FDA Inspections

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1 FDA Inspection Program

1.1 Inspection of Type 361 Product Manufacturing Establishments (cGTP)

The inspection program for HCT/P is under the Center for Biologics Evaluation and Research (CBER) at the FDA. The recent history of the inspection program is shown in Fig. 1.

The average time taken per inspection was between 34 and 41 h. The agency generally identifies establishments to be inspected from its listing of registered establishments. This list is compiled from an annual registration procedure that is described in Title 21 of the Code of Federal Regulations Part 1271 Subpart B [1]. The registration form is completed online (FDA Form 3356), and full instruction for registration can be found at: https://www.fda.gov/media/109160/download

The HCT/P inspection program covers only products that are minimally manipulated, intended for homologous use, are not combined with another article **and** do not have a systemic effect or are dependent upon the metabolic activity of other cells for primary function **and** are for autologous use or allogenic use in a first- or second-degree relative, or are for reproductive use [2]. Cells not meeting these specifications may be regulated as biological drugs or medical devices and are inspected under different regulations described later. If the HCT/Ps were recovered before May 25, 2005, the inspections are performed according to the Inspection of Tissue Establishment regulations [2].

The frequency of HCT/P establishment inspection is not predetermined but is based upon potential risk, whether the establishment previously received an official action finding and whether the FDA has received information about potential

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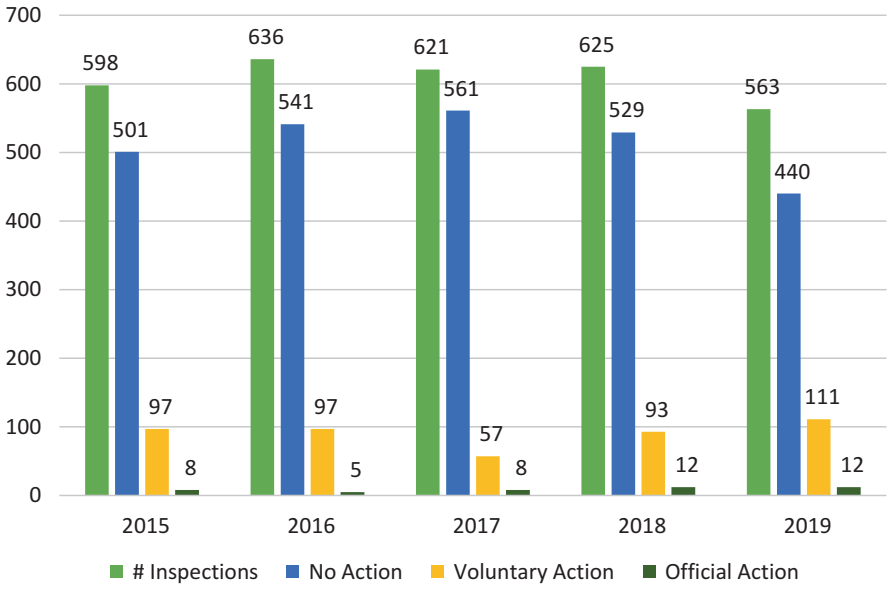

Fig. 1 Number of FDA HCT/P establishment inspections by year and actions taken

violations. Inspections are usually unannounced with the exception of those relating to medical devices, inspections under the bioresearch monitoring program (unless being performed for cause), and pre-licensing biologics inspections.

At the start of the inspection, the inspector will issue the establishment with a Form FDA-482 "Notice of Inspection" and ask to see the most responsible person at the establishment. They will identify themselves and show their official credentials. The purpose of the inspection will be explained, and they will inform you as to which records they will want to see, whom they may want to interview, and which procedures they may wish to observe.

The inspection will be based on the elements of the current Good Tissue Practice regulations shown in Tables 1a, 1b and 1c.

There must be a quality program in place. Procedures must exist for receiving, investigating, evaluating, and documenting information related to core GTP requirements. Any corrective actions that are performed must be documented and their efficacy verified and, if appropriate, both short-term and long-term actions taken to prevent recurrence included. The program must include a system to ensure that all staff are properly trained and educated to perform their tasks. There must also be evidence of environmental control showing that systems are established and appropriately maintained. All deviations related to HCT/Ps must be investigated and documented. Investigations should include a review and evaluation of the deviation, efforts to determine the cause, and any corrective actions.

