HOW CAN WE GENERATE A CLINICAL GRADE CELLULAR PRODUCT?
MSC Therapy
For Neurodegeneration

Cells produced under:

GOOD MANUFACTURING PRACTICE (GMP)

with
QUALITY CONTROL (QC)
and
QUALITY ASSURANCE (QA)

STEM CELL HARVEST

STEM CELL TESTING and STORAGE

STEM CELL CULTURE

STEM CELL INJECTION

IMPROVED PATIENT
Stem cell therapy for blindness

Clinical trial with UC Davis GMP Facility. About 8 hours

Bone Marrow Harvest

GMP Facility

Quality Control and Quality Assurance

Stem Cell Sort
GMP
Good Manufacturing Practice
THE HISTORY

• In 1901, diphtheria patients were routinely treated with antitoxin derived from the blood serum of horses. There were no central or uniform controls in place and the antitoxin was often manufactured in local plants.

• In St. Louis, Missouri, that combination had tragic consequences. Thirteen children died of tetanus after being treated with diphtheria antitoxin made from the blood of a tetanus-infected retired, milk wagon horse named Jim.
THE HISTORY

• Soon after this and a similar tragedy in Camden, NJ, involving deaths and injuries related to a tainted biological product, Congress enacted the Biologics Control Act of 1902.

• July 1, 2015, marks the 113th anniversary of the law, which gives the FDA’s Center for Biologics Evaluation and Research (CBER) authority to regulate biological products and ensure their safety.
Definitions

- **Biologics** are medical products derived from living sources.

  - They include vaccines, blood and blood derivatives, allergenic patch tests and extracts.
  - Tests to detect HIV and hepatitis.
  - Gene therapy / gene transfer products, cells and tissues for transplantation.

- Biologics may form the basis of new treatments for cancers, arthritis, and other diseases.
Step Wise Approach to Application of Regulatory Requirements
pre - 2000

• Pre-Clinical (GLP*)
• Phase I (Start of GMP*)
• Phase II (Continued effort towards GMP*)
• Phase III (Complete Implementation of GMP*)

• * All these terms will be defined and discussed in detail in the slides to follow.
Then, in 2000, there was a tragic incidence in Philadelphia. An 18 year old died in a gene therapy clinical trial.

- This triggered the FDA March 6 letter
  - implementing strict GCP for all phases
  - implementing GMP for all phases
  - FDA audits announced and readiness urged

Reply to the letter with all above programs implemented was a MUST to continue with ongoing clinical trials.
NO MORE Step Wise Approach to Application of Regulatory Requirements post - 2000 (March 6 letter)

- Pre-Clinical (GLP/GMP)
- Phase I (GCP/GTP/GMP)
- Phase II (GCP/GTP/GMP)
- Phase III (GCP/GTP/GMP)

However, some of these requirements were relaxed again recently
Definitions

• GLP = Good laboratory practice (everything is well documented, materials can be traced exactly to their origin.)

• e.g.: You developed a packaging cell line for production of retroviral vector for gene therapy.

• EVERY STEP of the generation of the packaging cell line MUST BE DOCUMENTED.

• e.g.: The origin of the cells must be exactly known. Cells must be completely characterized.

• Therefore, DOCUMENTATION is the most important aspect of this lab practice.
Definitions

- **GMP** = Good Manufacturing Practice (a national standard for the production of pharmaceuticals that assures safe and effective drugs).

- **cGMP** = CURRENT Good Manufacturing Practice.

- **SOPs and DOCUMENTATION** for everything.

- QC and QA procedures in place.

- Important point to remember: QC and QA must be done by DIFFERENT people.

- Acceptance and release criteria defined and controlled (sterility and potency).

- Personnel training and testing for proficiency according to SOPs.

- **DOCUMENT, DOCUMENT, DOCUMENT**
Definitions

• **GMP Facility = Good Manufacturing Practice**
  Facility: A facility under strict environmental control to assure manufacturing of a sterile, potent and uncontaminated product for human administration.

• **POINT TO CONSIDER:**
  • It is not good enough to have a GMP facility, it is vitally important to run it at GMP level!!!
Definitions

- GCP = Good Clinical Practice: An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.
- GCP assures that the rights, safety and well being of trial subjects are protected, and that clinical trials are credible.
Definitions

• **GTP = Good Tissue Practice: Regulations that govern methods used in, and facilities used for manufacturing human cellular and tissue-based products.**

• Include all steps in:
  – donor screening and testing
  – product recovery, processing, storage
  – labeling, processing, and distribution
How does cGTP compare with cGMP

• “c” again, stands for “current”.
• cGTP requirements are less extensive in scope than cGMP requirements for drugs.
• They differ, because cGTP requirements are limited to preventing circumstances concerning the introduction, transmission and spread of communicable disease.
• They are intended to assure that products do not get contaminated during manufacturing, and that product function and integrity are not impaired through improper manufacturing.
WHY cGTPs to begin with?

