FDA 查厂须知

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美国 FDA QSR 查厂程序 (Content)

- 了解 FDA 查厂政策
- 了解 FDA 查厂程序
- 了解 QSIT
- 如何准备接受 FDA 查厂

Who are subject to QSR Inspection

Manufacturer (21 CFR 807.3(d))

"Manufacturer, preparation, propagating, compounding, assembly, or processing" of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in section 201 (h) of the Act. These terms including the following activities:

1/ Repackaging or otherwise changing the container, wrapper, or labeling of any device packaging in furtherance of the distribution of the device from the original place of manufacture to the person who makes final delivery of sale to the ultimate consumer;

2/ Distribution of domestic or imported devices; or

3/ Initiating of specifications for devices that are manufactured by a second party for subsequent commercial distribution by the person initiating specifications.

Who are subject to QSR Inspection

Re-manufacturer (21 CFR 820.3(w))

Is any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that changes the finished device's performance or safety specifications or intended use. Re-manufacturers are considered manufacturers.

Custom device manufacturers (FD&C Act Section 520(b))

Customer device is exempt from 510(k) and PMA, not exempt from GMP requirements.

Contract Manufacturers

A person that manufactures a finished device under the terms of a contract with another manufacturer. Contract manufacturer shall comply with applicable requirements of GMP and shall register their establishment with FDA.

Who are subject to QSR Inspection

Re-packagers, Re-labelers and Specification Developers

1. Re-packaging and re-labeling of a device and specification development are defined as manufacturing in 21 CFR 820.3(o) and 21 CFR Part 807, Establishment Registration and Device Listing for Manufacturing of Devices.
2. Package and/or label previously manufactured finished devices or accessories;
3. Receive finished devices in bulk (e.g. surgical tubing, syringes, media, etc.) and re-packs them into individual packages and label them;
4. Receive previously manufactured devices that have been packaged and labeled by another manufacturer, and combine them into a kit with other un-packaged devices which are received in bulk.

Who are subject to QSR Inspection

Manufacturers of Accessories

- When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and the production should comply with the QS regulation.
- Such as hemodialysis tubing, major diagnostic x-ray components.

Initial distributors of imported devices

- An initial imported (or initial distributor) takes first title to the devices imported into the US and further distributes the product. With regard to GMP, this initial distributor is responsible for maintaining compliant files and general record keeping requirements.
- Complaint files and MDR.

FDA Inspection Priorities

Priority A

Manufacturers of High Risk and Class III Devices

1. Manufacturers that have never been inspected;
2. OAI follow-up inspections
3. Manufacturers that received their last inspection more than two years ago and manufacturers for which there is an outstanding routine priority assignment.
4. Any other manufacturer of high risk or Class III device
5. Establishments that are only specification developers or re-packagers / re-labelers

FDA Inspection Priorities

Priority B

Manufacturers of Class II and Class I Devices

1. Manufacturers of Class II devices that have never been inspected;
2. OAI follow-up inspections of manufacturers of Class or I devices;
3. Manufacturers of Class II or I devices that never conducted more than 2 year recalls in the last 12 months;
4. Manufacturers of Class II or I devices that have recently experienced an increase in MDR reports;
5. Manufacturers of Class II devices that never received 510(k) clearance notification(s) within the last 2 years;
6. Any other manufacturers of Class II devices;
7. Establishments that are only Class II specification developers or re-packers / re-labelers;
8. Manufacturers of Class I devices that have never been inspected;
9. Manufacturers of Class I sterile devices;
10. Any other manufacturers of Class I devices.

FDA Inspection Policies

- QS/GMP Pre-Clearance Inspection for Class III PMA and Class III 510(k) Pre-amendment Devices
  - Level 2 QSIT
  - May cover all devices made by the inspected firm
- Initial Inspections
  - Newly registered and listed firms should receive a Level 2 QSIT inspection as soon as possible after manufacturing operations commence.
  - Generally, firms that manufacturers Class III device and devices listed as High Risk Devices should be inspected within 6 months and firms that manufacture all other Class II devices within 12 months;
  - For a manufacturer of only Class I, QS/GMP exempt devices the investigator will review the firm's complaint handling system and MDR practices;
  - Except for cause, any firms that manufactures only Class I QS/GMP exempt devices will not be inspected.

