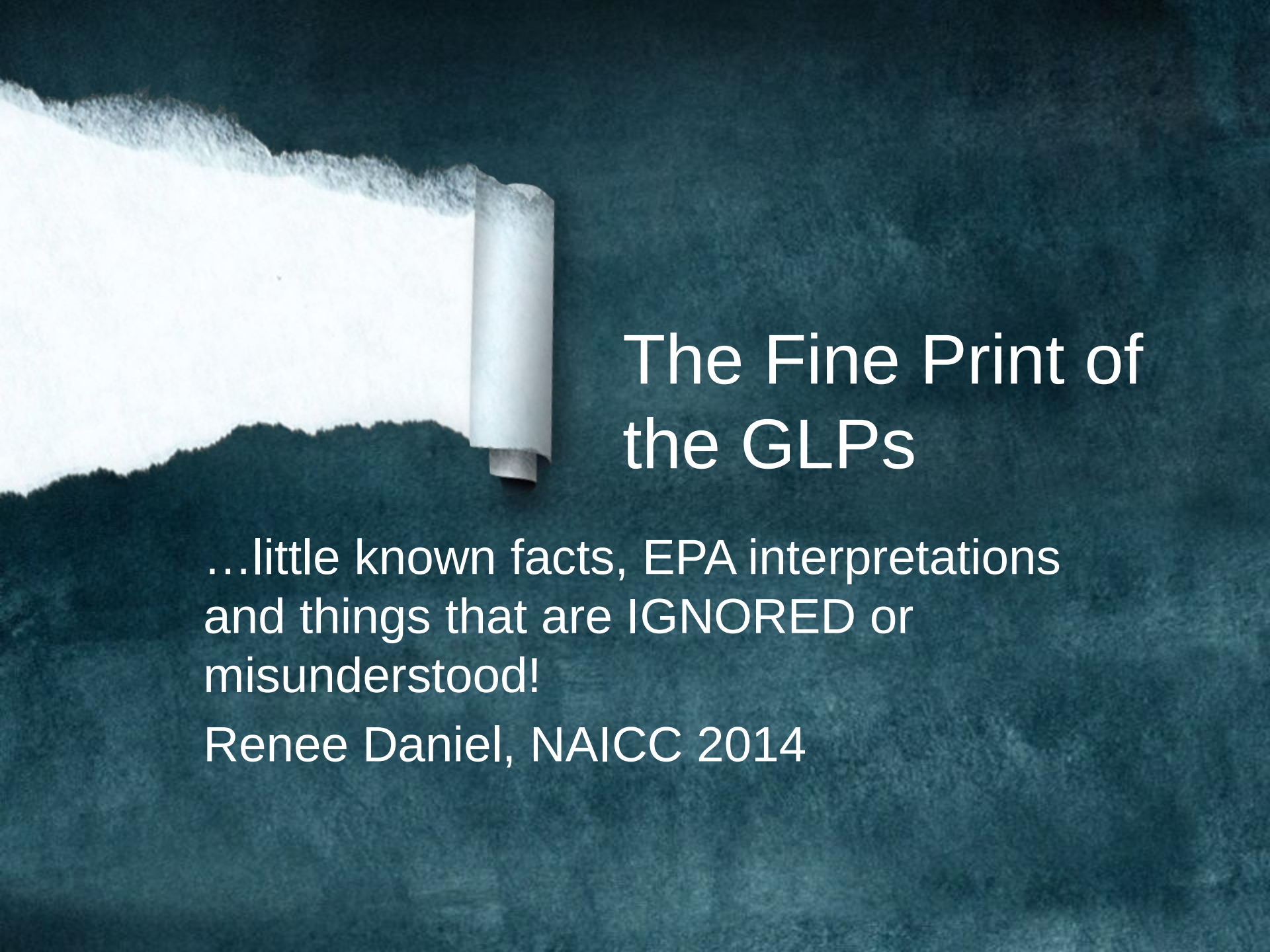

The Fine Print of the GLPs

…little known facts, EPA interpretations and things that are IGNORED or misunderstood!

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The Hidden Agenda

Discuss “fine print” of GLPs including little known facts, EPA interpretations and things that are IGNORED…or misunderstood!

- GLP Scope *(not a new kind of mouthwash)*
- GLP Compliance Statement *(ack really?)*
- Master Schedule Mysteries Unveiled
- Retain Sample and Container Retention
- Labeling Requirements *(EPA expects what?)*
- Who Needs Protocols?
- QA Reporting Enigma
- Whose Job is GLP Compliance Assurance? *(or who goes to jail!)*

GLP Scope – Sorting it all out…

- **Studies** that support or are intended to support applications for research or marketing permits for pesticide products regulated by the EPA including EUP, section 18 exemptions.
- Any **submission** sent to EPA intended to persuade EPA to grant, modify, or leave unmodified a registration or other approval required as a condition of sale or distribution of a pesticide.

Scope of GLPs – What is a Study?

- Any **experiment** in which a test substance is studied in a test system to determine or help predict its effects, metabolism, product performance (some efficacy studies), environmental and chemical fate, persistence and residue, or other characteristics in humans, other living organisms, or media.