• There were incidences that prompted regulation: e.g.: Allograft associated bacterial infections (MMWR 2002; 51:207-210).

• cGTP has been conceived for minimal tissue manipulation (freezing of blood cells, T-cell depletion, etc.), since there was an increasing need to assure the quality of tissues manipulated and administered on a routine basis.

• cGTP is contained within cGMP.

  If you’re doing GMP with tissue, then you’re already doing GTP, and there is nothing to be afraid of.
Do we need to comply with cGTPs?

- Absolutely, since cGTP has been signed into law.
- Effective date: May 25, 2005
- FDA enforces cGTP.
- 21 CFR Parts 16, 1270, and 1271: Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement; Final Rule
- 68612 Federal Register / Vol. 69, No. 226 / Wednesday, November 24, 2004 / Rules and Regulations
How do I go about starting a clinical trial involving biologics?

- Produce pre-clinical data according to good laboratory practice.
- Have everything completely documented (good lab books).
- Use cell lines that can be completely traced (if you don’t know the exact origin of the cell line, don’t use it).
- Have detailed information on the reagents available (make sure you REALLY know the sequence of your gene insert, etc.).
How do I go about starting a clinical trial involving biologics?

• Pre-clinical data for a Phase I Clinical Trial (a safety study) are:
• SAFETY DATA in vitro and in vivo - in mice or other relevant animal models. In vivo studies for safety are absolutely critical.
• Efficacy data in vitro and in vivo - the product should be able to produce therapeutic results that may translate into human studies.
• HOWEVER, THE FDA WILL MAINLY FOCUS ON SAFETY DATA FOR THE PHASE I STUDY.
How do I go about starting a clinical trial involving biologics?

- When it’s time to write an IND (Investigational New Drug) application, make sure you know EXACTLY want you want to test in the Phase I study, who will be sponsor, principal investigator, subinvestigator, etc.; define your patient population.
- Put ALL the hierarchy for the study in place.
- You need to consider the 3 parts of a clinical trial: cGCP, cGTP, cGMP.
- Define the endpoints of your clinical study and the timeframe of clinical follow-up.
- Follow up for gene therapy is 15 years.
How do I go about starting a clinical trial involving biologics?

• Involve the RAC (Recombinant Advisory Committee at the NIH) if you deal with gene therapy or recombinant DNA studies. This is the first institution to contact.

• Get IBC (Institutional Biosafety Committee) approval. The IBC is the institutional representative of the RAC.

• Establish a DSMB (Data Safety Monitoring Board).

• Have auditors in place to audit your clinical protocol.

• Get IRB (Institutional Review Board = Human Studies Committee) involved and the protocol approved.
How do I go about starting a clinical trial involving biologics?

- **Request a pre-IND meeting with the FDA.** Submit a short write-up of the planned IND, and discuss it with a panel of FDA regulatory persons. The agency will tell you what you HAVE to have in your IND, and will take into consideration your questions about what you can do or cannot do in your study.

- **SUBMIT THE IND.** The FDA has 4 weeks to answer. If you don’t hear back, you are automatically approved. However, this is VERY unlikely. Rather, expect a phone call from the FDA right before the end of the 4 week period.
Utilize Good Clinical Practice

• **AFTER APPROVAL OF THE IND:**
  • Have a part of your clinic devoted to clinical research (this will be the part where the cellular / biologics therapy will be administered), and have it perform to cGCP regulations.
  • Have absolute control over patient records that are related to your clinical protocol (data manager).
  • Keep confidential records absolutely confidential, but have a good system for CODED data retrieval.
  • Be always ready for an unannounced FDA audit and be able to produce your records upon demand from the agency.
Utilize Good Clinical Practice

• Have a good system in place to report adverse events.
• In gene therapy clinical trials, ALL adverse events need to be reported, regardless of their relation to the clinical trial. If a patient falls out of the bed, you report.
• YOU WILL BE JUDGED BY YOUR ADVERSE EVENT REPORTING!
• All these parts need to be able to interact well with each other.
• VITALLY! important when you get an FDA audit.
Utilize Good Manufacturing Practice

• Have a **GMP** facility with good **QC** and **QA**. **Quality Assurance is the Quality Control of the Quality Control.**

• Have a **DETAILED** step by step protocol (**Standard Operating Procedure = SOP**) for cell manipulations. **EVERY** step in the protocol needs to be signed off by **QC** and checked for accuracy by **QA**, which becomes a **“batch record”** for each manufacturing run.