The inspector will check to ensure that reporting requirements have been met. These include reporting within 15 days adverse reactions to the FDA that are fatal,

Table 1a Donor eligibility inspection of HCT/P establishments shown by regulations and major inspection elements

Regulation (21CFR Part 1271)	Inspection element
Donor requirements	Determine procedures in place to perform donor screening
Donor eligibility	Determine if each donor has a separate and complete record of all relevant medical records and that these are available for review. Verify adequacy of screening records
Donor screening	Determine if results and interpretation are in compliance with regulations
Donor testing	Check for documentation of responsible individual performing screening
	Determine whether all the required tests are being performed
	Are FDA-licensed, approved, or cleared donor screening tests being used?
	Is the testing laboratory CLIA certified or has met equivalent requirements?
	Are the results interpreted according to the manufacturer's instructions?
	Are adequate samples used for testing and do they meet the requirements specified in the product insert?
	Observe testing or verify through record review that appropriate controls are used and the testing procedure is followed properly.
	Verify equipment maintenance is per manufacturer's directions and establishment's SOP and that all equipment is appropriately qualified, calibrated, and maintained
	Confirm that testing problems are investigated, resolved, and documented
	Verify that positive or reactive tests are handled appropriately and that those from ineligible donors are handled in accordance with 21CFR Part 1271.65

life-threatening, result in permanent damage or impairment of body functions, or which necessitate medical or surgical intervention, including hospitalization. Any HCT/P deviations which meets all of the following criteria must also be reported: deviations related to distribution and core cGTP and is related to the prevention of communicable disease transmission or HCT/P contamination. These reports can be made using Form 3486 or submitted electronically.

The inspection findings are documented by the inspectors using Form 483 "Inspectional Observation" at the conclusion of the inspection. There will be a formal report on the inspections (see Establishment Inspection Report) with a classification of the findings. Actions may be taken based on these findings as shown in Table 2

Table 1b Labeling inspection of HCT/P establishments shown by regulations and major inspection elements

Regulation (21CFR Part 1271)	Inspection element
Labeling control requirements	Are there established and maintained procedures to control labeling?
	Are there appropriate labels in use for shipment of products from ineligible donors and in the case of urgent medical need?
	Is donor name and other personal information not used on labels except for autologous products and those from first- and second-degree relatives?
	Determine:
	All labels contain identification code, description of product, expiration date, and, if applicable, any required warning statements
	The name and address of the establishment that determined release criteria were met and made product available for distribution, storage temperature, appropriate warning statements, instructions related to the spread of communicable disease, and statement if donor is eligible or ineligible
	Establish that the summary of records accompanies the HCT/P including that testing performed by CLIA-certified laboratory, list of all testing performed, name and address of establishment that made donor eligibility determination, reason donor was ineligible if appropriate
	Additional items apply if the product was shipped under quarantine, if it was made available under the urgent medical use provision, and if the donor was ineligible, or the product is for nonclinical use

1.2 Inspection of Type 351 Product Manufacturing Establishments (GMPs)

Human cell and gene therapy product manufacturers are usually inspected under a Level 1 cGMP [2, 3]. This consists of an in-depth audit of three critical elements in at least four of the key systems (Table 3). In addition to the audit of the quality system, the Level 1 inspection should also include an audit of the production system [3].

cGMP inspections are normally conducted on a biennial schedule, or more often if warranted by circumstances.

The FDA has indicated that manufacturing for Phase 1 clinical trials does not have to fully conform to cGMP regulations [4]. In a guidance document, they recommend a comprehensive and systematic evaluation of the manufacturing setting to identify potential hazards and appropriate actions to eliminate or mitigate them. These can include the use of disposable equipment and process aids; use of commercial and prepackaged materials, e.g., water for injection; and use of closed systems for manufacturing. The basic requirements, however, are similar in terms of adequate facilities, trained personnel, quality program, maintenance of records, etc. It is advisable to review this guidance [4] before an inspection takes place.

