Development and Implementation of Quality Systems

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Karen Edward

Advanced Cell & Gene Therapy

Today's Topics

- US regulatory overview for Human cells, tissues and cellular and tissue-based products (HCT/Ps)
- People, place, process and performance mnemonic to organize and remember QS information – ISCT approach
- Quality System (QS) requirements for HCT/Ps using GTPs as model
- Strategies for assessing gaps, managing risk, and assigning priorities
- Detailed review of QS requirements and considerations for implementation

Good Tissue Practices

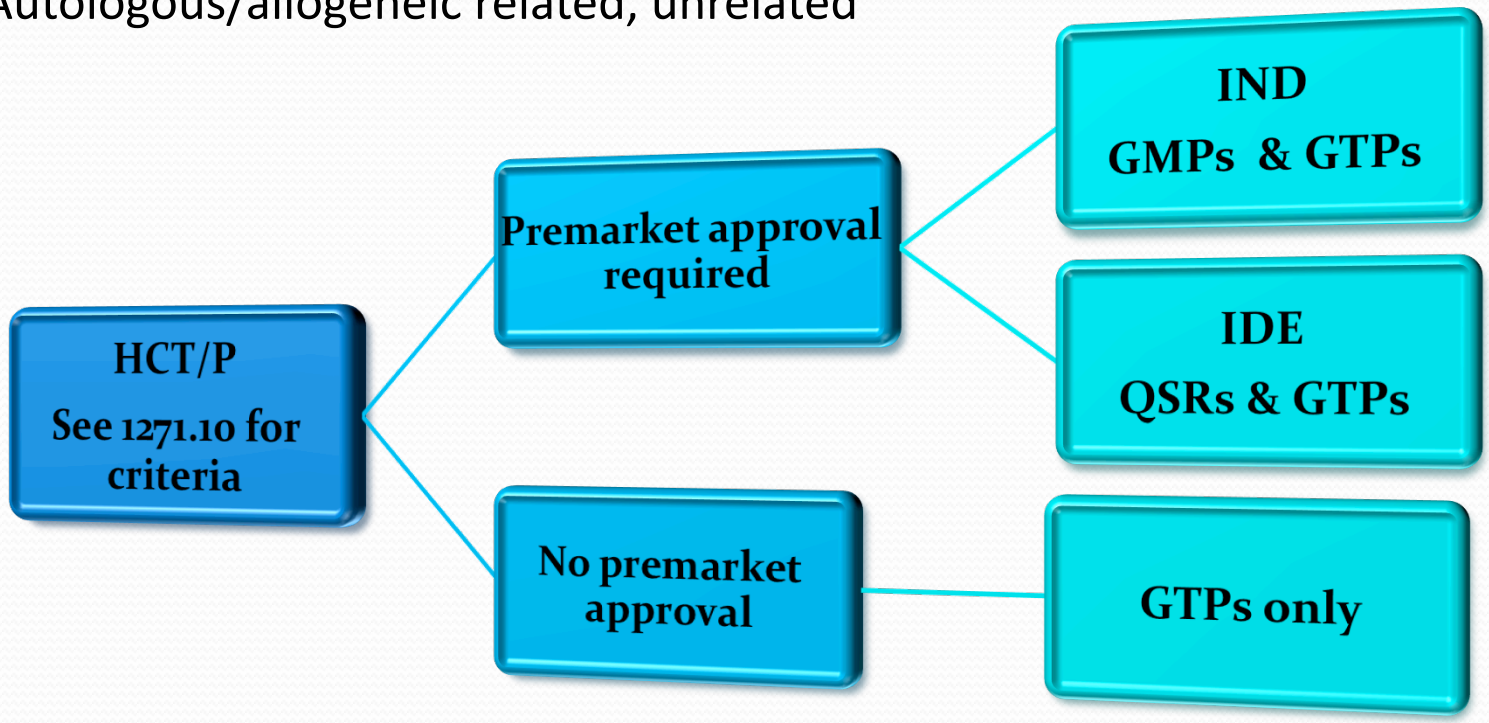
- 21 CFR 1271, the US regulation
  - Applies to human cells, tissues or cellular or tissue-based products (HCT/Ps)
  - Includes the following sections (and others focusing on definitions, reporting, etc)
    - Subpart B - Registration and listing
    - Subpart C - Donor Eligibility
    - Subpart D – current Good Tissue Practices (cGTP)

