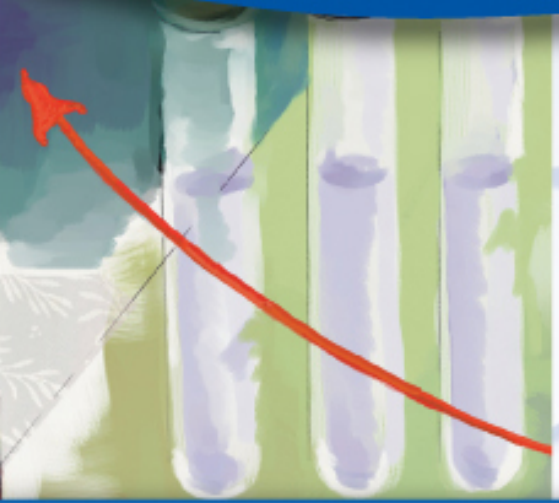
EMORY HEALTHCARE

EMORY MEDICAL LABORATORY

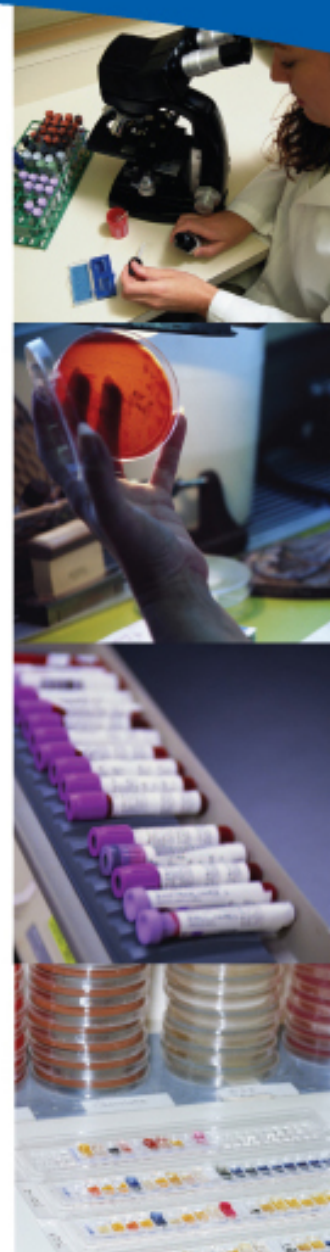


Good Manufacturing Practices (GMPs)

More than a few Numbers !

Where Do We Find Them?

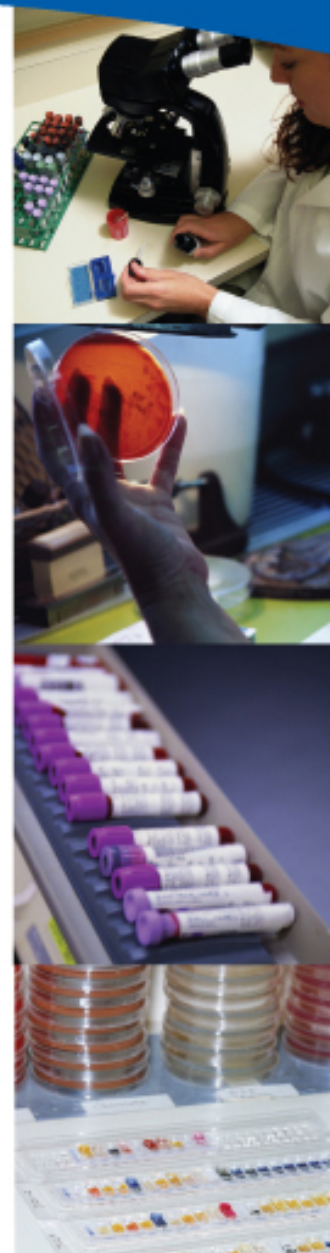
- Depends on what you want….
- Are you looking for good manufacturing practices for
  - Blood and Blood Products
  - Tissues (HCT/Ps)
  - Drugs
  - Laboratory Practices
  - Agriculture



Where Do We Find Them?