In a GMP inspection, a major element will be the use of written approved standard operating procedures (SOPs) and associated records. This may include

Table 1c Inspection of other components of HCT/P establishments shown by regulations and major inspection elements

Regulation (21CFR Part 1271)	Inspection element
Facilities	Is the facility suitable for all functions that are being performed?
	Is the facility in good state of repair?
	Are manufacturing areas maintained in a clean, sanitary, and orderly manner?
Environmental controls	Are there procedures in place for control of:
	Temperature and humidity?
	Ventilation and air filtration?
	Cleaning and disinfecting of rooms and equipment?
	Maintenance of equipment used to control conditions for aseptic processing?
Equipment requirements	Determine whether equipment is appropriately designed, located, installed, maintained, and cleaned to prevent introduction and transmission of communicable diseases
	Is equipment capable of producing valid results?
Supplies and reagents requirements	Have all supplies and reagents been verified to meet specifications designed to prevent conditions that increase introduction and transmission of communicable diseases?
	Reagents must be sterile where appropriate
Recovery requirements	Has each HCT/P been recovered in a way that prevents introduction and transmission of communicable diseases?
Processing and process control requirements	Are there appropriate processing and process controls to prevent introduction and transmission of communicable diseases?
	Confirm if there is no pooling of cells from two or more donors
	Is sampling of HCT/Ps representative of the material to be evaluated?
	Determine:
	Which procedures have been validated?
	The review process for validations and verifications
	If sterility testing is contracted out how the sampling and testing methods were validated and review the documentation If performed internally review documentation
	How changes are made to validated processes; are they documented, signed, and dated; was the procedure revalidated; was the change approved by the appropriate individual?

(continued)

Table 1c (continued)

Regulation (21CFR Part 1271)	Inspection element
Storage requirements	Do storage conditions prevent mix-up, contamination, and cross-contamination of HCT/Ps, supplies, and reagents?
	Is there a proper quarantine area?
	Are HCT/Ps stored at the correct temperature?
	Have expiration dates been assigned if appropriate?
	Are there corrective actions when proper storage conditions are not met?
Receipt, pre-distribution, shipment, and distribution requirements	How does the establishment receive and evaluate incoming HCT/Ps?
	How is pre-distribution of HCT/Ps accomplished within the institution and to outside establishment?
	How is the documentation achieved that:
	HCT/Ps have met release criteria?
	Are HCT/Ps packaged and shipped to prevent contamination?
Records	Does the establishment have equipment logs, labeling records, and packaging records?
	Are records maintained, well-organized, and readily available?
	If stored electronically how are they backed-up?
	Does record identify person doing the work?
	Are entries signed and dated?
	Do records provide complete history of work?
	Can record be related to the particular HCT/P?
	Are donor eligibility records complete?
	Review procedures for preparing the summary of records
	Are records accurate, indelible, and legible?
	If donor is ineligible does use meet requirement for the first- or second-degree blood relative, or urgent medical need?
	Records must be maintained concurrently with the performance of each step

observation that these are being followed. Training records will be reviewed to ensure that staff have the appropriate educational background, training, and experience and that they are adequate in number.

The inspector will also verify through observation whether the establishment is adhering to applicable regulations. One way to help determine this is to look at documented deficiencies as an indicator of the state of control. Other elements of the inspection are shown in Tables 4a, 4b, 4c, 4d, 4e and 4f, together with examples of the types of deficiencies that may be reported. There are additional elements for specific types of products, for example, vaccines and allergens. The most relevant regulations for the cellular therapy community pertain to master and working viral seed banks. There should be a complete history, including passaging and testing profiles. The storage must be secure, and it should be at multiple locations with adequate control to prevent unauthorized access and materials loss due to equipment

Table 2 Types of FDA HCT/P inspection findings

Finding	Explanation
Untitled letter	Violations do not meet the threshold of regulatory significance for a warning letter; however, regulatory concerns exist that cannot be addressed through other means
Warning letter	Violations of regulatory significance suggesting systemic problems exist within one or more areas of operations
Order of retention, recall, and destruction	Significant deviations suggesting that HCT/P was manufactured in violation of the regulations
	Conditions of manufacture do not provide adequate protection against risks of communicable disease transmission, or the HCT/P is contaminated
Order of cessation of manufacturing	HCT/P is manufactured in violation of regulations, and there is not adequate protection against the risk of transmission of communicable disease, or the HCT/P is contaminated, or there are reasonable grounds to believe that a danger to health exists
Prosecution	Gross, flagrant, or intentional violations; fraud, danger to health or continued; or repeated course of violative conduct

Table 3 Key systems and critical elements of a cGMP inspection

Key systems	Critical elements
Quality system	Standard operating procedures
Facilities and equipment system	Training
Materials system	Records
Production system	
Packaging and labeling system	
Laboratory control system	
Donor eligibility system (only for certain HCT/Ps)	

failure. There must be a complete inventory which correlates with the amount of material on hand, and the storage locations should be fitted with an alarm system. Similar regulations apply to master and working cell banks, with additional attention to the passage numbers at which the cells are used. Establishment of new working cell banks from the master bank should be documented in the annual report to the FDA.