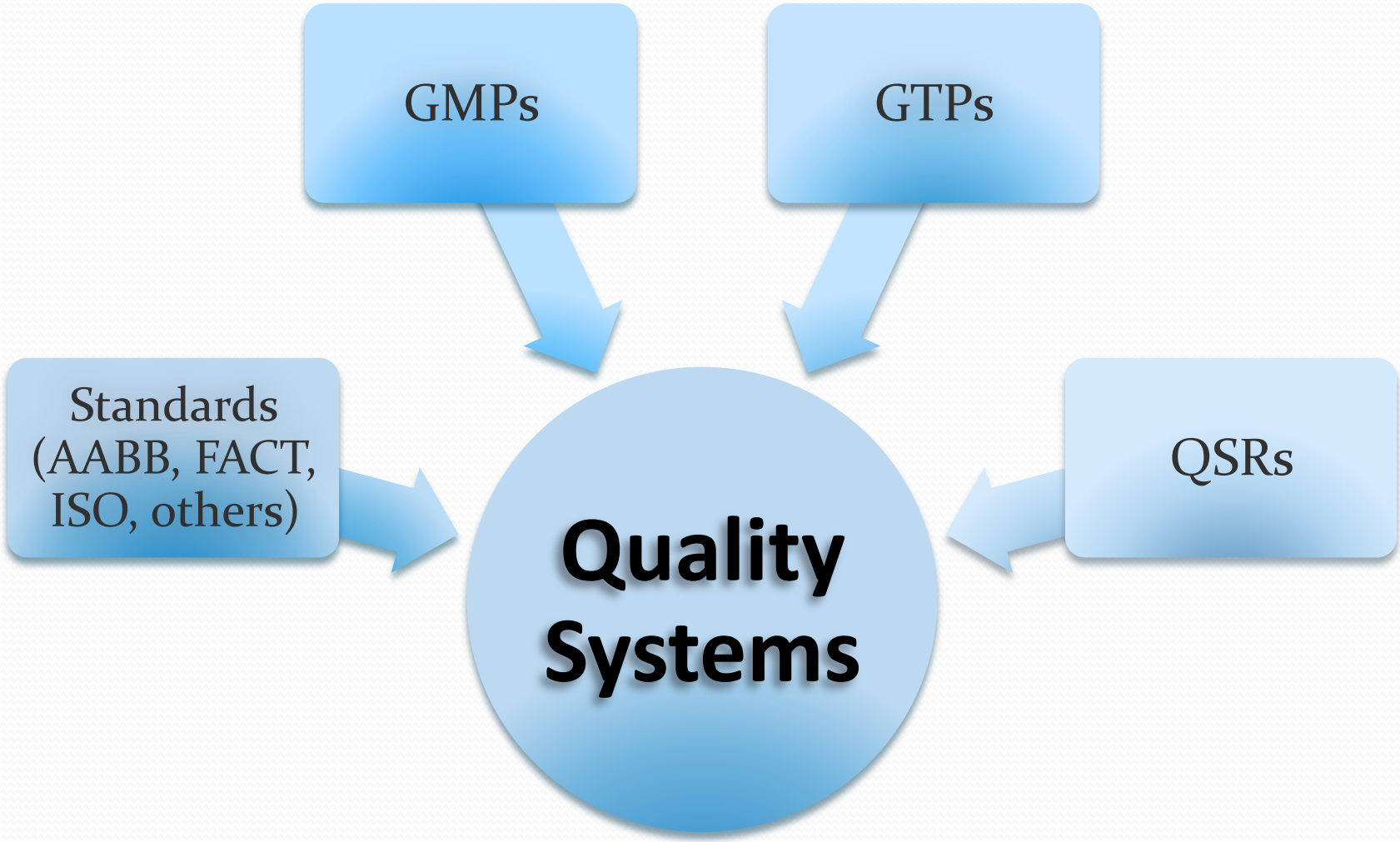
21 CFR Part 1271

- These three rules form the platform for regulation of all HCT/Ps
- For certain HCT/Ps ("361 HCT/Ps"), these regulations comprise the sole regulatory requirements
- For HCT/Ps regulated as drugs, devices, and/or biological products, the tissue regulations supplement other requirements (GMP, QSR)