- www.access.gpo.gov
  - GPO Access
  - A – Z Resource List
  - Code of Federal Regulations

- US Government Bookstore



Good Practices

21 CFR 58
21 CFR 110
21 CFR 210
21 CFR 211
21 CFR 606
21 CFR 820
21 CFR 1271

Good Practices

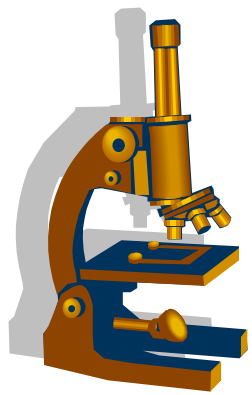
21 CFR 58 - Laboratory
21 CFR 110 – Water (food)
21 CFR 210 - Drugs
21 CFR 211 – Drugs
21 CFR 606- Blood
21 CFR 820 - Devices
21 CFR 1271- Tissue


OH NOOOOOO!!

Assumptions

Audience Representation

1. Majority: Blood Banks / Transfusion Services
2. Tissue Facilities
3. Manufacturing



Good Manufacturing Practices

ARE

Cross – Functional Framework

Checklist for what you need

Outline for procedures development

ARE NOT

Total procedure

Only way to manage a process

21 CFR PART 606

Current

Good Manufacturing Practice for Blood and Blood Components

Part 606

Blood & Blood Components

A. General Provisions
B. Organization & Personnel
C. Plant & Facilities
D. Equipment
E. Reserved (for growing pains)
F. Production & Process Controls
G. Finished Product Controls
H. Laboratory Controls

Part 606 (con’t)

I. Records and Reports


MrBill.com
Ohh Nooo!!!

Part 606
Subpart A – *Definitions*

- Blood
- Unit
- Component
- Plasma for further mfg
- Plasmapheresis
- Plateletpheresis
- Leukapheresis
- Facilities
- Processing
- Compatibility Testing
- **Distributed**
- **Control**

Distributed

(1) The blood or blood components have left the control of the licensed manufacturer, unlicensed registered blood establishment, or transfusion service; or

(2) The licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacturing of a licensed biological product.

Control

(1) Control means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

How We Organize & Run Our Business

B. Organization & Personnel

Adequate in number, education, training, experience or a combination to ensure the product is safe, pure, potent, effective and we can maintain identity

Series of acronyms: SQuIPP

C. *Plant & Facilities*

Clean & **orderly**

Suitable size, construction & location to facilitate cleaning, maintenance & operations

More detail for space related to:

Donor privacy

Exposure of equipment unrelated to collections

Space to store in an orderly manner **quarantined products separate from finished products**

Does this mean anything to me? Plant & Facilities

Space to store any products you might collect separated from general inventory

Space to quarantine products your blood supplier identifies as needing

AND

LABEL, LABEL, LABEL

any and all types of locations where product is stored!

D. *Equipment*

a) The type of equipment – used in collection, processing, compatibility testing, storage and distribution
   - Clean & orderly
   - Observed, standardized & calibrated on a schedule as prescribed in the Standard Operating Procedures
   - Use it as it was intended

D. *Equipment* (con't)

CFR provides a few examples of types of equipment, however the section states

includes but are not limited to

Types of Equipment

- Temperature Recorder
- Laboratory thermometers
- Electronic thermometers
- Refrigerated centrifuge
- Microhematocrit centrifuge
- General laboratory centrifuge
- Hemoglobinometer
- Water bath
- View box
- Serologic rotators
- Autoclave

SO?

- What does the CFR Say we need to do to the equipment?
  - Performance Check at a defined frequency, such as compare against a thermometer, each day of use
  - Calibration at a defined frequency, such as every 3 months

Reminder: Manufacturer's instructions always supersede CFR requirements

Additional Sterilization Requirements

Materials used in collection
Disposal of contaminated materials

The effectiveness of the sterilization procedure shall be no less than that achieved by an **attained** temperature of 121.5^0 C maintained for 20 minutes by saturated steam or by an **attained** temperature of maintained at 170^0 C with dry heat.

Supplies & Reagents

- Are listed under equipment
- Section doesn’t tell us anything we don’t already know...
  - Stored ...safe, sanitary & orderly
  - Surfaces that come in contact with products shall be sterile, pyrogen-free and not interact to have an adverse effect on SQuIPP
- Inspect the containers that will hold blood

