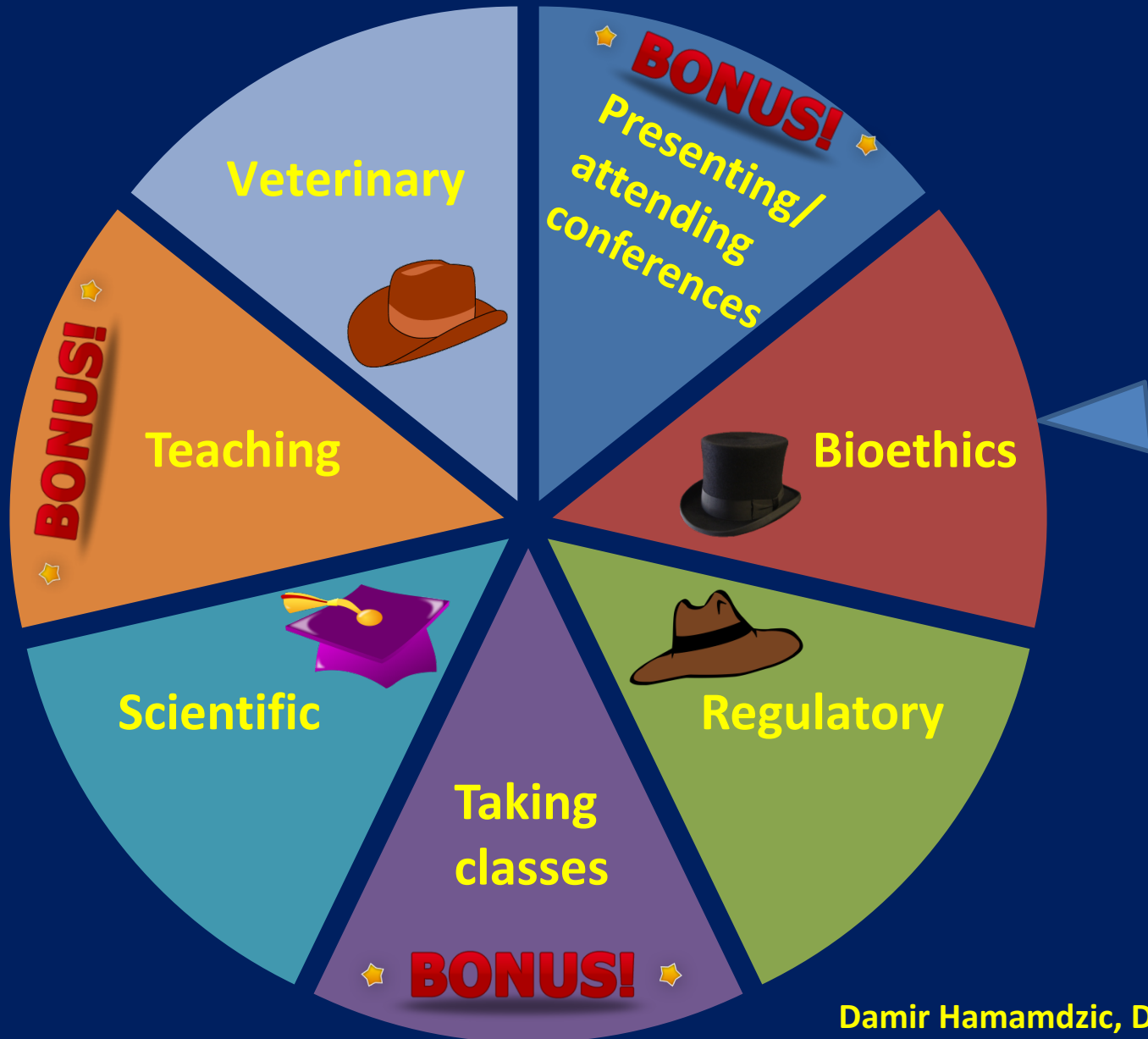


# **"From Bedside to Bench and Back: regulatory requirements for collaborations between pharma industry