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
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
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
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: SQuIIPP
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°C maintained for 20 minutes by saturated steam or by an *attained* temperature of maintained at 170°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

<table>
<thead>
<tr>
<th>Reagent or solution</th>
<th>Frequency of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-human globulin</td>
<td>Each day of use.</td>
</tr>
<tr>
<td>Blood grouping reagents</td>
<td>Do.</td>
</tr>
<tr>
<td>Lectins</td>
<td>Do.</td>
</tr>
<tr>
<td>Antibody screening and reverse grouping cells.</td>
<td>Do.</td>
</tr>
<tr>
<td>Hepatitis test reagents</td>
<td>Each run.</td>
</tr>
<tr>
<td>Syphilis serology reagents</td>
<td>Do.</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Each day of use.</td>
</tr>
</tbody>
</table>

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)
<table>
<thead>
<tr>
<th>Subpart</th>
<th>Section</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Subpart A</td>
<td>General Provisions</td>
<td>1271.150</td>
</tr>
<tr>
<td>Subpart B</td>
<td>Organization &amp; Personnel</td>
<td></td>
</tr>
<tr>
<td>Subpart C</td>
<td>Plant &amp; Facilities</td>
<td>1271.190 (a) &amp; (b) 1271.195</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Current GMP for Blood &amp; Blood Components, 606</th>
<th>Current Good Tissue Practice, Part 1271, Subpart D</th>
</tr>
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<tbody>
<tr>
<td>Subpart D</td>
<td>Equipment</td>
</tr>
<tr>
<td></td>
<td>1271.200 (a)</td>
</tr>
<tr>
<td>Subpart F</td>
<td>Production &amp; Process Controls including Donor Eligibility</td>
</tr>
<tr>
<td></td>
<td>1271.220</td>
</tr>
<tr>
<td></td>
<td>1271.50-eligible</td>
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<tr>
<td></td>
<td>1271.80-testing gn</td>
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<td>1271.85-testing sp</td>
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<td>Subpart G</td>
<td>Finished Product Control – Labeling</td>
</tr>
<tr>
<td></td>
<td>1271.250 (a) &amp; (b)</td>
</tr>
<tr>
<td>Subpart I</td>
<td>Records &amp; Reports</td>
</tr>
<tr>
<td></td>
<td>1271.270</td>
</tr>
</tbody>
</table>
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”**

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<tr>
<td>But never fear! 610.53</td>
<td>Storage 1271.260</td>
</tr>
<tr>
<td>Assortment including 820.198</td>
<td>Complaint File 1271.320</td>
</tr>
</tbody>
</table>
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

21 CFR 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.
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

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

SOPs
Deviations from SOP
What is in the batch
Calculations
Equipment to make
Sampling/Testing
Time Limits
Control - contamination

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