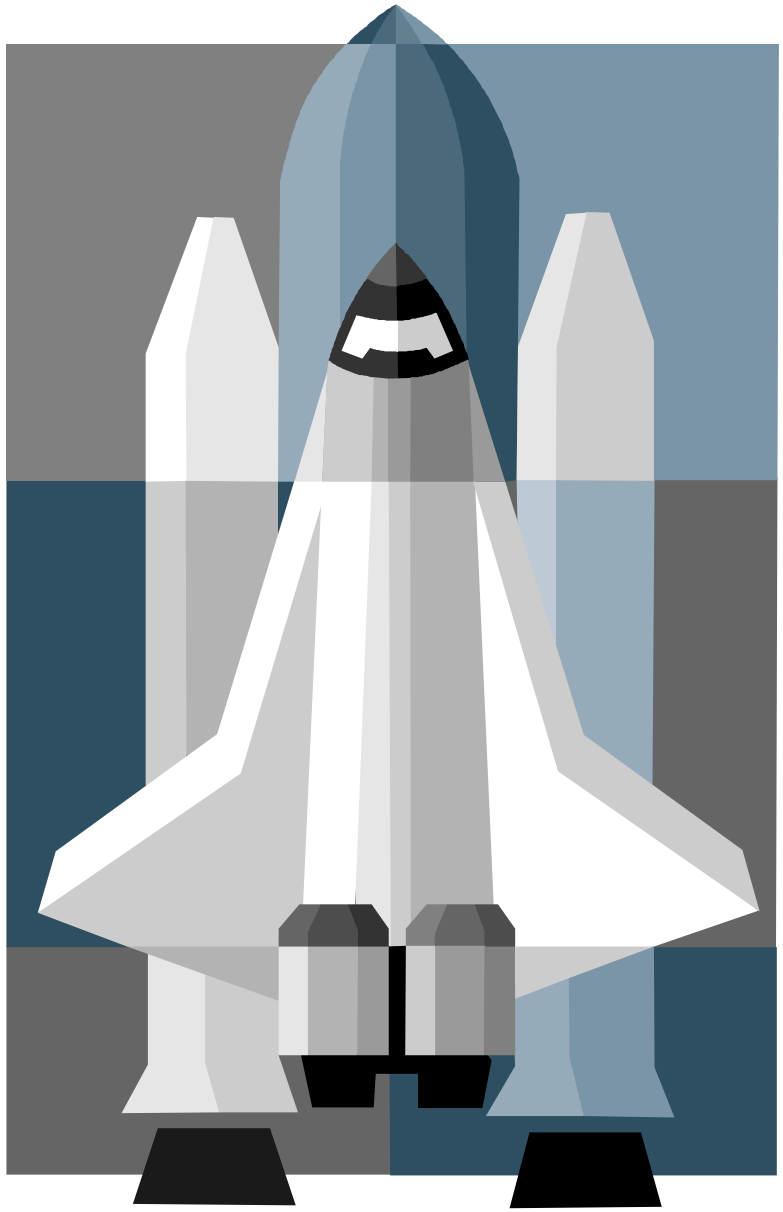
Reagent Quality Control

Reagent or solution	Frequency of testing
Anti-human globulin.....	Each day of use.
Blood grouping reagents.....	Do.
Lectins.....	Do.
Antibody screening and reverse grouping cells.	Do.
Hepatitis test reagents.....	Each run.
Syphilis serology reagents.....	Do.
Enzymes.....	Each day of use.

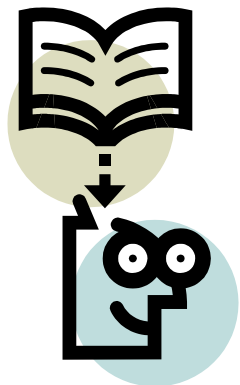
And your SOP has to say what you do!

What More do We Know about Reagents?

- If they don’t have an expiration, they must be stored such that they are used FIFO
- You have to use them in accordance with manufacturer’s instructions
- Use disposables where ever possible for items that come in contact with blood



F. *Production & Process Controls*



Or what we know as an SOP

606.100, *Standard Operating Procedures*

- Gives us an exemption for a clinical investigation
- Tells us we have to remember the product requirements in 21 CFR 640
- Reminds us we have to maintain and follow all steps
- **Provides our outline**

What SOPs do We Need?

- Donor acceptability
- Methods for donor qualification – acceptable values
- Preparation of phlebotomy site
- Tracking all products to the donor
- Collection procedures
- Testing & repeat testing of products
- Pretransfusion testing including recipient identification
- Investigation of donor & patient reactions
- Storage temperatures and control

Oh No, More

- Expiration dates
- Criteria to determine if returned product is acceptable for reissue
- Tracking method for blood from donor to final disposition, transfused, or otherwise
- QC procedures
- Equipment maintenance & calibration: schedules & procedures
- Labeling
- Pheresis – to ensure re-infusion of donor's own cells

Are We there yet?

