FIFRA-88, GLP, AND QA: PESTICIDE REGISTRATION

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The 1988 amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA-88) has decreased the number of pesticide registrations in the United States. Subsequent implementation of the U.S. Environmental Protection Agency (EPA) Good Laboratory Practice (GLP) and quality assurance (QA) standards has increased costs of maintaining these registrations. The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) maintains approximately 30 Section 3 (federal) or Section 24c (state) vertebrate pesticide registrations for the Wildlife Services (WS) program to control wild mammals and birds that damage crops, impact endangered species, or pose human health risks. Under FIFRA-88, APHIS summarized, performed, and submitted or gained waivers for >500 studies requested by the U.S. EPA to assess potential hazards/effects of these pesticides. A summary of FIFRA-88 milestones for registration of 3-chloro-p-toluidine hydrochloride (CPTH), the active ingredient (AI) in a "low-volume, minor-use" avicide (DRC-1339, Starlicide), is used to illustrate GLP/QA/animal welfare issues involved in this process. Trends in the development of new pesticides and veterinary drugs are compared to provide some perspectives on future career paths for QA professionals.

Under the 1947 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) legislation and a number of subsequent amendments (i.e.,

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1972, 1975, 1978, and 1980), Congress controlled and regulated the production and distribution of pesticides in the United States (U.S. EPA, 1984). Numerous issues of human safety and environmental contamination were involved. Although the U.S. Environmental Protection Agency (EPA) was initially directed to resolve these issues by 1977 (5 years after its founding), the magnitude of the task, combined with the "tiered study" concept whereby observations of health hazards, secondary toxicity, and environmental persistence could "trigger" more in-depth research, slowed progress.

In 1988, Congress again amended FIFRA (FIFRA-88) to speed reregistration of U.S. pesticides (U.S. EPA, 1991a). The next year, the EPA implemented the 40 Code of Federal Regulations (CFR) Part 160, which expanded the Good Laboratory Practice (GLP) and quality assurance (QA) provisions of FIFRA for these data-gathering efforts. Many Society of Quality Assurance (SQA) members owe their livelihoods to FIFRA-88. This legislation generated numerous QA jobs via "start-up" laboratories seeking to contract for and conduct the myriad of studies required to reregister pesticides.

Staff of the National Wildlife Research Center (NWRC) provide scientific expertise to the Animal and Plant Health Inspection Service (APHIS) to maintain approximately 30 FIFRA Section 3 (federal) or 24c (state) pesticide registrations needed by the Wildlife Services (WS) program to control wild mammals and birds that damage crops, impact endangered species, or pose human health risks (Fagerstone et al., 1990). Seven active ingredients (AIs) are used to make diverse wildlife damage management products/baits: carbon (CAS 7440-44-0), sodium nitrate (CAS 7631-99-4), sodium cyanide (CAS 143-33-9), sodium fluoroacetate (CAS 62-74-8), CPTH (CAS 7745-89-3), zinc phosphide (CAS 1314-84-7), and strychnine alkaloid (CAS 57-24-9). Most of these (use <68,000 kg/year) are considered "low-volume, minor-use" pesticides—chemicals that target a specific species, but whose registration/data-gathering costs would be difficult to justify based on sales. Under FIFRA-88, APHIS and NWRC staff summarized, performed, and submitted or gained waivers for >500 studies requested by the U.S. EPA to assess potential hazards/effects of these pesticides (Ramey et al., 1992, 1994).

Consider the aniline derivative CPTH. This is an avicide currently manufactured by PM Resources, Bridgeton, MO.* It is sold commercially under the name Starlicide Complete for use by certified pesticide applicators to control starlings and blackbirds in feedlots. CPTH is the AI, whereas Starlicide Complete is an end-use product. CPTH is highly

*PM Resources recently purchased the registration of Starlicide from Purina Mills, St. Louis, MO.

toxic (LD50 < 10 mg/kg) to most target species but is only moderately toxic (LD50 > 100 mg/kg) to most raptors and mammals (Decino et al., 1966; Schafer, 1981). This selectivity, coupled with use patterns and bait formulations that mitigate nontarget exposures, affords a safe, effective pesticide for wildlife damage management (Savarie & Schafer, 1986; Schafer, 1984).