• **Have a supply of clinical grade reagents.** If they are not available clinical grade, you need to **MAKE** clinical grade reagents out of them. Testing for sterility, stability potency and adventitious agents will often be sufficient. Also, certificates of analysis from the manufacturers can be substituted for these tests.

• **ASK FDA FOR GUIDANCE** with such reagents.
What exactly is a GMP facility?

- **GMP Facility = Good Manufacturing Practice Facility:** A facility under strict environmental control to assure manufacturing of a sterile, potent and uncontaminated product for human administration.

**POINT TO CONSIDER:**
- It is not good enough to have a GMP facility, it is vitally important to run it at GMP level!!!
- This was made very clear in a recent Type C meeting with FDA for approval of the new facility at UC Davis.
- SOPs for environmental cleaning, monitoring, presence of personnel 7 days a week.
A state of the art GMP facility at the UC Davis Medical Center
UC Davis Institute for Regenerative Cures at the UC Davis Medical Center in Sacramento
The Stem Cell Program received 20 million dollars in funding from the CIRM large facilities grant to build the UC Davis Institute for Regenerative Cures.
GMP Facility in the UC Davis Institute for Regenerative Cures:

6 Manufacturing labs (Class 10,000)
3 intermediate labs (Class 100,000)

Multi-use facility with high flexibility and versatility.

Construction start date: 9/2008
Opened: 3/2010
OUTSIDE ENVIRONMENT:
35,000,000 particles greater or equal 0.5 micron per cubic foot per minute (ISO 9)

Class 100,000 Cleanroom (= ISO 8)
Less than 100,000 particles greater or equal 0.5 micron per cubic foot per minute
(most likely GTP compliant)

Class 10,000 Cleanroom (= ISO 7)
Less than 10,000 particles greater or equal 0.5 micron per cubic foot per minute
(most likely GMP compliant)

Class 100 Cleanroom (= ISO 5) = Biosafety Cabinet
Also required for hard disk manufacturing!
Legend:
G=Gowning Room
IEN=Intermediate Entry Room
IEX=Intermediate Exit Room
M=Manufacturing Room
IMAG=Imaging Room
AU=Autoclave Room
HW=Hallway
TECHNICAL DESIGN

- All mechanical equipment in walkable interstitial ceiling space for easy service access.
- Ceiling light fixtures sealed, lamp change performed from interstitial ceiling without breaching room integrity.
- Individual air handlers for each room; 2 main intake and exhaust fans for redundancy. One of each can handle the complete load of the facility.
- Computerized facilities management and monitoring system for room pressurization, temperature humidity and equipment.
PRESSURIZATION OF THE GMP FACILITY for cellular manufacturing
PRESSURIZATION OF THE GMP FACILITY for cellular manufacturing
CHALLENGES FOR THE GMP FACILITY

1. Make true clinical grade, GMP FACS sorting (an inherently open technology) possible.


3. Make short lived radioactive isotope manufacturing and cell labeling for clinical Positron Emission Tomography (PET) possible.
Requirement for FACS based GMP grade cell sorters (according to type-C prefacilities meeting with FDA):

1. Sorter to be placed inside a negative pressure, Class 10,000 area.
2. Sorting to be performed in a Class 100 environment (Biosafety Cabinet).

UC DAVIS designed a validated biosafety cabinet in conjunction with Baker and BD that allows a FACS sorter (FACS Aria) to slide into the biosafety cabinet through a large cutout in the back.

This became the first, true GMP grade BD FACS sorter.
UNIQUE FEATURE OF THE UC DAVIS GMP FACILITY:

PRESSURIZATION SWITCHABLE FOR REQUIRED MANUFACTURING CONDITION
One Way Manufacturing Process Flow (Personnel, Product)

1. Enter Gowning Room; 2. Enter IEN; 3. Enter Manufacturing Room; 4. Manufacture; 5. Enter IEX; 6. Enter Degowning Room; 7. Exit facility
UC DAVIS STEM CELL PROGRAM

GMP LAB

6 manufacturing suites
3 intermediate rooms

Additional Features:
- cell and tissue imaging
- GTP and QC lab

Large LN2 freezer farm
Large lockable storage
To be GMP/GTP compliant:

Facility Quality Control: Strictly regulated by SOPs

- Automated facility monitoring system:
  Air pressures, temperature, biosafety cabinets, incubators, refrigerators and freezers with pager alarm to key personnel.