For aseptic processing emphasis is put on ensuring that all transfers, transports, and storage stages are carefully controlled to maintain sterility. Wherever possible closed systems should be used. If this is not possible, the product must be handled in a unidirectional Class 100 (ISO 5) environment located in a Class 10,000 (ISO 7), or better, surrounding room. Monitoring activities should include obtaining the identity of detected microorganisms. There must be microbial surface monitoring at the end of production before cleaning and also personnel monitoring. There should be a process simulation performed to demonstrate that process controls are adequate to protect the product [5]. These should model the worst case scenario, e.g.,

Table 4a GMP inspection: Elements of quality system and deficiencies

Element	Deficiencies
Quality system	Employees not trained, experienced, sufficiently educated, or sufficient in number
Component and in-process materials release	Failed to review records at least annually to evaluate quality
Change control	Procedures for production/process control not drafted, reviewed, and approved
Batch release	Quality audits not performed
Record review	Complaint procedures not drafted or followed and no documentation of findings
Validation protocols	Failure to conduct investigations into unexplained discrepancies. Failures to meet specifications not documented did not include conclusions, did not examine other batches, or did not extend to other products with associated discrepancies
Evaluation of biological product deviations	Out of specification procedure, deviations not recorded or justified and failure to conduct investigations
Complaint handling	Change control procedures did not approve or reject procedures/ specifications impacting product strength, quality, and purity and did not draft/review/approve written procedures
Evaluation of returned/ salvaged products	Stability investigations not performed and/or failure to review records and ensure appropriate investigation if appropriate
	Quarantine procedures not written or followed and rejected components, closures, and containers not identified and controlled to prevent use
	Finished product distribution records not established or implemented to facilitate product recall if necessary
	Adverse event reports not reported to CBER
	Significant manufacturing changes implemented before CBER approval

maximum number of open operations. The inspector may ask to observe aseptic technique.

At the conclusion of the inspection, a Form 483 will be issued that lists significant findings that relate to observed or potential problems detected at the establishment. The most critical observations are listed first. It may include deficiencies from prior inspections that have not been corrected.

1.3 Establishment Inspection Reports (EIR)

The establishment will receive an EIR after the inspection. This provides documentation of what the inspector(s) did from the time at the establishment until the issuance of the Form 483. It includes a summary of the findings, a history of the

Table 4b GMP inspection: Elements of facilities and equipment system and deficiencies

Element	Deficiencies
Facilities and equipment system	Buildings not in good state of repair, not of suitable size and construction to facilitate cleaning, maintenance, and proper operations
Appropriateness of buildings and facilities, including maintenance, equipment qualification and maintenance, cleaning and validation of cleaning, prevention of contamination, and cross-contamination including contaminants on product contact equipment	Inadequate ventilation and no equipment to adequately control air pressure, microorganisms, dust, humidity, and temperature air filtration not used where appropriate
	Inadequate space to prevent mix-ups and/or contamination
	No separate or defined areas or control systems
	Building not maintained in a clean and sanitary condition, not free of pest infiltration, no pest control written procedures, and not designed to prevent contamination
	Cleaning records not retained for 3 years
	Equipment not of appropriate design, size, or suitably located for cleaning and maintenance
	Equipment surfaces not constructed to prevent changes to product and/or free of contaminants. Equipment lubricants, coolants, etc. in contact with product
	No cleaning or maintenance logs. Improper or insufficient cleaning
	No written procedures for equipment cleaning and/or maintenance
	Improper or no calibration or inspection
	Equipment not properly identified

establishment, a listing of individual's responsibilities and persons interviewed, a discussion of the quality operation and training program, manufacturing design and operations, product testing, recall procedures, objectionable conditions and responses, and a description of general discussion with the management.