- Preparing recovered plasma including separation, pooling, labeling & storage
- Examine prior donations (look back)
- Donor deferrals
- Review of records prior to lot release

- Investigations of discrepancies

And the Good News Is...

An organization may use current SOPs such as the manuals of organizations as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part

1. *American Association of Blood Banks*
2. *American National Red Cross*
3. *Other,...*

On to Tissue

Or HCT/Ps

Human Cells, Tissues, & Cellular &

Tissue Products

The Basic Principles for cGTPs 21 CFR 1271.150(a)

- Intent of GTPs along with donor eligibility is to prevent the introduction, or spread of communicable diseases by HCT/Ps
- Don’t acquire them contaminated & don’t contaminate during manufacturing
- The communicable diseases include (but are not limited to) those transmitted by viruses, bacteria, fungi, parasites and TSE

What are CGTPs looking for that CGMPs Don’t?

- Donor eligibility (606.100 – the procedure, 640.3, Suitability of the Donor)
- Exemptions and alternatives (610.9)
- Quality Control Program (211.22)
- Tracking (211.196)

21 CFR

cGMP for Blood & Blood Components, 606		*Current Good Tissue Practice, Part 1271, Subpart D*
Subpart A	**General Provisions**	1271.150
Subpart B	**Organization & Personnel**	
Subpart C	**Plant & Facilities**	1271.190 (a) & (b) 1271.195

General Provisions

When these appear – in all sections – typically if there is a conflict between regulations

Drugs vs. blood products, or HCT/Ps

The regulations more specific to the product supersede the general requirement

Comparison (con't)

Current GMP for Blood & Blood Components, 606		*Current Good Tissue Practice, Part 1271, Subpart D*
Subpart D	**Equipment**	1271.200 (a)
Subpart F	**Production & Process Controls including Donor Eligibility**	1271.220 1271.50-eligible 1271.80-testing gn 1271.85-testing sp

Comparison (con't)

Current GMP for Blood & Blood Components, 606		*Current Good Tissue Practice, Part 1271, Subpart D*
Subpart G	Finished Product Control – **Labeling**	1271.250 (a) & (b)
Subpart I	Records & Reports	1271.270

Labeling

- ISBT 128
- Organizational Support –

AABB
ABC
ARC
ASBMT
FACT
ICCBBA
ISCT
NMDP

I. More Records and Reports
These are a few of our favorite things

- Adverse Reaction File (606.170, 1271.350 (a))
- Biologic Product Deviations (606.171, 1271.350 (b))

“Contrasts”

Current GMP for Blood & Blood Components, 606		*Current Good Tissue Practice, Part 1271, Subpart D*
But never fear! **610.53**	**Storage**	1271.260
Assortment including 820.198	**Complaint File**	1271.320

Receipt, predistribution, shipment & distribution (1271.265)

- Receipt – evaluate each incoming HCT/P for microorganisms, inspect for damage, accept, reject or quarantine based on [pre] established criteria
- Predistribution – if you ship within or between establishments and the product doesn't meet established criteria... have criteria for prevention of communicable diseases been met?

Receipt, predistribution shipment & distribution (1271.265)

- Availability for distribution – review of all manufacturing and tracking records must be complete, and acceptability must be documented by a responsible person
- Packing / Shipping – designed to protect the product from contamination
- Procedures to address all of the above

Let’s Do Drugs!

By the numbers it’s 2 sections

21 CFR 210, CGMP in Manufacturing, Processing, Packing or Holding of Drugs; General

21CFR 211, CGMP for Finished Pharmaceuticals

21 CFR 210

Status: The regulations in this part and 211 through 266 contain current minimum good manufacturing practice for methods to be used in, and the facilities or controls to be used for the manufacture, processing, packing or holding of a drug meets the requirements...safety, and has identity and strength, quality & purity that it purports, or is represented to have.