FDA Inspection Policies

- Routine Inspections
  - Ideally, firms that manufacturers devices listed as High Risk Devices and 80% of other Class III devices manufacturers will receive an Level 2 QSIT inspection once within 2 years;
  - After the first 2 years, the non-violative manufacturers should receive less intensive Level 1 QSIT inspections.
- Class I Device Manufacturers
  - All Class I devices, including those exempt from most of the QSR requirements, must comply with the compliant file requirements as well as reporting requirements of the MDR regulation;
  - Class I manufacturers should receive lowest inspectional priority unless addressed by a special assignment or a health hazard is apparent.
- Follow-up Inspections
  - A level 3 QSIT inspection will be initiated after a warning letter is issued.

Investigation Trends

- 海外查厂均为Class II, III
- 加重管理阶层的责任
- CAPA
- MDR and Customer Complaint
- Electronic records and signatures: 21 CFR Part II

不同的查厂计划

- Compliance
- Surveillance
- MDR / Complaint
- Special Requests
- Emergencies

FDA Compliance Program

- CP 7382.845 Inspection of Medical Device Manufacturers
  - PAC 82845B Baseline QS inspection
  - PAC 81011 Medical Device Reporting
  - PAC 81845T Medical Device Tracking
  - PAC 81845R Corrections & Removals
  - PAC 82845S Sterilization Controls

查厂所根据的法规

- Code of Federal Regulations, Title 21 (21 CFR)
  - Part 820 Quality System Regulation
  - Part 803 Medical Device Reporting
  - Part 806 Device Corrections and Removals
  - Part 821 Medical Device Tracking
  - Part 11 Electronic Records & Signature

查厂手册

- Investigations Operations Manual (IOM)
  - Chapter 5 – Section 550 – Devices
  - Chapter 10 – Section 1025 - Devices
- FDA Compliance Policy Guides (CPG)
  - Chapter 3 - Devices

查厂指引

- Guideline on General Principles of Process Validation, FDA, May 1987
- Global Harmonization Task Force (GHTF) Process Validation Guidance
- General Principles of Software Validation, FDA, June 1997 (draft)
- Medical Device Quality Systems Manual; A Small Entity Compliance Guide, FDA, 1997
- The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices, 1997
- Do It By Design: An Introduction to Human Factors in Medical Devices, FDA, 1996

查厂涵盖的产品标准

- FDA recognized Standards (ISO, IEC, AAMI, ANSI, ASTM, IEEE, AOAC, etc.)
  - www.fda.gov/cdrh/databases.html

查厂人员的准备工作

- Know the reason for the assignment (Compliance Program, Complaints / MDR's, Special Requests)
- Review the firm's previous Establishment Inspection Reports
- Study the previous FDA-483
- Review correspondence, including the firm's response to the last inspection or Warning Letter
- Make plans to verify any promised corrective action

查厂人员的准备工作

- Review FDA databases
  - MDR's
    - www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmdr/search.cfm
  - PMA's
    - www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm
  - 510(k)'s
    - www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
  - Device Classification (product code)
    - www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification
  - Registration
    - www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/registration

确认查厂涵盖的产品的范围之优先顺序

- Class III Devices (highest risk)
- Class II Devices
- Class I Devices (lowest risk)
- Sterile or Non-Sterile
- Automated Processes (validation)
- What was covered last inspection?