It will state whether the facility is found to be acceptable and provide classification of the findings. These are official action indicated (OAI), voluntary action indicated (VAI), or no action indicated (NAI). A VAI indicates that re-inspection is required within 12–24 months. An OAI indicates that a warning letter will be issued until the observations have been addresses and have been verified by the FDA through an inspection.

A warning letter may be issued subsequently that lists violations of regulatory significance that cause one or more systems not to be a state of control. For licensed

Table 4c GMP inspection: Elements of materials system and deficiencies

Element	Deficiencies
Material system	Procedure not written or followed for receipt, identification, sampling, testing, and approval of components, product containers, and closures
Validation of computerized inventory systems, storage and distribution controls, detection and prevention of counterfeiting	Items not stored to prevent contamination or cross-contamination or held under quarantine until approved and released
Monitoring of utility systems	Representative sample of each component not collected for testing or examination
Review of calibration and maintenance and verification of following manufacturer's recommendations and/or user manuals	Tests not conducted to verify the identity of each product component
Addition of or modifications to equipment	Containers and closures not inspected visually
	No written specifications for components, containers, or closures and failure to reject those not meeting specifications
	Items not retested after prolonged storage or quarantined if specifications not met
	Inadequate containers and/or closures, e.g., no written cleaning methods; not shown to be nonreactive, additive, or absorptive; sealing not performed to maintain integrity; etc.
	Cell cultures and lines not properly stored to prevent contamination and deterioration, not identified by lot number and date of preparation, no records maintained on periodic verification, and freedom from contaminants

product manufacturing other actions may include license revocation or suspension, seizure of products, injunctions in the case of the existence of a current health hazard, and finally prosecution. Deficiencies are listed by the systems shown in Tables 4a, 4b, 4c, 4d, 4e and 4f.

2 EU Inspections

cGMP in Europe is regulated by the European Medicines Agency [6, 7], and inspections are performed by the appropriate national competent authority (NCA). Manufacturing sites outside the EU are inspected by the NCA of the Member State where the EU importer is located, unless a mutual recognition agreement is in place between the EU and the country concerned. If an MRA applies, the authorities

Table 4d GMP inspection: Elements of production system and deficiencies

Element	Deficiencies
Production system	Deficiencies in written procedures for production and/or process control
Written procedures	Deviations not recorded
Equipment identification	No identification of compounding and storage containers, major equipment, etc.
Yield calculations	Yields and percentage of yield not calculated at each appropriate phase of manufacturing and packaging
Batch production and control records	No batch or control records
Time limits for phases of manufacturing	No established time lines for each phase of production
Use of in-process controls, tests, and examinations	No established or followed written procedures for in-process controls, tests, and examinations
Consistency of in-process and final specifications	In-process specifications inconsistent with final specifications
Prevention of contamination	No written procedures for the prevention of contamination
Production and control records	Processing procedures and deviations not recorded or documented at the time of performance
Storage temperatures	HCT/Ps not stored at appropriate temperatures and temperatures not periodically reviewed or maintained. No recommended temperatures for performance at each step of manufacturing to inhibit contamination
Record retention	Records not retained for appropriate times
	HCT/Ps pooled during manufacturing

mutually rely on each other's inspections. The results of national cGMP inspections and details of nonconformances are reported on the EudraGMDP website [8].

3 Behavior During a Regulatory Inspection

Establishments should pre-designate one or more people to facilitate inspections. It is also a good idea to have a written SOP for regulatory inspections. This will contain the procedure to be followed, the people to be notified, the names of additional contact people, where the meeting will be held, how requests for documents will be handled, and behavior to follow during the inspection. All staff and relevant ancillary people must be trained on this SOP. It is critical that the staff are already familiar with the relevant regulations upon which the inspection will be based and have ready the appropriate guidance documents.