This article presents an overview of the FIFRA-88 process implemented by EPA and (1) describes the FIFRA-88 process using reregistration of CPTH as an illustration, (2) provides examples of GLP/QA/animal care issues that surfaced during the data collections/submissions for CPTH reregistration, and (3) gives our perspectives on trends in pesticide and veterinary product registrations with implications to the future of QA.

FIFRA-88 AND 40 CFR PART 160

FIFRA-88 mandated that all pesticides containing an AI registered prior to 1 November 1984 be "reregistered" within a 9-year period (by 24 December 1997). This involved approximately 600 groups of AIs (technical products) and approximately 45,000 formulated products (U.S. EPA, 1991b).

Part 158 (Subpart B) of 40 CFR includes a list of the 12 subdivisions (D through R) included in the pesticide assessment guidelines (GDLNs) of chemical/environmental/human health hazards studies that can be required to register/reregister a pesticide (U.S. EPA, 1996). Each subdivision contains a matrix of the studies used to assess risks based upon a chemical's "use pattern" [i.e., terrestrial (food/nonfood crop), aquatic (food/nonfood crop), greenhouse (food/nonfood crop), forestry, domestic outdoor, and indoor] and "test substance" status (i.e., technical grade active ingredient, manufacturing-use product, or end-use product). Examples of Subdivision F Studies (hazard evaluation) are GDLNs 81-1 Acute Oral Toxicity (LD50 Rat), 81-2 Acute Dermal Toxicity (LD50 Rabbit), 81-3 Acute Inhalation Toxicity (Rat), and 81-4 Primary Eye Irritation (Rabbit). Results of these studies are then used by the U.S. EPA to determine environmental and health risks posed by the pesticide and the use pattern.

Coincident with FIFRA-88 were the U.S. EPA's own initiatives to implement 40 CFR, Part 160 (16 October 1989)—the GLP/quality assurance unit (QAU) regulations that many SQA members also know well (U.S. EPA, 1989). Part 160 specifies GLP and QA functions for FIFRA studies (U.S. EPA, 1996). Although not exhaustive, notable GLP mandates include: (1) Each study must be described a priori in a written protocol and signed by the sponsor, laboratory director, QA officer, and study director; (2) one study director is designated as ultimately re-

sponsible for the conduct of the study; (3) standard operating procedures (SOPs) are required for routine tasks used in the studies and must be made available to technical staff conducting the research; (4) the validity of the raw data must be confirmed by the sponsor, laboratory director, and study director in a written GLP statement included with the final report; and (5) all raw data, original correspondence, final report, etc. must be archived for the "life" of the registration in secure storage.

Set-up of a QAU having a separate line of authority from research but reporting directly to the laboratory's management is outlined in Part 160. Examples of QAU functions include: (1) Maintain a "master" schedule of all 40 CFR studies (pilot or research probes could be excluded) in progress at the laboratory, (2) inspect portions of actual research procedures or data collections, and (3) verify (with signature) the authenticity of raw data and the accuracy of the submitted data/report in a QA Evaluation Statement included with the Final Report.

FIFRA-88: THE PROCESS AND CPTH

Implementation of FIFRA-88 involved five phases, with either the U.S. EPA or registrants required to perform certain actions (U.S. EPA, 1991a, 1991b). A brief description of each phase follows, with actions/dates for the reregistration of CPTH (Table 1).