查厂计划

- Telephone the firm to confirm the inspection date and time
- Request copies of the firm’s Quality Policy, high level Quality Systems Procedure, Quality Manual and Quality Plan (the firm is not required to supply these documents) for review before the inspection
- Also ask for labeling and any other publicly available literature about their medical devices

查厂计划

- Follow CP 7382.845 Inspection of Medical Device Manufacturers. Use the “top-down” approach. Review the 4 major sub-systems
  - Management Control
  - Corrective and Preventive Actions (CAPA)
    - Medical Device Reporting
    - Corrections and Removals
    - Medical Device Tracking
  - Design Controls
  - Production and Process Controls (P&PC)

查厂人员的随身装备

- Basic Forms: FDA-483, FDA-484
- Compliance Programs, notebook, the Code of Federal Regulations, camera, guidance documents, etc.
- Anything that is necessary to help complete the assignment (flashlight, ruler, stapler, post-its, sampling plan, etc.)

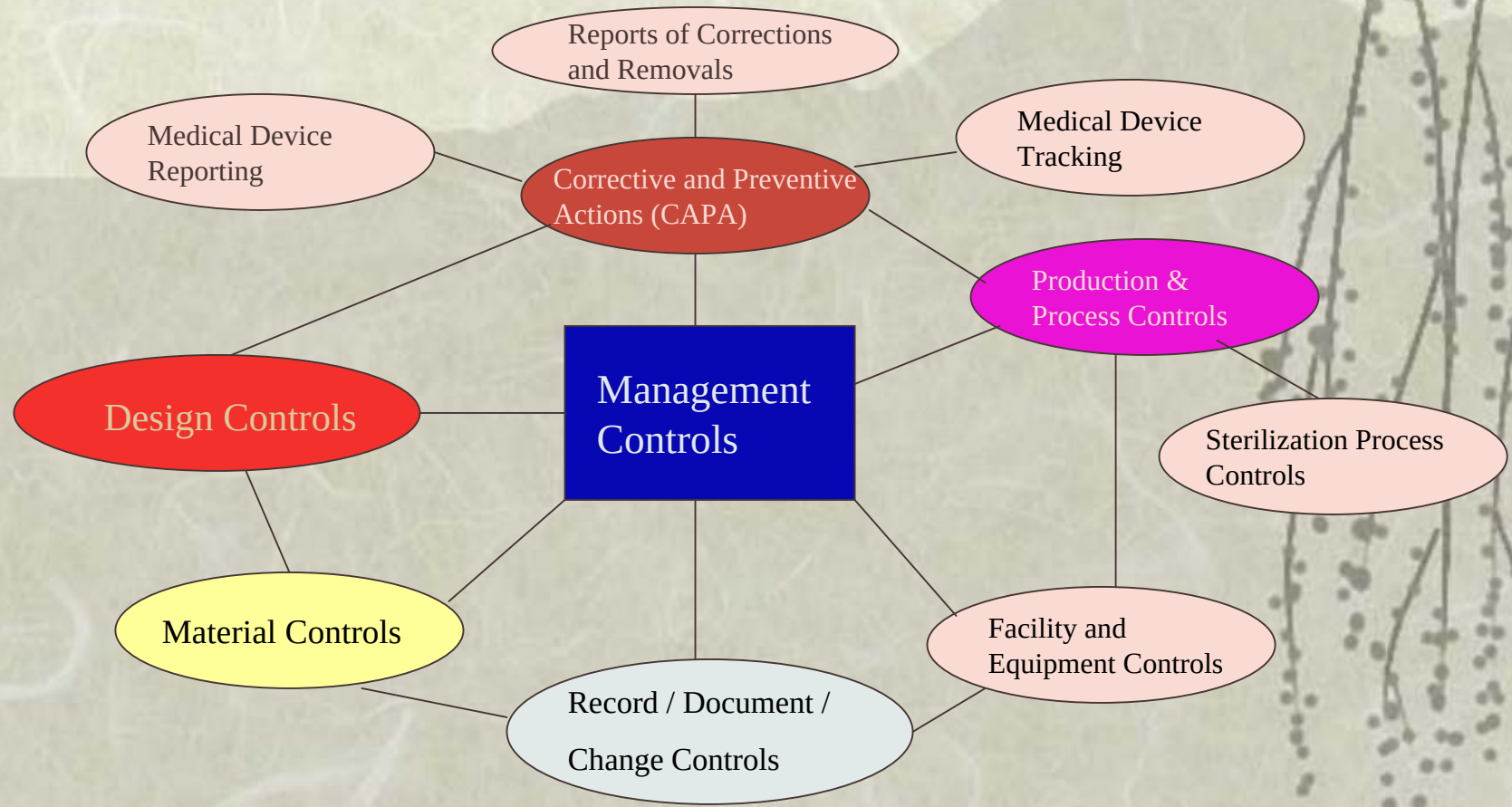
稽查与查厂标准

- FDA Inspection of Medical Device Manufacturers
  (Investigation Operation Manual 7382.845)