Table 4e GMP inspection: Elements of packaging and labeling system and deficiencies

Element	Deficiencies
Packaging and labeling system	No written labeling procedure or procedure not followed
Acceptance operations for packaging and labeling systems	Labels not sampled or tested on receipt and/or did not meet specifications. Labels for different doses not stored separately
Control of label issue, examination of issued labels, and reconciliation of used labels	Labeling issue not controlled and labels not examined for identity or conformance
Line clearance for packaging and labeling	Label quantities not reconciled
Accompanying records	No destruction of excess labels
Expiration dating	No procedure to ensure correct labels are used and no procedure to prevent mix-ups
Examination of labeled finished products	Lot or control numbers not used for products
Labeling control	HCT/Ps do not have code to relate to donor and product records, no tracking system, and no procedure to relate old and new codes
	Shipping conditions not established for HCT/Ps and packaging and shipping containers not designed to protect from contamination
	Accompanying records for HCT/Ps not adequate
	No expiration dates used or related to storage conditions on label
	No examination or documentation of examination of labeled finished products
	Inadequate labeling records

A sign-in sheet should be used for all those attending the inspection meeting, and the inspectors should complete the visitor log when entering the facility. The meeting should take place in a room with adequate space and sufficient chairs for the inspection team and establishment staff. The locations of toilets and water fountains and beverages should be provided. An offer should be made to bring in lunch for the team (which will be paid for by them) or to provide the location of nearby eating facilities. Normally, after initial introductions and an explanation of the purpose of the visit, the team will indicate when they want to meet with establishment staff and when they wish to be alone. They should be provided with contact information for the establishment representative.

They should be accompanied at all times (except when they ask to meet alone) by a facility representative(s) who takes meeting notes and designates who should meet with the team when information is requested. It is a good idea to have a current table of contents available to enable the establishment staff to rapidly find and provide copies of requested procedures. A list should be maintained of all documents provided to the inspection team, and there should be a designated person available

Table 4f GMP inspection: Elements of laboratory control system and deficiencies

Element	Deficiencies
Laboratory control system	No specifications, standards, sampling plans, test procedures, or control systems available or reviewed by a quality program
Written procedures and control systems	Procedures not written or followed for instrument calibration
Calibration and maintenance of analytical instruments and equipment	No written procedures to describe sampling methods or number of units from each batch to be tested
Adherence to and validation/ verification of written analytical methods	Accuracy, sensitivity, specificity, and reproducibility of test methods not established or documented
Testing and release for distribution	Laboratory testing does not determine conformance to final specifications
Specification, standards, and representative sampling plans	No testing for objectionable microorganisms
Stability testing program	Controls did not include sound and appropriate specifications, standards, sampling plans, and test procedures
Special testing requirements	Stability testing programs did not include sample size and test intervals or storage conditions for samples
Adequate reserve samples	Adequate reserve samples not retained or stored under appropriate storage conditions per product label and not examined visually at least annually
Required testing performed on correct samples	Samples not representative or adequately identified
Laboratory records	Laboratory records did not include full testing documentation including calculations performed

to make copies. Ideally there should be a person available to retrieve requested documentation from the files or to locate it electronically. Only documents specifically requested by the team should be provided. The speed with which documents are provided indicates familiarity with the quality system and facility operations. Requests for information should be answered directly and specifically without offering supplementary details.

Staff should be familiar with how to interact with inspectors. During observation of procedures, it is acceptable to tell an inspector to wait until questions can be asked or answered. If the staff member does not know the answer, they should indicate this and tell the inspector that they will find out the answer or refer him/her to another staff member. They should not be evasive. Again, the staff member should not volunteer supplementary information, but should directly answer the question posed.

Toward the end of the day, the team will usually indicate how they wish to close out the day's activities. This may include meeting with certain establishment staff and requests for additional information to be provided on the following day and/or the agenda for the next day. If deficiencies have been detected during the day, it is

usually acceptable for the establishment to try to correct these and to provide the team with evidence of their correction on the following day.

On the final day of the inspection, an exit interview will normally be held, after the team has met together to plan their findings. Usually the establishment representative can decide who will attend this meeting. The team will normally thank the establishment for facilitating the inspection, and FDA inspectors will then present their findings and the Form 483. There may be an opportunity for the establishment to seek clarification of the findings and ask to supplementary questions. The team should be thanked for performing the inspection. In the United States responses to deficiencies may be made at the meeting or should be submitted to the District Office within 15 days of the inspection. A formal EIR will be provided by CBER after the inspection (see Establishment Inspection Report). Actions to be taken will be documented.

4 Complaints About FDA Inspections

If you have complaints about the inspectors or the conduct of the inspection, these should not be raised during the inspections itself. The District Office should be contacted in writing after the inspection.