and academia"**

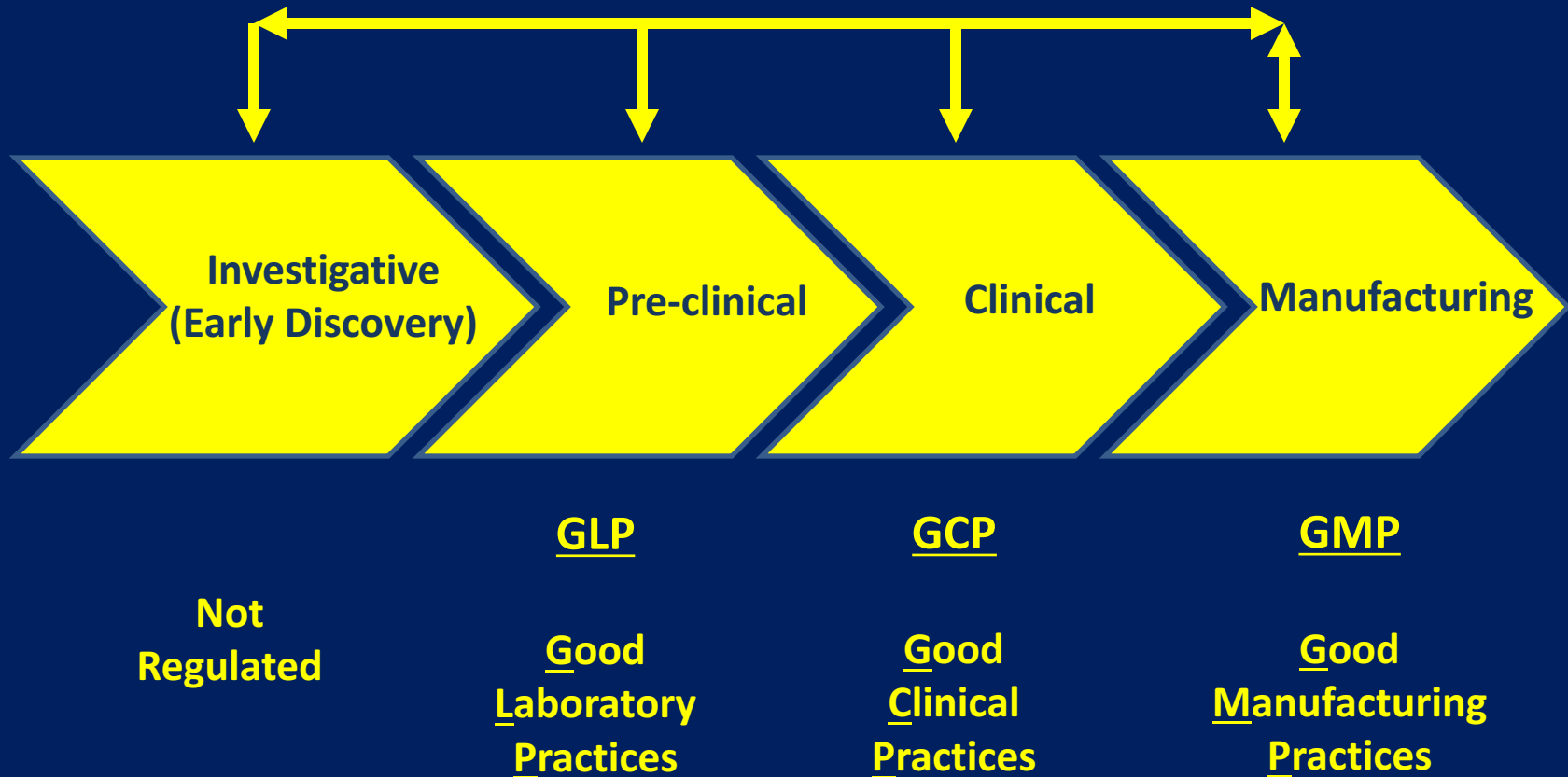
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# Let me introduce myself...