- Manual monitoring by personnel 7 days a week:
  Air pressures, temperature, biosafety cabinets, incubators, refrigerators and freezers.

- Environmental monitoring:
  Touch and settling plates, with alert and action levels according to USP.

- Environmental cleaning:
  Performed daily.

- Recertification of the facility:
  Performed annually.
Manufacturing room for cellular manufacturing

The actual work environment
GMP Manufacturing

The actual work environment
Products currently manufactured in the UC Davis GMP facility

- Bone Marrow CD34 + cells (ischemic retina) under UC Davis IND
- Mobilized Peripheral Blood CD34+ cells, transduced (HIV treatment)
- MSCs, non transduced and transduced (Huntington’s disease, critical limb ischemia) – CIRM - UC Davis Disease Team Grant
- Retinal progenitor cells from donor tissue (retinitis pigmentosa)
- Corneal cells from donor tissue (cornea repair)
- Micro-organs for drug delivery (transduced)
- hESC derived neuronal stem cells (ALS, Huntington’s disease)
- iPSC derived, gene corrected keratinocytes (Epidermolysis Bullosa)
- AAV vector for direct injection into the brain (Tay-Sachs Disease)
- Lentiviral vector (HIV gene therapy, critical limb ischemia and Huntington’s disease)
- Retroviral vector (cancer treatment)
- Novel drug formulations (Allopregnanolone for traumatic brain injury) under UC Davis IND
- Study drug for stable isotope tracer studies
- Nanoparticles (encapsulation of chemotherapeutic agents)
- Drug and placebo formulations for other clinical trials
Cellular manufacturing at the UC Davis GMP facility
Large scale cellular manufacturing at the UC Davis GMP facility

10 layer cell factory (traditional method)

Closed system hollow fiber bioreactor (modern approach)
GMP Grade FACS Sorting
The FIRST BD FACS Aria in a Class 100 Biosafety Cabinet

The actual work environment
Validated storage, freezing, autoclaving

-20deg C, -80deg C, liquid nitrogen

Pass through autoclave

The actual work environment
GMP Grade Hot Cell

The actual work environment
Good Manufacturing Practice for the final product:

- Define release criteria that go hand in hand with release testing = Certificate of Analysis for your product:
  - Sterility (gram stain, 14 day culture according to 21CFR, maybe replacable with Bactec, if validated in comparability study)
  - Endotoxin - LAL assay
  - Mycoplasma (PCR and culture according to USP).
  - Viability if cellular product (greater than 70%).
  - Product Characterization - the characterization tests will depend on the biologics you have in the trial.
  - Perform “in process” tests and tests after the finished manipulation of the product. Talk to the agency for specific requirements regarding your product.
Important things regarding both GMP / GTP / GCP:

- **Have proper labeling** and keep track of everything (bar code system very helpful).
- Have proper reagent lists with reagents received/logged in, reagents used for what purpose, and reagents logged out.
- Keep track of expiration dates - do not use reagents that are expired.
- For all human cell manipulations, a BSL 2 environment and universal precautions are required.
Important things to consider when dealing with the FDA:

- **DO** what you said you will do.
- **DON’T** do more than what you said you will do.
- Let the agency tell you if you need to do things in addition.
- **Comply** 100%.
- If you have an incidence that was caused by non-compliance, **ALL THE CLINICAL TRIALS IN THE HOSPITAL** could be shut down (remember the non-compliant Johns Hopkins asthma study that shut down all their clinical trials).
Regulations for Biological Products
Title 21    Code of Federal Regulations

• Part 312 - Investigational New Drugs (INDs) and
  Part 314 - New Drug Applications
• Parts 210, 211 Current Good Manufacturing
  Practices (cGMPs) (FD & C Act)
• Part 600 - 680 Biologics (PHS Act)
Part 312: Investigational New Drugs

- Part A: General Provisions
- Part B: IND Applications
- Part C: Administrative Actions
- Part D: Responsibilities of Sponsors and Investigators
- Part E: Drugs Intended to Treat Life-threatening and Severely Debilitating Illnesses
- Part F: Miscellaneous