5 FDA Pre-inspection Opportunities

In the United States, the FDA offers a number of opportunities for pre-operational inspection of the manufacturing facility [9]. These are of four types:

5.1 Design Review

A design review usually involves a review of conceptual drawings, proposed plant layouts, and flow diagrams for the entire facility including critical systems and areas. Such reviews provide an opportunity to emphasize the importance of the fundamental principles of good design as outlined in the cGMPs. As a result, extensive changes in design can be made with little cost and very minor delay to the design and construction cycle. The FDA expects the facility to prepare complete final plans and to identify, if possible, specific questions regarding how the facility will meet cGMPs or areas where the FDA's comments are specifically desired. When the review includes a meeting with the facility, advance delivery of the package of documents to the District Office is recommended. This type of review is particularly valuable for academic cGMP facilities.

5.2 Pre-construction Review

A pre-construction review involves a study of the plan, elevation, and isometric drawings for all manufacturing areas and utility and process systems for the plant; i.e., drainage and water systems; product systems; compressed air systems; heating ventilation and air-conditioning (HVAC) systems; and all equipment, layouts, and piping in the manufacturing and laboratory areas. Further examples, where applicable, include zones of positive air pressure; HEPA filtration and laminar flow; air locks; protective clothing; change rooms; toilet and washup facilities; pedestrian traffic patterns; raw materials and components, and similar considerations.

The various packages of prints, specifications, design standards, and vendors' descriptions should be supplied in advance to permit meaningful review and comment prior to any meeting.

5.3 Construction/Equipment Installation and Qualification Review

Facilities may request an FDA on-site review of specific portions of the plant, while construction is in progress. This is an excellent opportunity to review piping systems and methods of construction before they are concealed by walls, floors, and ceilings. These reviews or site visits may be done in phases. The final inspectional review of validation and control data from production runs can then be accomplished quickly and more efficiently.

5.4 Pre-production Review

At the pre-production stage, the review will normally be an inspection. Additionally, facilities may request investigators to visit new buildings or production areas during inspections on the same campus. Investigators conducting the review should provide the facility with general feedback and can provide examples of what they have seen at similar facilities.

6 Conclusions

Regulatory inspections are a component of GMP/GTP compliance. They may be random or based upon specific issues. In either case it is important to have (i) an understanding of the regulations against which compliance is being evaluated and (ii) procedures in place on how your facility will deal with the inspection. These

include keeping good documentation of what happens, knowing how to deal with requests for information, behavior of staff, and ensuring effective and timely follow-up. Attention to such details will ultimately result in a smooth and effective inspection.

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References

1. Code of Federal Regulations. *Drug good manufacturing practices (GMP)*. Title 21, Parts 210 and 211. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211. Last accessed 13 July 2020.
2. Code of Federal Regulations. *Human cells, tissues, and cellular and tissue-based products*, Title 21 Part 1271. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=127. Last accessed 13 July 2020.
3. CBER. (2010). *Compliance program guidance manual chapter – 45 biological drug products inspection of biological drug products 7345.848*. https://www.fda.gov/media/73834/download. Last accessed 13 July 2020.
4. Federal Drug Administrations. (2008). *Guidance for industry: CGMP for phase 1 investigational drugs*. https://www.fda.gov/media/70975/download. Last accessed 13 July 2020.
5. U.S. Department of Health and Human Services Food and Drug Administration. (2004). *Guidance for industry: Sterile drug products produced by aseptic processing—Current good manufacturing practice*. September 2004. https://www.fda.gov/media/71026/download. Last accessed 13 July 2020.
6. European Medicines Agency. *Human regulatory, good manufacturing practice.* https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice. Last accessed 13 July 2020.
7. European Commission. (2017). *Good manufacturing practice guidelines on good manufacturing practice specific to advanced therapy medicinal products*. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf. Last accessed 13 July 2020.
8. European Medicines Agency. *Eudra GMDP Website. Compliance with good manufacturing practice*. http://eudragmdp.ema.europa.eu/inspections/gmpc/index.do. Last accessed 13 July 2020.
9. Food and Drug Administration. *Pre-operational reviews of manufacturing facilities*. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/field-management-directives/pre-operational-reviews-manufacturing-facilities. Last accessed 13 July 2020.