21 CFR 1271.10 – definition 351, 361 products

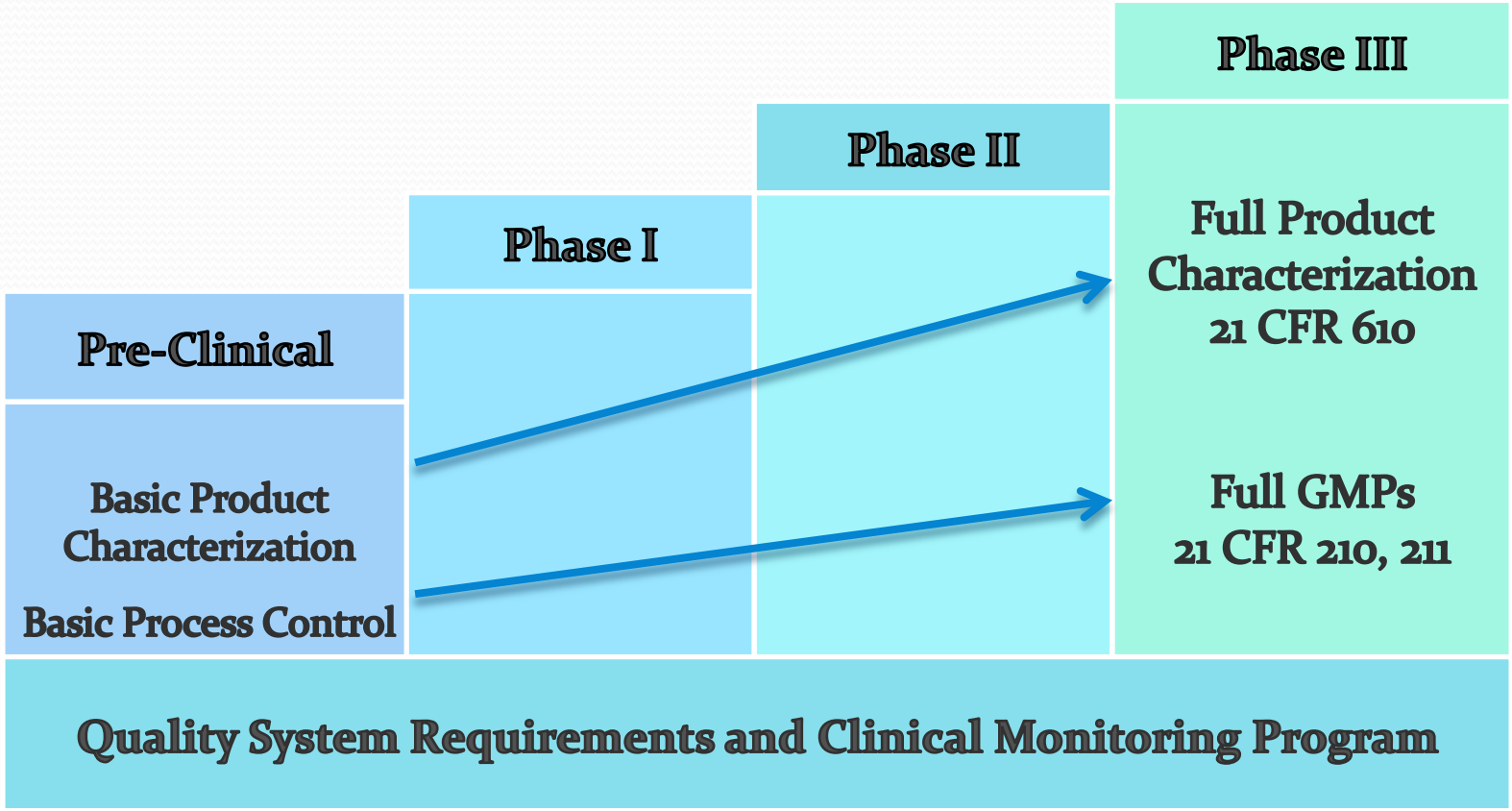
- Manipulation
- Homologous , non-homologous use
- Combination product
- Systemic effect
- Autologous/allogeneic related, unrelated