Phase 1 (EPA Released Lists of AIs)

The U.S. EPA began the process by publishing Lists A, B, C, and D of chemicals subject to reregistration in the *Federal Register* (see U.S. EPA, 1991a). A total of 194 pesticides (350 AIs) were on List A (22 February 1989); registration standards had already been issued for these AIs and were not subject to the remaining reregistration phases. Lists B (25 May 1989), C (24 July 1989), and D (24 October 1989) then named 229, 288, and 286 pesticides, respectively, in descending order of expected environmental/human health risks—a sort of "triage" approach to exposure and risk assessment.

CPTH appeared on List B. This list contained chemicals that were registered prior to 24 December 1988 but that the U.S. EPA believed lacked sufficient data for adequate risk determinations.

Phase 2 (Registrant Declared Intent to Reregister and Paid Initial Fees)

Within 90 days of List publication, companies that formulated, sold, or manufactured the AIs had to notify the U.S. EPA on whether they

Table 1. Milestones of the five-phase FIFRA-88 process showing key actions/dates for the reregistration of CPTH

1 EPA List	2 Purina/APHIS Intent to Reregister	3 Purina/APHIS Commit (New Studies)	4 EPA Reviews Phases 2 and 3	5 EPA Decision
B	a. Yes b. Identify and agree on studies c. Pay fee (installment 1)	a. 1967 Registration studies provided b. New studies (n = 38) 16 product chemistry 7 wildlife aquatic 8 hazard evaluation 5 environmental fate 2 residue chemistry	Data call-in	a. Registration eligibility decision (RED) b. Product-specific studies (n = 19) 12 product chemistry 6 hazard evaluation 1 efficacy
Statutory date 5/25/89	8/23/89	5/25/90	7/25/92	12/24/97
Actual date 5/25/89	8/23/89	2/25/92[a]	8/23/94[a] Photodegradation, soil: GDLN 161-3	2/20/96[a] RED technical product

[a]Actual dates altered by special waivers/extensions.

would seek reregistration. This also entailed a commitment to provide new GLP/QA studies (if needed) and pay fees for each AI ($50–150k/AI plus $700/year for the first end-use product and $1400/year for each additional such product) to be registered. With low-volume, minor-use chemicals, special waivers of some fees occurred.

The low-volume production and income from CPTH yielded little interest by Purina Mills to support the total costs of reregistration. Nevertheless, after APHIS pledged to perform many data requirements, company officials committed to provide some studies and seek reregistration of CPTH. This is an example of a "low-volume, minor-use" pesticide serving a key bird management function, with government and industry forming an informal consortium to retain availability of the AI and end-use product. Purina Mills agreed to maintain the registration, to officially submit the needed studies, and to pay required fees for CPTH.

Phase 3 (Registrant Summarized Past Studies, Stated Adverse Effects, and Paid Final Fees)

By October 1990, registrants were required to provide the U.S. EPA with summaries of past studies, to reformat former data, and to identify "adverse" effects from prior studies bearing on diverse issues (e.g., efficacy, human health effects, environmental fate). Remaining fees were also to be paid.

CPTH was originally registered in 1967; however, only minimal environmental safety and human health hazards data were required at that time. Data from studies used in the original registration and reports of adverse effects were provided to the U.S. EPA by Purina Mills.

Phase 4 (EPA Reviewed Phase 2 and 3 Submissions and Issued Final Data Call-Ins)

By July 1992, the U.S. EPA was expected to have reviewed the Phase 2 and 3 data. Data call-ins for additional studies concerning a particular AI were issued, with a 4-year completion date imposed (due in 1996).

The reregistration of CPTH required that 38 studies be submitted: 16 product chemistry (Subdivision G), 7 wildlife/aquatic hazards (Subdivision E), 8 human/domestic animal hazards (Subdivision F), 5 environmental fate (Subdivision N), and 2 residue chemistry studies (Subdivision O). APHIS provided all but the product chemistry studies. Moreover, these were completed by August 1994 with the exception that several extensions were requested and granted by the U.S. EPA to develop analytical chemistry methods (see Figure 1). Results of many of the APHIS-provided studies have been published in the open litera-

