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QUALITY ASSURANCE AND THE SCIENTIFIC METHOD

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Here, he discusses several issues related to Good Laboratory Practices (GLPs), Quality Assurance (QA), and the scientific method. Thanks are due to Donald Elias and Laura Greiner (NWRC) for reviews of an earlier draft of this paper.

INTRODUCTION

As all RMRCSQA members know, during the 1980s the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) implemented 40 *Code of Federal Regulations* (*CFR*) Parts 160/792 and 21 *CFR* Part 58, respectively. These regulations outlined GLPs for data collections needed to register pesticides, toxic substances, and drugs in the U.S.; QA concepts for study oversight were also described in these parts (see Sterner and Fagerstone, 1997). What you may not have considered is the relationship of these regulations to the scientific method.

THE SCIENTIFIC METHOD

The scientific method is the step-wise process whereby researchers ponder questions, formulate hypotheses, design and conduct studies, draw inferences, replicate results, and report findings to build a base of objective data about phenomena in the universe (see Gibbs and Lawson, 1992; Christensen, 1991; Sterner, 1998). It guides the scientist in deriving "real world" tests to obtain objective, empirical information about how things function in the world around us. That is, scientists use their unique reasoning skills to design specific studies that exemplify (test) some specific theoretical prediction. This is what makes the vocation challenging, stimulating, and fun for most of us.

Adherence to "the method" requires that a researcher identify an approach to be taken in testing some aspect of a theory. Generally, three approaches are recognized, and these need not be mutually exclusive. The descriptive approach involves natural observation, survey, archival, or case studies. The correlational approach entails analyzing linear, curvilinear, or multivariate relationships among variables. The experimental approach compares the effects of manipulated variables relative to a "point of comparison" (placebo) -- only 1-thing-changed-at-a-time approach. In experiments, independent variables are manipulated (e.g., hours of chemical exposure, mg/kg drug dosages) to assess their impacts on dependent variables (e.g., µg/g plant residues, mean litter size); only the experimental approach affords cause-and-effect statements about manipulations and results.

Research questions are phrased as null (H_0) and alternative (H_1) hypotheses--a way of forcing a dichotomous (yes or no) outcome to the question. Both H_0 and H_1 cannot "hold" at the same time.

Suppose that a researcher is working for a major chemical firm and evaluating new rodenticides; application of a 5% anticoagulant bait placed in rat burrows is posited to cause decreased numbers of rats in prescribed areas after placement. The investigator could obtain population indices for a number of separate burrows/areas and then apply placebo baits (carrier only) and 5% anticoagulant baits at half of the burrows/areas using random assignment. [Note.-- Random assignment is a crucial concept; it circumvents the need for random selection of burrows/areas from the total set of all burrows/areas anywhere in the world. By assigning test or placebo baits to burrows/areas at random, the researcher ensures unbiased manipulation while working with a limited sample.]

Possible null and alternative hypotheses in this scenario might be:

1. H_0: Rat Index Anticoagulant burrows = Rat Index Placebo Burrows
2. H_1: Rat Index Anticoagulant burrows ≠ Rat Index Placebo Burrows.

This would be an example of 2-tailed, non-directional hypotheses (greater or fewer rats post-baiting is

considered reason to reject H_0). Conversely, 1-tailed (uni-directional) hypotheses might be:

1. H_0: Rat Index Anticoagulant burrows ≥ 31% Rat Index Placebo Burrows
2. H_1: Rat Index Anticoagulant burrows ≤ 30% Rat Index Placebo Burrows.

That is, application of the 5% test bait is predicted to lower rat activity and numbers in burrows/areas by at least 70% relative to the sites which received the placebo. Interestingly, this is the form of hypotheses cited by EPA in the 1982 Product Performance Guidelines (EPA, 1982), but which are currently under revision (see EPA, 1998).

Following such a field study, the researcher would apply a statistical analysis (say a *t*-test) to these means and decide if H_0 was rejected (alpha 0.05; a *t*-value ≥ to that obtained is likely to occur ≤5 times per 100 analyses by chance)—the anticoagulant decreased rat indices sufficiently, or it did not. A replication would be advisable if the statistics were significant; however, who has the money/time for such sound research practices in these days of "publish:perish" or "compete: go-bankrupt"?

Finally, a scientific or technical paper should be prepared detailing the methods and results, and the data and report filed for posterity in a "safe" place.

Of course, the research process could be continued. Perhaps the company will want to know whether 4.5% anticoagulant baits will "work" as effectively as 5.0% baits or perhaps a new carrier will be shown to attract rats more readily. Products could be developed to make more profits by using less chemical with equal or better efficacy--R&D pushes onward.