GMPs
GTPs
Standards (AABB, FACT, ISO, others)
QSRs
Quality Systems

FDA "sliding scale"

Requirements increase with product development



GTP core requirements

Section	Citation	Section	Citation
Establishment of Quality Program	1271.160	Supplies & Reagents	1271.210
Donor Eligibility	Part C	Recovery	1271.215
Facilities	1271.190	Labeling	1271.250
Environmental Controls	1271.195	Storage	1271.260
Equipment	1271.200	Receipt and distribution	1271.265

Other GTP requirements

Section	Citation	Section	Citation
Personnel	1271.170	Complaints	1271.210
Procedures	1271.180	Records	1271.270
Process Validation	1271.190	Reporting	1271.350
Process Changes	1271.195	Inspections	1271.400
Tracking	1271.200		

How do you begin working on QS?

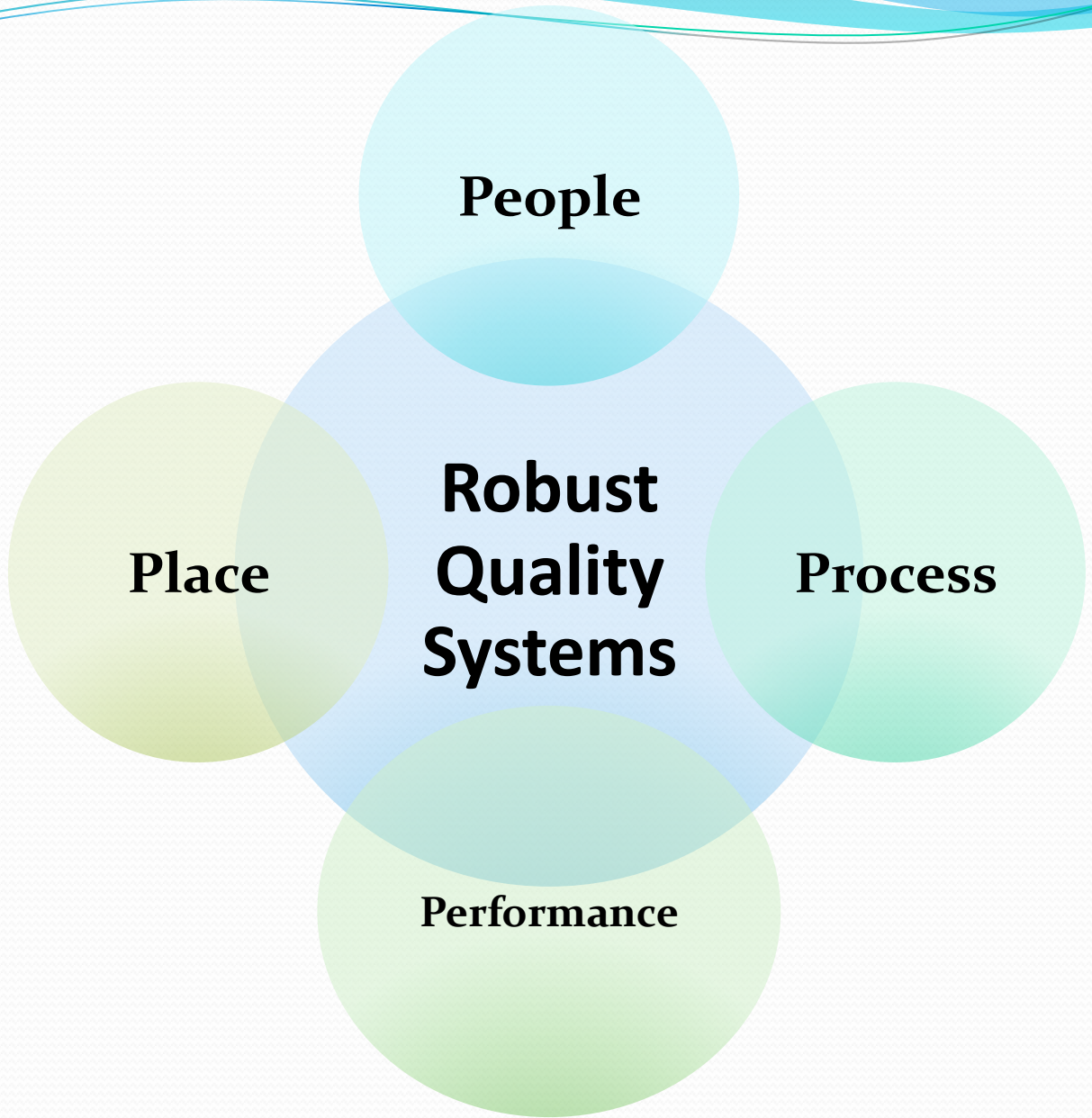
- It depends on where you are in your development
- Are you building a new facility? Is this your first venture in cell therapy?
- Do you need to upgrade or modify your facility or processes based on new guidance, standards or regulations?
- Begin with a gap analysis
  - Investigate and understand what you currently have in place
  - Assess gaps: develop a “crosswalk” of regulations and standards; determine if you are in compliance or not; if not, identify gaps and what needs to be done to fill the gaps

