

APPENDIX F

PROTOCOL FOR PHARMACEUTICAL ROUND ROBIN PROFICIENCY TESTING PROGRAM

1. SCOPE

The Pharmaceutical Round Robin Proficiency Testing Program is intended for accreditation of industrial hygiene laboratories that develop methods and analyze samples for the purpose of evaluating potential occupational exposure to pharmaceutical compounds in the workplace. Laboratory accreditation in this program is based upon a review of the laboratory quality systems as defined in Modules 2A and 2B and the following program specific requirements, and successful participation in the proficiency testing program defined below and in accordance with the requirements defined in Modules 6A and 6B.

The Fields of Testing (FoTs) applicable to the Pharmaceutical Round Robin Proficiency Testing Program are detailed in the IHLAP Scope/PT Table maintained on the AIHA web site (www.aiha.org).

2. FACILITIES

Laboratories must comply with the requirements of Module 2B for this section.

3. PERSONNEL

Laboratories must comply with the requirements of Module 2B for this section.

4. ANALYTICAL METHODS

Laboratories must comply with the requirements of Module 2B, Sections 2B.1 through 2B.4 (as applicable) and the following.

4.1 Sample Handling and Preparation

4.1.1 Due to the increasing potency of pharmaceutical industrial hygiene samples and the unique hazards this poses, the following procedures shall apply to both proficiency samples and client samples.

- a) Sample handling procedures shall ensure the safety of all employees handling pharmaceutical industrial hygiene samples.
- b) Sample handling procedures shall minimize cross contamination.
- c) Samples shall be extracted using in-situ extraction procedures.
- d) Effective decontamination and cleanup procedures shall be followed.

5. PROFICIENCY TESTING

5.1 Participation

Laboratories must comply with the requirements of Modules 6A and 6B for this section, in addition to the following.

Participation in the Pharmaceutical Round Robin Proficiency Testing Program is a qualification prerequisite for this accreditation program. The Pharmaceutical Round Robin Proficiency Testing Program is designed to share samples among participating laboratories to document that accurate analytical results can be generated by independent analysts following documented procedures. As a round robin program, each laboratory takes turns being the lead laboratory and coordinating the testing round. The PT analytes used in the Pharmaceutical Round Robin Proficiency Testing Program are listed in Table 5-1.

Table 5-1

INDUSTRIAL HYGIENE – PHARMACEUTICAL TESTING	
FIELD OF TESTING	PHARMACEUTICAL ROUND ROBIN PT ANALYTE AVAILABLE
High Performance Liquid Chromatography (HPLC)	Diflunisal Glipizide Triamcinolone
LC/MS	Not applicable
GC/MS*	Not applicable

* GC/MS is appropriate only when the sampling methodology is a filter for collection of pharmaceutical dusts.

5.2 Background and Definitions

For the purposes of this program, the laboratory responsible for preparing the spiked sample sets is referred to as the coordinating laboratory. The laboratories participating in the program are referred to as the participating laboratories. A coordinating lab can also act as a participating lab, however, the coordinating lab is not then exempt from being a participating lab and must have firewall provisions in place to appropriately execute both functions during a round. Thus, the activities associated with being the coordinating lab which include preparing, qualifying and supplying the cassettes necessary for the round are separate from the activities associated with being the participating lab which include analyzing the extraction efficiency spikes and sample spikes to be reported for the round. Firewall provisions must minimally include separate analysts assigned to each function, coordinating lab and participating lab, and separate lab notebooks maintained for each function. The Pharmaceutical Round Robin Committee is made up of managerial staff members representing the labs involved in the Pharmaceutical Round Robin Proficiency Testing Program. One committee member shall be designated as the non-AIHA PT Program Administrator and shall execute the responsibilities described in Module 6A.

The samples consist of active pharmaceuticals spiked onto filters encased in cassettes. The samples are appropriately identified as blank or sample, appropriately stored as per method recommendations, appropriately shipped similarly as routine samples obtained from clients, appropriately analyzed as per method requirements, and results obtained, appropriately reported as per this protocol. A Pharmaceutical Round Robin Proficiency Testing round will be performed twice per year, during the second and fourth quarters. A flowchart illustrating the Pharmaceutical Round Robin Proficiency Testing process is provided in Figure 5-1.

5.3 Responsibilities and Procedures

During each round, the coordinating laboratory is responsible for:

1. Selecting one of the PT analytes and corresponding validated method included in the Pharmaceutical Round Robin Proficiency Testing Program. The methods used must be validated for the following parameters: specificity, limit of detection, limit of quantitation, linearity, extraction efficiency, retention efficiency and stability. The methods included in the Pharmaceutical Round Robin Proficiency Testing Program shall optimally have a recovery of $100 \pm 5\%$. Included with this method will be a detailed description of the technique to prepare extraction efficiency samples. Method constraints include in-situ sample extraction, HPLC with UV detection and C18 columns or equivalent. No methods for controlled substances will be used. The analytical methods are controlled documents that have unique id's, managerial review and signoff, revision dates and number. The data collected will be processed with

appropriate data processing software capable of performing the necessary calculations to produce accurate reliable results.