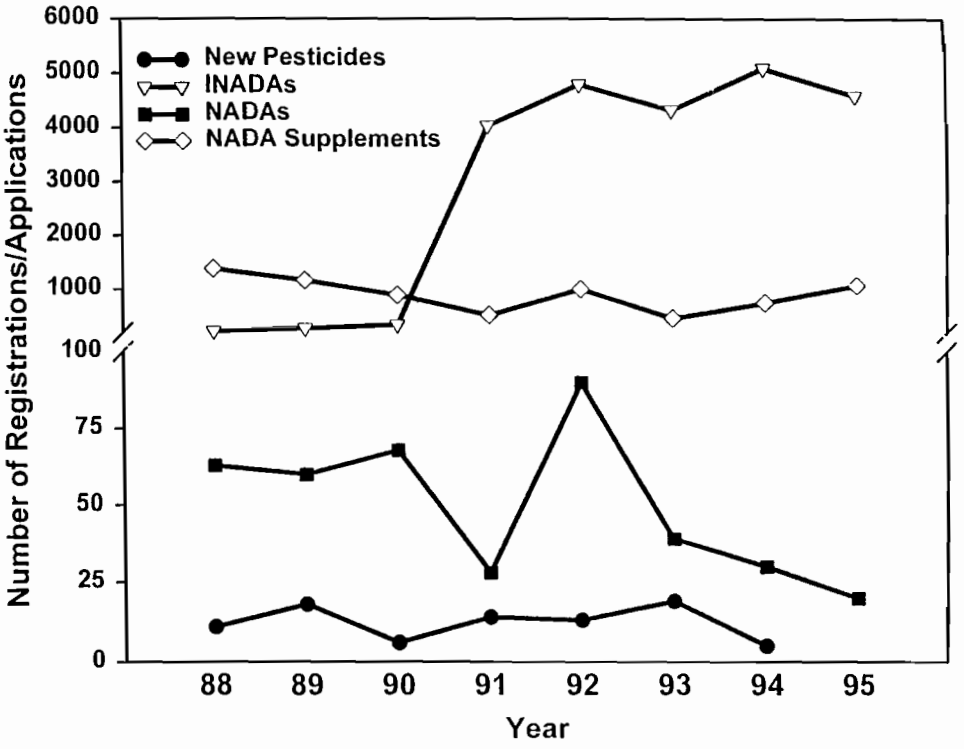

Figure 1. Graph of (first-time) U.S. pesticide registrations, INADAs, NADAs, and NADA Supplements between 1988 and 1995.

Note. EPA data for pesticides are not available since 1994; FDA data for INADAs, NADAs, and NADA Supplements are not available since 1995 [see annual *FDA Almanacs* (FDA, 1992–1996) and FDA Quarterly Activities Report (FDA, 1988) for FDA data].

ture (see Irwin et al., 1996; Spanggord et al., 1996a, 1996b; Sterner et al., 1994; Stankowski et al., 1997).

Phase 5 (EPA Issues Decisions)

Registration eligibility decisions (REDs) were to have been issued for all of List A, B, C, and D AIs by December 1997. The U.S. EPA was expected to have reviewed all Phase 2, 3, and 4 data and to have decided whether or not to reregister the AIs by this date. Studies that will have to be submitted for reregistration of end-use products must also be identified by December 1997. This deadline will not be met for all chemicals; however, APHIS has received six of seven REDs for their AIs. Only zinc phosphide (an acute rodenticide) lacks a RED, and the U.S. EPA is expected to issue this decision in October 1997.

The RED for CPTH was issued on 20 February 1996, approving CPTH for reregistration. Nevertheless, 19 product chemistry, hazard

evaluation, and efficacy studies for Starlicide Complete and DRC-1339 end-use products were required by 20 November 1996. Several risk-mitigation measures were also outlined (e.g., prebaiting to ensure less bait availability to nontargets, lower and uniform application rates on existent labels) that were to be added to the use directions on labels. PM Resources has complied with these RED requirements for CPTH and most end-use products; however, the company has requested cancellation of Starlicide Complete (i.e., APHIS may acquire the registration).