Next…

- Establish risk-based approach for filling gaps, example:
  - Priority 1 – extremely high regulatory risk: patient or donor safety risk (donor eligibility, safety testing, process control, adverse event reporting)
  - Priority 2 – high regulatory risk: accuracy or reliability of results, reporting or decision-making (validation, QC, environmental controls, critical equipment)
  - Priority 3 – medium/low regulatory risk (process improvement, document control, recordkeeping)
- Assess scope of work and required resources
- Get approval from senior management to proceed

Finally

- Establish “Quality Improvement Project”
  - Organize gaps based on quality system
  - Assign resources: project manager, subject matter experts (facilities, manufacturing, QC testing, document control), oversight by QA
  - Set timelines
  - Define SOPs for writing or revision, write and approve
  - Train staff – very important!
  - Final implementation, gaps closed


People
Place
Robust Quality Systems
Process
Performance

Quality Systems

- Basic tenets
  - PEOPLE – organization, expertise, training, competency
  - PLACE – facility, equipment, environmental controls
  - PROCESS – document control, donor evaluation, raw materials, tracking and traceability, process development, manufacturing, QC testing, storage, transportation, administration
  - PERFORMANCE – audits, deviations, OOS, adverse reactions, SAEs, complaints, regulatory reporting, process improvement

