified in running and reviewing the model are forwarded to the respective data set owners for resolution.
 - b) Sites are identified in which the last inspection was classified as open or final official action indicated (OAI). The list of OAI sites is reviewed by ORA, OS, and OC for concurrence and the OAI sites are removed from routine surveillance inspection planning (i.e., OAI site reinspection is determined as part of the enforcement effort).
 - c) Sites currently on Import Alert are removed from routine surveillance inspection planning.

³ This MAPP is intended for CDER staff; ORA is included for completeness only.

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- d) Any site that is newly registered, or otherwise without any prior routine surveillance inspection, is typically inspected within 30 days and/or as a for-cause assignment. OS may collaborate with ORA to verify that a new site is, in fact, subject to routine surveillance inspection.
- 1.3 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 OS 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 OS will investigate the reasons for the removal request.
 - 3.2 If the request is due to 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 the 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 OS investigation confirms that the FDA information needs to be revised and the discrepancy between the FDA and the site is corrected.
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REFERENCES

- 1. FDA (2004), Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach, Final Report.
 - 2. FDA (2006), ICH Q9 Guidance — Quality Risk Management.
 - 3. FDA (2007), Pharmaceutical Quality for the 21st Century — A Risk-Based Approach, Progress Report.
 - 4. FDA (2017a), Compliance Program 7356.002 — Drug Quality Assurance.
 - 5. FDA (2017b), Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations.
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DEFINITIONS

Acronyms

OC: Office of Compliance, CDER

ORA: Office of Regulatory Affairs

OS: Office of Surveillance, OPQ, CDER

SAP: Surveillance Action Plan, the Office of Surveillance product that includes the SSIL and has quarterly progress reports

SSIL: Site Surveillance Inspection List, the output list of prioritized sites from the SSM that are selected for inspection as part of the routine surveillance human drug CGMP Compliance Program 7356.002

SSM: Site Selection Model, a risk management tool that supports a consistent, science-based approach for allocating inspectional resources for routine surveillance CGMP inspections

EFFECTIVE DATE

This MAPP is effective September 26, 2018.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/26/18	Initial	N/A