Scope of GLPs – What is NOT in Scope?

- Basic exploratory studies carried out to determine whether a test substance or a test method has any potential utility (as long as they are not submitted to EPA to support a registration).
- Technically, any submission that does not meet the GLP definition of a study such as literature and bioinformatic searches.

Scope of GLPs – Efficacy Studies

- GLP only required if EPA submission required by 40 CFR 158.640
  - Product **claims to control pest microorganisms that pose a threat to human health** or a **claim to control vertebrates** (such as rodents, birds, bats, canids, and skunks) that may directly or indirectly transmit diseases to humans.
  - However, each registrant must ensure through testing that his products are efficacious when used in accordance with label directions and commonly accepted pest control practices. The Agency reserves the right to require, on a case-by-case basis, submission of efficacy data for any pesticide product registered or proposed for registration.

GLP Compliance Statement

- GLPs (40 CFR part 160.12) only allow 3 choices for GLP statement content
  - Study was conducted according to GLPs
  - Study was conducted according to GLPs except for……
  - Not the sponsor, didn't conduct study, don't know if GLP

  Note that saying "study was non-GLP" is not a choice

  •. According to Denise Rice, OPP Director of Quality Assurance, a complete and accurate description of the exceptions is needed to help determine usability of data. Some exceptions may have less impact but some may render the data unusable or relegate the study to supplemental.

Master Schedule Mysteries Unveiled

- QA does not have to be in charge of the master schedule (MS) but has to have a current copy (or access to MS if electronic).
- Technically, all studies conducted at facility are required to be on MS but since non-GLP studies are outside scope of GLPs this is sometimes interpreted as “don’t need to be on master schedule”. EPA GLP preamble indicates that MS only needs to list studies that will be or will likely be submitted to EPA.

Master Schedule Mysteries Unveiled

- No requirement stated for frequency of updates but MS has to be current (e.g., change when information changes).
- No requirement to print, initial and date.
- Must be indexed by test substance (e.g., sorted by test substance such as on a spreadsheet)
  - Typically, whatever will be registered by EPA and “sold” to the customer so may be an event in the case of GMO studies

Master Schedule Mysteries Unveiled

- Must contain
  - test system (e.g., crop, soil, rats),
  - nature of study (e.g., Residue, Soil Dissipation, Protein Expression), usually in protocol title
  - date study was initiated (i.e., date SD signs protocol),
  - current status of each study (can use simple terms like protocol, in-progress, reporting)
  - identity of the sponsor (this is not the management company, typically whoever is paying for the study and/or will “sell” product),
  - name of the study director.

Retain Samples and Container Retention

- Retain samples are required for studies of more than 4 weeks experimental duration. EPA GLP preamble clarifies that this is from experimental start (e.g., application) to experimental termination (last data collection) not initiation to completion.
- Storage containers shall be assigned to a particular test substance for the duration of the study so even empty containers such as seed envelopes need to be retained or the disposal included in the compliance statement.

Required Labeling

- Reagents/Solutions – identity, concentration, storage requirements, exp. date (includes tank mix adjuvants).
- Test, Control, Reference Substance – name (or CAS or code number), batch number, exp. Date (if any), any storage conditions necessary to maintain integrity.
- Samples – test system, study, nature, collection date

Who Needs Protocols

- Any testing facility listed in protocol must have a copy of the protocol if they are conducting a GLP analysis (including soil characterization) otherwise they cannot meet the GLP requirements.
- Every person that has a copy of the protocol needs a copy of all amendments or a record that the missing amendments do not relate to the facility.

QA Reporting Enigma

- After each study inspection – report any **problems likely to affect study integrity** found during the course of an inspection to study director and management immediately.
  - No requirement to send every inspection report but this is typically done so that QA is not assessing significance of problems and so that management knows inspections are being conducted.

QA Reporting Enigma

- GLPs require that QA submit periodic written status reports on each study to SD and management noting ANY problems and corrective actions taken.
- This requirement is in the GLPs because it was initially thought that QA would not send every inspection report to study director and management. Status report was supposed to be a tool to keep them informed of status of study with respect to minor problems and corrective actions that have been taken.

QA Reporting Enigma – What is a QA to do?

- Bottom line is that EPA expects the intent of the status report requirement to be met.
- CRO and Sponsor QA SOPs should outline how this is done within their facility.
- For CRO QAs, the intent of the requirement is met as long as each study inspection is reported to SD and management, and the inspection report includes corrective actions **taken** for all problems noted. In addition, the report would need to be sent immediately if any significant problems are noted.

Whose Job is GLP Compliance Assurance Anyway?

- QA – **Monitor** each study to assure management that facilities, equipment, personnel, methods, practices, records and controls conform with GLPs and review final study report to assure that methods and SOPs are accurately described and that results accurately reflect raw data….and **report.**
- Management – **Assure** that GLP deviations reported by QA are communicated to study director and corrective actions are taken and documented.
- Study Director – **Assure** that all applicable GLP regulations are followed.

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