# Traditional Pharmaceutical Discovery Process and Regulations



# Good Laboratory Practices (GLP)

## 30,000 foot overview

- A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.
- GLP regulations are published in the Code of Federal Regulations (21CFR part 58).
- GLP apply to In vitro and In vivo procedures in which a test article is studied prospectively in test systems under laboratory conditions.
- GLP do NOT apply to studies utilizing humans, Clinical Trials, Field Trials in animals, or basic exploratory studies.
- GLP are not guidelines. They have the force of law.

# Basic Elements of GLP

1. Personnel (Qualification, Training Records, updated CV/Resumes).
  - Study Director
  - Staff
  - Quality Assurance/Quality Control (QA/QC)
2. Facilities.
  - Laboratory Operation
  - Animal Care
  - Equipment
  - Reagents
  - Storage

3. Documents.
  - Standard Operating Procedures (SOP)
  - Study Protocol
  - Reports
  - Archiving
4. Test and Control Articles
  - Characterization
  - Handling (Chain of Custody)
  - Storage
5. Electronic Media and storage
  - Validation and data backup and security.

FDA web-site for further reading:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58>

# Final Thoughts on GLP

- There is a “pecking order” to GLP studies:  
GLP Regulations > Study Protocol > SOP
- For Each GLP study the following statement is necessary:

**Institution name**

**Protocol No. 09802**

**Title of the study**

**This study was conducted at the Institution name in compliance with the U.S. Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58) and applicable Standard Operating Procedures except as noted in the report or raw data:**

**Study Director’s name and Signature:**

**Date:**

***This becomes a legally binding document***

# Good Clinical Practices (GCP)

## 30,000 foot overview

- GCP is an international, ethical, and scientific quality standard for designing, conducting, recording, and reporting trials involving humans
- Compliance with this standard provides public assurance that the rights, safety, and well being of trial participants are protected, consistent with the principles of the “Declaration of Helsinki”, and assuring data integrity.
- Guidelines for Good Clinical Practices – International Conference on Harmonization (ICH).
- Clinical material must be tested for safety and efficacy in humans. These tests in humans must abide by GCPs.
- Sponsor is responsible for Standard Operating Procedures (SOP).

# Basic Elements of GCP

- **Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).**
- **Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.**
- **The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.**
- **The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.**
- **Clinical trials should be scientifically sound, and described in a clear, detailed protocol.**
- **A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.**



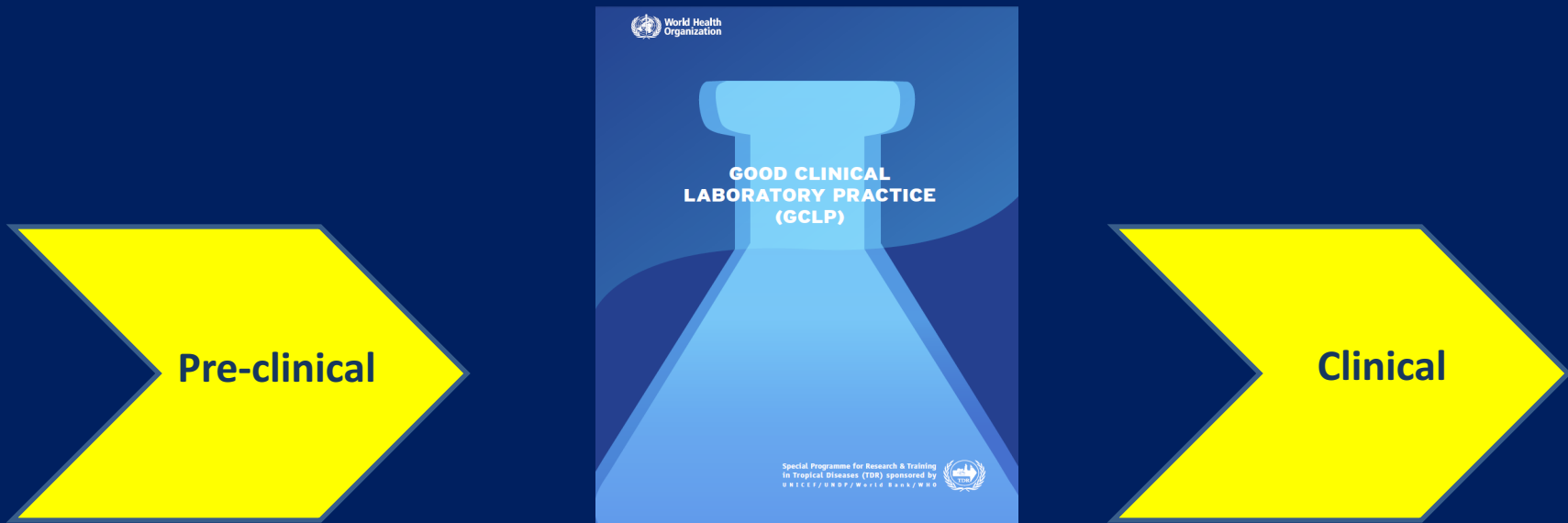
## Basic Elements of GCP (continued)

- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

# Traditional Pharmaceutical Discovery Process and Regulations



# Traditional Pharmaceutical Discovery Process and Regulations



Pre-clinical

GOOD CLINICAL  
LABORATORY PRACTICE  
(GCLP)

Clinical

GLP

GCLP

GCP

Do NOT  
Apply to  
Clinical  
Studies

Bridging  
the Gap

Do NOT  
Apply to  
Pre-  
Clinical  
Studies

# GCLP

## 30,000 foot overview

Good Clinical Laboratory Practice (GCLP) applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.



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# Basic Elements of GCLP

## SCOPE:

- GCLP guidelines should be adopted by any organization that analyses samples generated by a clinical trial.
- The GCLP principles apply to the analysis of a blood sample for routine safety screening of volunteers (hematology/biochemistry) and to pharmacokinetics or even the process for the analysis of ECG traces.
- GCLP applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.
- GCLP guidelines and principles should be adopted by pharmaceutical companies, contract research organizations (CROs), central laboratories, hospital laboratories, clinics, Investigator sites and specialized analytical services.

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- **GCLP guidelines and principles should be adopted by pharmaceutical companies, contract research organizations (CROs), central laboratories, hospital laboratories, clinics, Investigator sites and specialized analytical services.**

# Basic Elements of GCLP

## 1. Organization and Personnel.

- Trial Facility Management.
- Analytical Project Manager (PI).
- Trial Staff.

## 2. Facilities.

- Laboratory Operation.
- Trial Facilities.
- Archive Facilities.
- Waste Disposal.
- Storage.

## 3. Equipment, materials, reagents.

## 4. Documents.

- SOPs.
- Training records.
- Reports.

## 5. Planning of the work.

- Analytical Plan
- Trial Materials
- Handling (Chain of Custody)
- Storage
- Method validation
- Analytical Results and Report

## 5. QA/QC

- Validation and data backup and security.

WHO web-site for further reading:

<http://www.who.int/tdr/publications/documents/gclp-web.pdf>

## Why is GCLP important?

- More and more pharmaceutical companies are outsourcing their R&D to academic institutions because of access to the source of knowledge and to cut costs.
- This works well for the academic institutions, too.

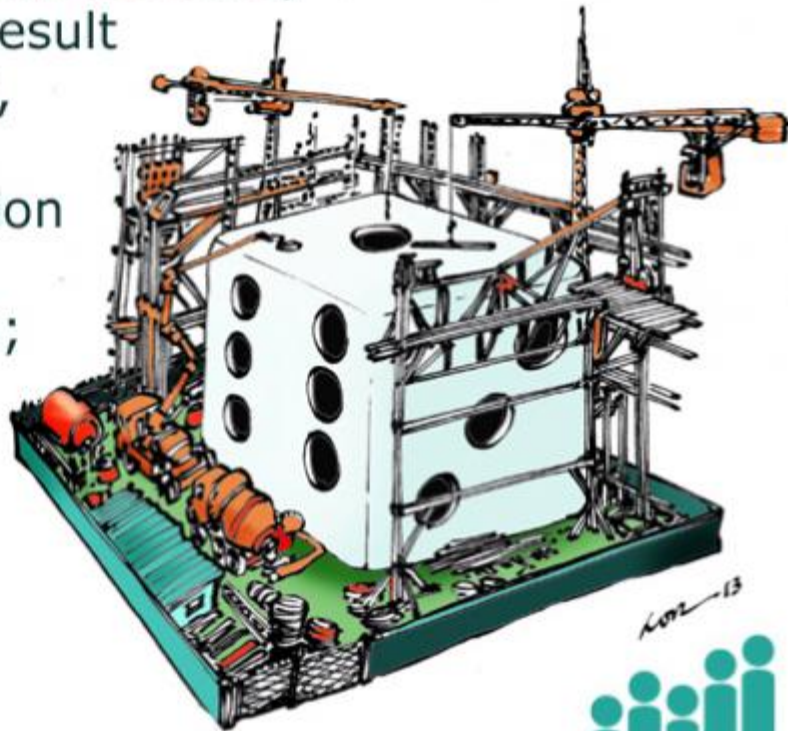
## But who is responsible for regulatory and ethical issues?