Types of Operation	Programs
❖ Foreign inspection	❖ Quality system inspection
❖ Domestic Inspection	❖ For cause inspection
❖ Domestic Investigation	❖ Medical Device Report
❖ Field examination/Test	❖ Tracking
❖ Sample analysis	❖ Corrections and Removals
❖ Sample collection	❖ Sterilization inspection

**: For cause investigation are generally more in-depth than the QSIT approach. These inspections should be directed toward finding the quality problem, tracking the root cause and assuring that appropriate corrective and preventive actions are initiated. For cause inspections are most often initiated as a result of a serious health risk, which was brought to the attention of FDA.

FDA Quality System Inspection Technique (QSIT)



FDA Quality System Inspection Technique (QSIT)

Inspection level	Reason for Inspection	QSIT Subsystems Inspected
1	Abbreviated	CAPA plus one subsystem
2	Baseline (Comprehensive)	Management Controls, Design Controls, Facility and Equipment Controls, CAPA
3	Compliance Follow-up	After Warning Letter

Foreign Inspections should cover registration and listing requirements

QSIT 查厂策略

- Focus on evaluating whether the QS and subsystems have been implemented effectively.

- Top down approach vs. bottom up
  - Top down: System
  - Bottom up: Nonconforming Event

QSIT 查厂重点

- Quality System Regulation
  - 1. Corrective and Preventive Actions
  - 2. Design Controls
  - 3. Production and Process Controls
  - 4. Management Controls
  - 5. Records/Document/Change Controls
  - 6. Material Controls, and
  - 7. Facility and Equipment Controls
- Medical Device Report Regulation

Design Controls 21 CFR 820.30

- General:
  1. Each manufacturer of any class III or II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.
  2. The following class I devices are subject to design controls:
     - i. Devices automated with computer software; and
     - ii. The devices listed in the following chart.

Section		Device
868.6810	----------	Catheter, Tracheobronchial Suction,
878.4460	----------	Glove, Surgeon's
880.6760	----------	Restraint, Protective
892.5650	----------	System, Applicator, Radionuclide, Manual
892.5740	----------	Source, Radionuclide Teletherapy,

接受QSR 查厂的准备

1. Obtaining information on GMP requirements;
2. Determining the appropriate quality system needed to control the design, production and distribution of the proposed device;
3. Designing products and processes;
4. Training employees;
5. Purchasing and installing processing equipments;
6. Drafting the device master records;
7. Procuring components and materials;
8. Producing devices;
9. Evaluating finished devices;
10. Packaging devices;
11. Distributing devices;
12. Processing complaints and analyzing service and repair data;
13. Servicing devices;
14. Auditing and correcting deficiencies in the quality system; and
15. Preparing for an FDA inspection.

Prepare for FDA Inspection

- 接获 FDA 查厂通知，确认查厂的类别（Type or Level ），查厂人员查厂时间越长，发现缺失的机会越大。
- 无违反法规记录的厂商，通常只会接受 Level 1, QSIT 查厂 : CAPA + 1 subsystem
- 新进注册的厂商，正在申请 PMA/510(k)，违犯法规记录的厂商可能会接受 Level 2 QSIT 或 Follow-up 查厂 : CAPA + Design Controls + Management Controls+Product and Process Controls.
- FDA 查厂人员依规定收集 Medical Device Reporting (MDR) data (MAUDE), Registration and Listing data, 5109k) and PMA summary data (OSCAR) 等内部资料库，因此维持良好很重要。
- 由于过去 FDA 的经费不足，FD&C Act 规定之两年一次查厂执行率只有一半 (David Feigal, CDRH)。因此 FDA 的例行查厂有点像 cherry picking.