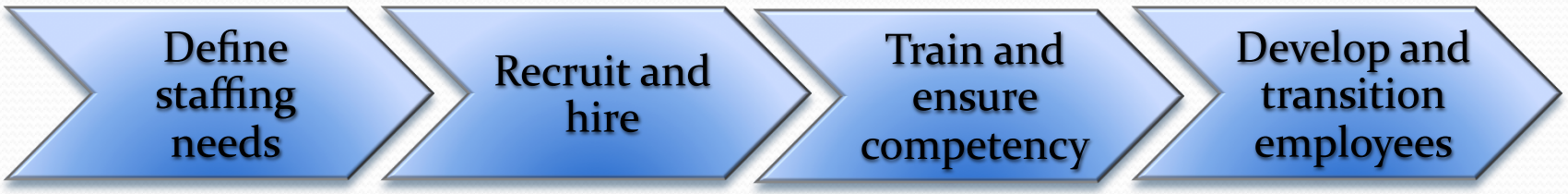
People

Organization

- Describe purpose, structure, operations and QA systems in Quality Manual or Plan
- Ensure lines of accountability are clear and overall responsibility and authority is well-defined
  - ✓ Minimize or eliminate conflicts of interest
  - ✓ Determine ultimate responsibility for operations, quality, compliance, medical direction
  - ✓ Assign a position with authority and responsibility for QA and adequate resources to manage QA functions: document control, training oversight, EM tracking and trending, deviations, complaints, product release, audits, regulatory reporting
  - ✓ Maintain updated organizational chart

Employee lifecycle

- People are the foundation of your organization and directly responsible for its success
- Recruiting, hiring, training, and developing employees is key should be standardized and SOPs established early



Training and competency

- Needed for all employees – a standardized process, covered in SOPs and well documented
- Employee training records should be organized and current
  - Auditors and inspectors ***will*** review training records
- Be sure to include how "trainers" are identified and assessed
- Establish a reasonable program for ongoing competency:
  - Assess aseptic processing, gowning, cell counts, and other critical and routine procedures on a regular basis, e.g. annually
  - Include regular SOP review, one-on-one SOP observation, use standardized samples for QC testing competency
- GTP/GMP training should be performed annually

Facilities

Operations and Maintenance

Utilities

Equipment

Environmental Controls

Facility design and construction

Facility design

Place

- Hire architects and engineers who know how to design GMP facilities; refer to appropriate regulations and guidance docs
- Involve manufacturing and quality personnel at the earliest stages of design; develop process flows for materials, product, personnel, waste
- Take time to properly design, things to consider:
  - Facility use – clinical research and/or commercialization
  - Types of products/processing, closed or open systems, throughput, numbers of personnel
  - Segregation of operations, functional units, design for ease of cleaning
  - Space needs for support labs, raw materials, product receipt and distribution, storage, changing rooms, offices
  - Room classification, air changes, pressure cascade
  - Type C meeting with FDA is suggested to address specific facility-related questions

Utilities

Place

- Includes HVAC (Heating, Ventilation, Air Conditioning) systems and controls, plumbing and piping for water and gases
- Commissioning of utility systems – the process of ensuring that systems are designed, installed, functionally tested, and capable of being operated and maintained to perform in conformity with the design intent . . . commissioning begins with planning and includes design, construction, start-up, acceptance and training, and can be applied throughout the life of the building.
- HVAC systems should be validated to ensure "a high degree of assurance that it will consistently produce a result that meets pre-determined acceptance criteria."

Facility controls

Place

- Facility access – limit access to critical personnel
- Building and equipment monitoring systems should be validated
- Facility startup and shutdown SOPs should be established
- Work with facilities engineering dept and contractors to understand facility systems operations, controls, acceptance criteria, maintenance, including scheduling and documentation
  - Room pressures, temperature, humidity
  - Clean room certification and air balancing
- Develop a plan for facility risk mitigation – what happens when the Air Handling Unit (AHU) fails? Or power fails? How is notification and management of clinical product handled? How is the facility re-qualified?
- Develop a plan in the event of emergencies or disaster - communication, how to work in facility, manage staff, operations and clinical products

Equipment

Place

- Perform I/O/PQ using standardized process and templates as outlined in the Master Validation Plan
- Begin writing SOP and supporting documentation using manufacturer's operator manual as guide
- Set up Calibration, PM and schedules; determine who will perform these activities
- Determine cleaning requirements: routine, product changeover, and in the event of accidental exposure
- Documentation should be in place for all activities and records kept near each piece of equipment or in a location that is accessible for staff performing these activities
- Staff should be trained for daily use and operation as well as cleaning and maintenance