- Has anyone noticed that “Translational Research” is all the rage?
- Biologics, more than classical pharmaceuticals are at the forefront of the latest advances in Medicine.
- Biologics require physical proximity of the “test article” to the hospital bed.
- CAS9 CRISPR technology will revolutionize medicine, but is a regulatory and ethical minefield.



# Thank You

Quality is never an accident;  
it is always the result  
of high intention,  
sincere effort,  
intelligent direction  
and  
skillful execution;  
it represents  
the wise choice  
of many  
alternatives.



William A. Foster



## Scenario #1

**A cancer gene therapy clinical study funded by a pharmaceutical company is being initiated at the “Great Eastern University Hospital”. Patients are hospitalized and white blood cells are removed by apheresis, infected with a non-replicating viral vector to express cancer specific co-receptors. The cells are cultured and propagated in vitro for 7-15 days and subsequently delivered back to the patient. These cells are expected to attack and shrink the cancer.**

## Scenario #2

An investigator at the “Great Eastern University” is developing a mesenchymal stem cell therapy for type I diabetes melitus. Biopsies are performed, tissue digested and cells are differentiated and cultured in large quantities, followed by freezing and storage in the -80C freezer in the investigator’s research lab. Two days prior to injection, cells are thawed and cultured in a tissue culture facility. At the day of injection, a technician collects the cells into a sterile tube and delivers cells to the hospital across the campus on ice.

## Scenario #3

Patients are entered into an AIDS research study at the “Great Eastern University” to investigate the effectiveness of a novel protease inhibitor after a low dose IL-2 treatment. Preclinical research indicates that the compound is most effective after IL-6 serum levels are allowed to peak to 200 pg/ml. The investigator will follow patient serum levels daily by performing ELISA in investigator’s research lab. When serum levels reach 180-200 pg/ml the treatment will be initiated.

## Scenario #4

An investigator at the “Great Eastern University” is initiating a clinical study to test a novel multivalent vaccine for prevention of Dengue fever. There are three strains of Dengue virus and pre-existing immunity against any one of the strains, results in hypersensitivity to proteins of the other two strains. Therefore, pre-existing immunity against any one of the strains is a reason for exclusion from the study. When enrolling subjects, the investigator will screen the patient by performing RT-PCR and titer the serum antibody levels by ELISA in her research Laboratory. These results will be documented and the decision to enroll a patient will be made based on the results.

## Scenario #5

FDA performs a routine audit of a clinical study at the “Great Eastern University” evaluating a novel treatment of childhood leukemia. Auditors request to review the Master Study Binder. During the review of clinical results, they come across the RT-PCR results determining if patients have an active adeno-associated virus infection. Study protocol states that blood will be collected by a clinical nurse, serum sample will be sent to the hospital clinical lab for routine blood work, and an additional 5 ml anticoagulated blood will be transferred to investigator’s research laboratory for adeno-associated virus specific RT-PCR analysis. Review of the study protocol revealed that this laboratory test was approved by IRB, indicated by a sentence: “Adeno-associated virus specific RT-PCR will be performed in accordance to GLP regulations and guidelines.”