FDA 通知查厂

- 信函/电话通知
- 确认日期
- 要求品质文件
- 联系工厂

准备工作

- 整理所有的文件与记录 Establish and Maintain = Establish + Define + Document + Complete + Implement
- 确保作业人员熟识于遵守 SOP (or QSP)
- 文件与记录既未规定要放在同一场所，但接受查厂时，最好能在现场立即取得提供查厂人员，以便查厂作业顺利进行
  - Device master records
  - Standard operation procedures
  - Medical device reports
  - Donor screening (if applicable)
  - Design history files
  - Process Validation
  - CAPA
  - Device history records

准备工作

- 规划查厂应对计划
- 指派联络人员
- 审查程序书
- 审查前次查厂记录
- 准备品质文件
- 行程安排, 查核部门人员, 指派, 清理厂区
- 加强训练
- 审查品质手册与品质目标
- 代理人
- 与查厂人员事先沟通
- 厘清 **FDA** 要求
- 确认查厂种类
- 查厂范围与相关适用法规
- 翻译人员
- 演练

FDA 查厂人员会调查事项

- 医疗器材
- 训练记录
- 材料
- 包装
- 标示
- 设备
- 生产场所
- 注册与列名资讯
- 样品

- 生产记录
- 设计变更
- 客户抱怨档案
- 运销记录
- 矫正与预防措施记录
- **DMR**
- **DHR**
- **MDR**

迎接

- 将工厂里外打扫干净，整理整齐，查厂人员在敲门前已经开始查厂了：察看厂外部与建筑物的清洁，门外不要放置垃圾。
- 可以准备一份检查表，确保厂内机器，设备，组件，物料均放置适当，以强化查厂人员对工厂环境管制作业的信心。
- 召集了解 **QSR** 的主管或代表，由法规主管率领，陪同引导查厂人员，取出相关文件与记录。
- 由法规主管全程陪同，不要让查厂人员独自在厂区察看。
- 法规主管最好具备法律知识，了解 **FDA** 查厂人员的作业方式与法律授权范围，如任意询问现场员工或抽样。
- 管理阶层在查厂当日应留在工厂备询，无须全程陪同。
- 准备一份最新的组织图。
- 抵达每一个部门，部门代表应迅速接待，切莫让查厂人员呆立或关门不应。
- 查厂人员不得收受任何赠品或金钱，但可以提供午餐。

保密资料

- 以下资料可以拒绝被查：
  - 财务报表
  - 销售统计
  - 价格
  - 个人资料
  - 管理审查记录
  - 内部稽核记录
  - 供应商稽核记录

查厂之进行

- 开始会议
- 要求 FDA人员识别证明
- 公司简介
- 查厂范围
- 每日会议
- 审查查厂发现事项与观察事项
- 变更
- 矫正措施

- 结束会议
- 出席人员
- 总结报告
- FDA 483表
- 厘清相关缺失议题
- 立即矫正措施
- 口头措施计划
- 管理阶层

应做的事情

- 制定接受查厂的计划
- 提供相关文件程序书
- 切实回答问题
- 陪同查厂人员
- 记录
- 影印并签署 FDA 取走的文件
- 与 FDA 人员合作
- 保持礼貌但坚持法律上的权益

应避免做的事情

- 说太多或回答“不可能做到”
- 同意录音
- 签署声明书
- 同意取得档案
- 猜测正确答案
- 回答假设的问题
- 争论

查厂之后

- 工作分派
- 文件更新
- 向管理阶层报告
- 详细阅读 **Form 483 Notice of Inspectional Observations**

  - NAI: No action indicated

  - VAI: Violative action indicated

  - OAI: Official action indicated

- 确认矫正计划的适当性
- 执行矫正措施
- 将矫正计划与记录寄给指定的 **FDA** 单位
- **FDA** 回复
- 跟催
- 注意其他可能法规措施
- 改善
- **EIR**

Thank you very much !!