Cleaning and sanitation

Place

- Identify cleaning contractor - in sourced or outsourced. How are contractors qualified?
- SOPs – for cleaning contractors and manufacturing staff should cover prep of reagents, storage, expiry dating; detailed steps of cleaning and documentation of activities in real time, review records
- Training and competency – access, gowning, train cleaning staff using your SOPs. How is training assured, who is responsible for oversight?
- Establish frequency and scheduling of cleaning activities
- Cleaning agents – sourced from qualified vendors, sterile, GMP, documentation available on intended use and effectiveness, CoAs, rotation to prevent resistance
- Equipment – mops, buckets should be cleaned and segregated
- Cleaning validation – if using functionally closed systems, and a rigorous cleaning program is in place full cleaning validation might not be needed until commercialization

Environmental monitoring

Place

- Objective: to verify facility is meeting applicable standards for particulates, total and viable and verify facility cleaning and gowning practices are working
- What are the standards? FDA, ISO, USP, PDA
- Sampling locations, frequency of sampling, action levels (i.e. ISO, USP)
- Establish alert levels based on historical data gained from routine operation of manufacturing process
- Maintain SOPs for all aspects of EM, including tracking and trending and operation of equipment
- Best to have staff other than those who manufacture the product conduct EM sampling; QA should review excursions and trending data and modify sampling plan based on review of data

EM for GTP facilities

Place

- "Where appropriate" is defined in the regulations as a required practice unless you can provide rationale defend otherwise
- Perform baseline EM
  - Determine most critical areas to monitor and reasonable period of time to generate adequate data set
  - Compile and analyze data
  - Make appropriate procedural and facility changes based on conclusions, and risk to product
- Establish basic EM program
  - Could be as simple air and surface viable testing in BSC
  - Set action/alert limits
  - Most importantly how will you use the data? Investigational tool in the event of positive product sterility, or aseptic processing training

Process

Process *includes recovery, manufacturing, testing and all systems needed to support and conduct these activities*

Donor eligibility

Process

- Particular to GTPs due to risk of transmission of infectious diseases from living cells/tissues
- Certain exemptions, e.g. autologous donors
  - If manufacturing a variety of products consider having one system to support autologous, allogeneic, unrelated, and bone marrow donors
- Donor Screening + Testing = Donor Eligibility
- Screening includes physical exam and health questionnaire
- Testing for relevant communicable disease agents or diseases using FDA approved or cleared test kits; testing labs should be registered with the FDA and qualified
- Identify "responsible person" is in your organization determining eligibility, and "urgent medical need"

Donor eligibility (2)

Process

- "Summary of Records" accompanying the HCT/P from recovery to administration should include the following information:
  - Testing performed by CLIA certified laboratory
  - A listing and interpretation of the results of all communicable disease tests (delete all donor personal information)
  - Name and address of establishment making donor eligibility determination
  - Reason for ineligibility, if applicable
- Specific labeling may apply:

  FOR AUTOLOGOUS USE ONLY

  NOT EVALUATED FOR INFECTIOUS SUBSTANCES

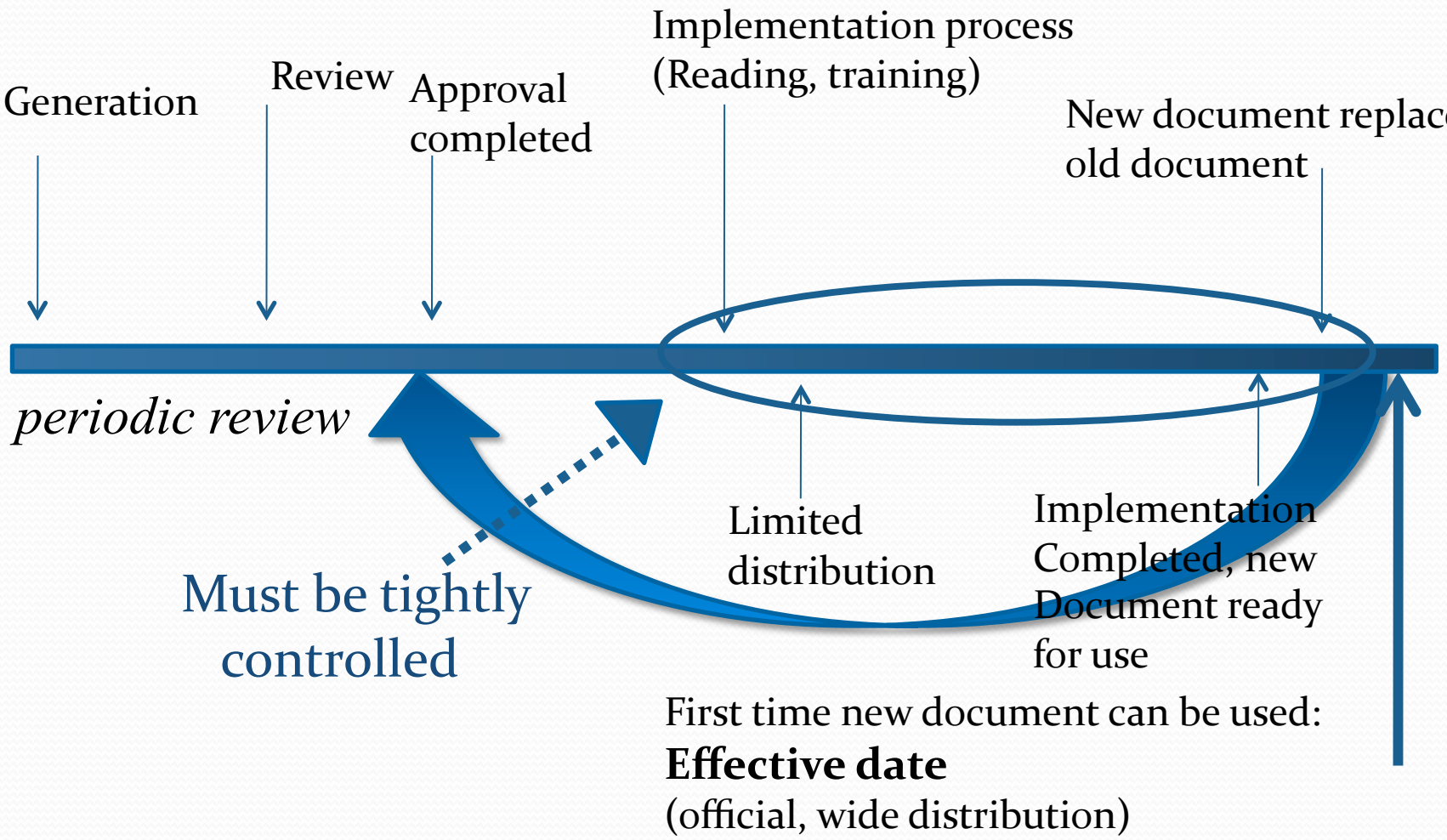
  WARNING: Advise patient of communicable disease risks or Reactive test results (name disease agent or disease)
- Quarantine products in cases of donor ineligibility or when donor eligibility is incomplete

Procedures and records

Process

- Comprehensive records management – organized for ease of retrieval, controlled storage, secure, fire-proof cabinets for patient records
- Records include – SOPs, batch production records (BPRs), logbooks, forms, protocols, reports, plans
- Document control – document numbering, version control, master document files, retention and archival
- GMP/GTP documentation practices: accurate, indelible, legible; provide sufficient detail to follow activity or process; identify person(s) performing work and dates completed
- Under GTP, records should be maintained a minimum of 10 years

Document timeline



Electronic records

Process

- Examples of computer software
  - Environmental Monitoring and Control (Building Monitoring Systems)
  - Databases: Quality Systems (Tracking Deviations, Change Control, Investigations), Laboratory Information Management Systems
  - Materials Management
- 21 CFR, part 11, Electronic Records; Electronic Signatures
  - Requirements for software design, validation, audit trials, signatures, and documentation for software and systems in processing electronic data.
- Consider criticality of software, does it affect product, safety, quality and record integrity
- If you keep "hard copies" of all required records these could be considered the authoritative document for regulatory purposes, and Part 11 compliance might not be required. However, records need to be complete.