FIFRA-88 AND 40 CFR (PART 160): A PERSPECTIVE

Since 1988, APHIS has summarized, submitted, or received waivers for >500 studies needed to register/reregister the 7 AIs mentioned. This experience has afforded some insight into performance requirements of diverse studies sought by the U.S. EPA for these AIs as well as into GLP, QA, and animal welfare issues relevant to FIFRA-88 data submissions.

Conducting/monitoring mandated studies sought by the U.S. EPA require adherence to GDLNs published by the agency. Of course, the performance of any routine, standardized study is the bane of most scientists; it implies the conduct of noncreative, "canned" research. Granted, registration studies rarely involve basic research; however, the studies are critical to determination of crop tolerances for safe human/animal consumption, to establishment of aquatic usages in/near fisheries, or to identification of secondary hazards to nontarget wildlife. Moreover, interpretation of vague GDLNs, attention to enormous numbers of details (e.g., ≤90-day pre-/poststudy technical product assays, timeliness of SOPs, evidence of training for all participants), preparation of accurate, complete final reports/archives, "weathering" a QAU data audit, not to mention a possible on-site EPA inspection and the potential defense of an archived study, requires a focus on detail and organization generally lacking in "basic" research.

In an attempt to aid retrieval of common items most requested during U.S. EPA audits, the NWRC QAU required submission of a 14-point list upon archiving of each study. Items included: (1) address of the facility performing a study, plus pertinent dates (i.e., study initiation, experimental initiation, experimental termination, and study completion), (2) page listings of key information in the protocol and final report involving amendments/ deviations, statistical methods, etc., and (3) pertinent chemical information on the pesticide, carrier(s), control substance(s), and vehicle(s) (i.e., suppliers, CAS numbers, lot numbers). Although neither a GLP requirement nor appreciated by study directors, the list excerpted key dates, addresses, and pages of the final

report to aid the QAU during on-site inspections. We recommend this technique to QAUs that possibly have large numbers of studies on the Master List or are concerned about the timely retrieval of materials during on-site inspections.

The study director's responsibility for test systems (animals) poses additional responsibilities [see CFR 9 (Parts 1–199); U.S. Department of Agriculture, 1996]. A personal example of the author's (R. T. Sterner) involved monitoring the Primary Eye Irritation Test—Rabbit (GDLN 81-4) for CPTH (Draize et al., 1944). This test involves placing a small amount of concentrated AI into one eye of each of six albino rabbits each (the other eye serves as a control). CPTH is acidic.

Although this study was conducted in accordance with all appropriate animal welfare legislation, experiences involved an unexpected phone call from the study director on day 3 of the test. He informed the author that "severe irritation" was present in several of the rabbits' eyes; "What do you want to do?" Well, the answer may seem straightforward today—euthanize animals that appear to be in "severe pain"—but, in 1990, the U.S. EPA provided very little guidance regarding these types of issues. The implication in the GDLNs was that the study should "go to term" (14 days) so that results would not be compromised. The decision was made to go several more days and have the Study Director "watch the situation"; however, on day 8 (after multiple, daily communications), the study was stopped by the sponsor (APHIS) and the rabbits euthanized. To protect the data, a veterinary ophthalmologist was contracted to examine, photograph, and sign a clinical opinion that "irreversible corneal damage" had occurred to the rabbits' eyes exposed to CPTH. Interestingly, the aforementioned data submission was accepted without discrepancy.

The "precautionary statements" contained in the upper right portion of this pesticide's "use" labels read as follows:

> Harmful if swallowed, inhaled, or absorbed through the skin. Avoid contact with eyes, skin, or clothing. Handle only with protective gloves, clothing, and face mask, or respirator. Wash hands with soap and water after handling.