21 CFR 210

Failure to comply shall render such drug to be ADULTERATED...responsible person shall be subject to regulatory action

21 CFR 210

Applicability: regulations in 210 – 266 as they may pertain to a drug & in 600-680 as they may pertain to a biologic for human use, shall be considered to **supplement** not supersede each other, unless the regulations explicitly provide otherwise

If you can't comply with all the regulations, the one applicable to the drug shall supersede

Other than definitions,

That’s all for 21 CFR 210

21 CFR 211

A - General Provisions

B - Organization & Personnel

C - Buildings & Facilities

D – Equipment

E – Control of Components, Containers & Closures

F – Production & Process Controls

G – Packaging & labeling

21 CFR 211

H – Holding & Distribution

I – Laboratory Controls

J – Records & Reports

K – Returned & Salvaged Drug Products

Personnel: Differences or Enhancements

211.22 **Responsibilities of quality control unit**

- Authority for all aspects
- Test products
- Approve or reject
- All responsibilities & procedures shall be in writing

Personnel: Differences or Enhancements (con't)

211.28: Personnel responsibilities

- Wear clothes appropriate for the duty
- Practice good sanitation & health habits
- Only authorized personnel shall be present
- Have illness or open lesions that may affect the product – they shall be excluded from contact with the product

C. Buildings & Facilities

- Design & construction
- Lighting
- Ventilation, air filtration; heating & cooling
- Plumbing
- Refuse & sewage
- Washing & toilet facilities
- Sanitation
- Maintenance

C. Plant & Facilities (606)

Clean & **orderly**

Suitable size, construction & location to facilitate cleaning, maintenance & operations

More detail for space related to:

Donor privacy

Exposure of equipment unrelated to collections

Space to store in an orderly manner **quarantined products separate from finished products**

Compare & Contrast

606

- Clean & orderly
- Size to facilitate cleaning, maintenance …
- Space for Equipment
- Space to separate products
- Space – Donor Privacy

211

- Design & construction
- Sanitation, Refuse & Sewage
- Maintenance
- Plumbing, Washing & Toilet Facilities
- HVAC, air filtration

Equipment Differences

606

- Specific examples of what to do

211

- Design, size & location
- Construction
- Equipment cleaning & maintenance
- Requirements for: automated, electronic, mechanical
- Filters

E. *Control of Components and Drug Product Containers & Closures*

- 606 this section is reserved
- General requirements
- Receipt & storage of untested
- Testing: approval/rejection
- Use of approved
- Retesting of approved
- Rejected

F. *Production & Process Controls*

606	211
SOPs	**SOPs**
	Deviations from SOP
	What is in the batch
	Calculations
	Equipment to make
	Sampling/Testing
	Time Limits
	Control – contamination
	Reprocessing/rework

Remember this List - 1?

- Donor acceptability
- Methods for donor qualification – acceptable values
- Preparation of phlebotomy site
- Tracking all products to the donor
- Collection procedures
- Testing & repeat testing of products
- Pretransfusion testing including recipient identification
- Investigation of donor & patient reactions
- Storage temperatures and control

Remember this List – 2?

- Expiration dates
- Criteria to determine if returned product is acceptable for reissue
- Tracking method for blood from donor to final disposition, transfused, or otherwise

Very Specific to the narrow range of products prepared

211 Production & Process Controls

Cover a broader scope because of the variable nature the finished pharmaceuticals

SOPs

Deviations from SOP

What is in the batch

Calculations

Equipment to make

Sampling/Testing

Time Limits

Control - contamination

G. *Packaging & Label Control*

- Materials examination & usage criteria
- Label issuance
- Packaging & Labeling Operations
- Tamper-evident packaging
- Inspection
- Expiration dating requirements

H. Holding & Distribution

- Warehousing procedures
  - Quarantine
  - Storage conditions
- Distribution procedures
  - Oldest distributed 1st
  - System to be able to facilitate recall

I. *Laboratory Controls*

Think out of the “testing box” for viral markers or the # of platelets

- Specifications, standards, sampling plans
- Procedures
- Determine: identify , strength, quality & purity
- Knew what was to be made ---> was it successful

I. *Laboratory Controls*

- What is tested to determine release?
- Is it stable?
- Are there any special requirements?
- Is there a system for reserved samples?
- If animals are used in testing...are there established, controlled specifications?
- Could there be penicillin contamination?

J. Records and Reports
What are these?

- Equipment cleaning & use
- Component, container & closure records
- Master production records
- Batch production
- Production record review
- Lab records
- Distribution records
- Complaint files

K. *Returned & Salvaged Drugs*

- How/why were they returned?
- Are they (components) reusable?

GMPs – Lessons Learned

Take Away Messages

- GMPs/GTPs: **Outline**
- Definition of Distributed
- Definition of Under [your] Control