REGULATORY COMPLIANCE OR METHOD ADHERENCE

Essentially, 40 *CFR* (Parts 160 and 792) and 21 *CFR* (Part 58) forced adherence to certain steps of the scientific method that were previously viewed as discretionary by scientists. Consider the following GLPs in view of "the method": (1) a protocol describing research methods, study design, and data analyses must be prepared and signed by the Study Director and Institutional Director before conduct of the study (of course, the chemical/drug Sponsor, Attending Physician/Veterinarian, Institutional Subject or Animal Care and Use Committee, etc. will have also approved the protocol); (2) One Study Director must be identified who has overall responsibility for all phases of the study (e.g., protocol, data collection, chemical/drug assays, reports, etc.); (3) Standard Operating Procedures (SOPs) should describe (i.e., procedures may be given in protocols) routine scientific tasks used to perform the research, and participants should be familiar with those that are used, (4) data must be recorded in ink, without erasures (i.e., corrections must be lined through, initialed, and dated); (5) the validity of the raw data must be confirmed by the chemical/drug Sponsor, Institutional Director, and Study Director in the form of a written GLP Statement (adherence and specific departures) with the "Final Report"; (6) a "Final Report" describing the procedures and results of each study must be prepared and signed by the Study Director to verify its authenticity and accuracy of statements; and (7) all raw data, original correspondence, final report, etc. must be archived in secure, readily-accessed storage for the length of time that the chemical/drug is registered (sold or used).

A VIEWPOINT

I believe that the "scientific-discretion issue," more than anything else, accounted for the "reluctant, less-than-enthusiastic acceptance" of GLPs by many scientists in the early '90s. Mandated GLP procedures smacked of "you're guilty until proven innocent", "scientists can't be trusted", and "scientists will commit fraud if given the chance". Whereas the conduct of basic (discovery) research in academia often involves a researcher going to his or her lab and observing or testing the effects of obscure variables on a measure (e.g., heat generated from a deuterium-water medium under electrolysis), scribbling penciled recordings on napkins, and storing these in a manila folder within a cardboard box in his or her closet, 40 and 21 *CFR* dictated strict study approval, data collection, and material archive procedures.

Additionally, although FDA was vague about specific study requirements (how an effect should be tested was left up to the scientist), EPA provided fairly detailed guidelines (see EPA, 1982) that gave recommended experimental-design and data-collection specifications studies used to support pesticide registrations. [Note.– In recent revisions of these guidelines, EPA has used a more "open-ended" (non-specific) tone (see EPA, 1998).] Scientists referred to such registration studies as "canned" (i.e., non-creative, directed). Add to this the fact that the QAU was set up to scrutinize compliance, and I think that you easily grasp how

scientists' skepticism may have originated.

Like many researchers, I remember the early 1990s as a near frantic period of writing SOPs, of enrolling in any and every GLP/QA training course available, of repeatedly amending protocols (i.e., inadvertently exceeding Study Completion Dates or altering a statement about the number or gender of animals involved in studies), of painstakingly preparing contents and packages of faxes, correspondences, etc. for archive files. I can also remember waiting months for sample analyses due to the workload placed on our analytical chemistry group; numerous validated analytical methods (not to mention sample analyses) were needed "yesterday".

CONCLUSIONS

In conclusion, I've tried to link GLPs to steps of the scientific method and to provide some perspective regarding scientists' adherence to both "the method" and GLPs. In the early 1990s, many scientists found questions of GLP incredulous; of course they followed good laboratory practices (i.e., all of that time and expense of graduate school wasn't wasted). The issue is (was) one of mandatory versus discretionary management of studies for accuracy, validation, and documentation.

QA professionals need to appreciate that "unwritten GLPs" have always been assumed under the steps of the "method", and that the imposition of GLPs onto environmental/pharmaceutical scientists is not a 1-way proposition. Just as scientists had to adapt to GLP/QA mandates affecting their credibility, QA professionals need to be cognizant of certain limitations of these mandates. To illustrate, I end with several questions (thought provoking ones, I hope):

1. What percentage of Laboratory Directors are prone to fraud?
2. How many data-transcription errors (1, 2, 3, etc.) equate to unreliable results (i.e., altered conclusion)?
3. What study deficiencies should trigger a replication?
4. Will 100% data checks salvage a chemical/drug from non-registration?
5. How, if at all, have GLPs/QA altered the probability that a pesticide/drug will be registered that could cause major undesirable environmental/health effects (e.g., DDE caused egg-shell-thinning in raptor eggs, Thalidomide induced F_1 deformities in humans, etc.)?
6. Do SOPs ensure that chemical analyses, animal identifications, etc. are performed as stated, even with a QA inspection?
7. Can a study be valid and reliable without having "integrity"?
8. If a janitor [formerly a member of Great Operatives Of File Saboteurs (GOOFS)] vacuums a laboratory's archive area while the Archivist is "out to lunch", when should a 100% audit of archive file contents be initiated (immediately, within a week, never)?

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