The RED indicated that the human health assessment studies showed CPTH to be "corrosive to the skin and eyes" (GDLNs 81-2 and 81-4) and a "mild to moderate skin sensitizer" (GDLN 81-7); the RED seeks that warnings of these effects be added to the precautionary statements.

This is evidence that the reregistration process works effectively. The submission of negative human health hazards data for the Draize test did not condemn CPTH to cancellation. Rather, it generated additional precautionary statements that conformed to results of the other Sub-

division F tests (e.g., primary dermal irritation, dermal sensitization). These statements warn users of potential safety/health concerns, but also convey that risks to humans can be mitigated by proper handling of the chemical and use of personal protective equipment.

PESTICIDE/DRUG REGISTRATIONS— SOME TRENDS/PREDICTIONS

FIFRA-88 expires on 24 December 1997. The condensed, 9-year timeline for these data submissions caused testing laboratories to flourish, but this intense period of data submissions is ending. Environmental scientists and QA professionals need to be cognizant of changes affecting these industries and professions.

Pesticide manufacturers will undoubtedly invest in many of the "product-specific" studies required for the end-use products by the REDs and will continue to develop a few new pesticides (see Figure 1); additionally, the U.S. EPA is now drafting GDLNs for additional studies (e.g., endocrinology, neurotoxicity). Although the ongoing regulatory process will avoid a sharp decline in the demand for 40 CFR tests, low numbers of new AIs will eventually reduce the volume of data call-ins and studies needed for pesticide registration. Between 1988 and 1994, only 86 new pesticide registrations (5–19/year) were submitted to the U.S. EPA (U.S. EPA, 1994). Moreover, of the approximately 600 groups of AIs cited in Phase 1 of FIFRA-88, 160 were canceled by registrants (U.S. EPA, 1991a); registrants chose not to pay the fees or to generate costly studies for those chemicals having low sales or high uncertainty of being reregistered. This, coupled with fewer new pesticide submissions, signals a longer term decline (say 10 years) in some traditional toxicology, environmental fate, and product chemistry studies needed to support registrations/reregistrations.

Additionally, some toxicology tests will undoubtedly be replaced by cell-culture-type tests shown to produce valid indices of toxicity/carcinogenicity. Data from these new tests will be counted/stored automatically by digitizing microscopes via computer links. Computerized models of potential chemical/biological/pharmacological effects will provide iterative data sets of possible outcomes that will serve in risk assessments.

Conversely, increased numbers of veterinary, "designer" drugs and vaccines are under development (not to mention biotechnology with its potential to also yield new pest-resistant, fast-growing, and greater yielding animals/plants). The veterinary pharmaceutical industry has recently undergone consolidation, with only a few major companies remaining. Costs of developing such expensive products require that these companies have sufficient capital to weather a failure; it takes

large outlays of cash to conduct and support the research needed to support/apply for these registrations.

What do these data suggest? That's correct—"downsizing" of pesticide QA/research functions and "upsizing" of veterinary/biotechnology QA/research functions. Decreased reliance on traditional toxicology and environmental fate work that many of us have performed/assured is "on the agenda." At the same time, clinical-type data collections for Investigational New Animal Drug Applications (INADAs) or New Animal Drug Applications (NADAs) with the Food and Drug Administration (see 21 CFR; FDA, 1996) will be "in demand"; this is evidenced by upward trends in INADAs and NADA Supplements (see Figure 1). QA professionals knowledgeable about Good Automated Laboratory Practices (GALPs) and Good Clinical Practices (GCPs) should find "hot" markets for their skills—cross-train into GCPs. Software-based data management and QA oversight/security of these files will be essential. Environmental scientists may witness a thrust toward the development of new, complex, more costly tests needed to provide improved predictions of carcinogenicity/teratogenicity, but the likelihood for increased numbers of traditional environmental fate/toxicity tests seems remote. As the period of FIFRA-88 ends, it is time for environmental scientists, QA professionals, and even laboratory owners/directors to reflect on "where we've been," "where we're at," and "where we're going."

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