2. Assigning personnel who have been adequately trained by review of related documents (SOPs, protocols, methods) and have shown proficiency in the analytical technique used for the round, to prepare and analyze the samples. Coordinating lab personnel must also be trained in the firewall provisions that are to be maintained to keep the function separate from that of participating lab. In addition, proficient performance as a participant in an earlier round must have been demonstrated.
3. Preparing the necessary number of spikes for QC purposes (ASAP spikes) and for participation in the round (sample spikes).

ASAP spikes:

- a) For each spike level, six (6) spikes will be randomly selected and analyzed as soon as possible (ASAP), prior to shipment of the spiked samples to participating laboratories, to verify that all spikes were prepared properly.
- b) The spike preparation process will be considered acceptable if each individual result determined for the ASAP spiked samples at each concentration level falls within $100 \pm 5\%$ theory, or within $\pm 5\%$ of the method's stated recovery, in units of % recovery. The theoretical spike amount is defined as the amount applied to a filter based on the actual weight of analyte added to a stock solution and spiked thereafter onto a filter.
- c) If the amount determined for any of the ASAP spiked samples does not meet the noted QC criterion, the spike preparation process is unacceptable and the remaining spikes must be discarded. The spike preparation process will be repeated until the ASAP spikes pass the QC test. The failure will be investigated to determine the cause of the problem, actions to be taken will be defined, pertinent parties will be notified, and all will be documented.

Sample spikes:

- a) One complete set of samples will be sent to each participating laboratory. Each spiked sample set will contain seven cassettes. One of the samples will be a labeled blank. The remaining six cassettes will have been spiked with different amounts of analyte to represent six different concentration levels. The concentration range of the spiked samples will be within the calibration range of the validated method so that appropriate extraction efficiency spikes can be prepared by the participating laboratories.

Total spikes:

- a) The total minimum number of spiked sample sets required is derived from equation 5-1. There will be at least $N+6$ number of sets created, where N = the number of participating laboratories and 6 represents the number of ASAP spikes required. Additional sets shall be created in the event a participating laboratory needs a replacement spiked set or to be available as a practice round following the close of the current round. The number of additional sets calculated in Equation 5-1 shall be rounded up to the nearest whole number.

Equation 5-1

$$\# \text{ Participating Labs} + 6 + \text{Additional Sets } ((\# \text{ Participating Labs})/3^* + 1) = \text{Total Number Sample Sets Required}$$

4. Supplying each participating laboratory with 20 additional blank cassettes for the extraction efficiency spiking study. These additional blank cassettes need not be assembled.

5. Storing the cassettes prior to shipment as per method recommendations and shipping the samples to the participating laboratories on a biannual basis, at the beginning of the second and fourth quarter of the year for the first and second round of the year, respectively. In conjunction with the shipment, the coordinating laboratory shall determine the due date for the round and clearly communicate the due date to each participating laboratory at the time of shipment. Laboratories shall have approximately 1 month after receipt of samples to submit results.

The cassettes will be securely sealed and labeled with id name. The cassettes will be packaged separately from the blank cassettes in the same shipping carton and shipped via overnight courier.

6. Handling all questions from participating labs with regard to complaints or technical guidance for conducting analyses. A record of all issues and responses generated from the round will be documented and reviewed by internal QA management of the lab as well as communicated to the Pharmaceutical Round Robin Committee for further review.
7. Submitting a summary report to the Pharmaceutical Round Robin Committee member responsible for performing statistics and determining proficiency which details the following:
 - a) Name of the coordinating lab
 - b) Date of report issue
 - c) Descriptive title
 - d) Labs will be identified by an id and not by name
 - e) Theoretical spike amount (the calculated amount based on the weight of analyte added to a stock solution) for each spike level in units of ug/filter
 - f) Results of the 6 sets of ASAP spikes (reported in units of ug/filter and % recovery versus theoretical) and calculated averages and coefficient of variation
 - g) Results received from all participating parties by the established due date (reported in units of ug/filter and % recovery versus theoretical). Late or unreported results shall be excluded from the summary report, unless otherwise pre-approved by the Pharmaceutical Round Robin Committee as temporary non-participation in accordance with Section 5.6 below.
 - h) Results from additional supportive studies if conducted with the round (i.e.: stability studies results at ambient versus -20°C control)
8. Maintaining a copy of the analytical method, lab notebook, correspondence for technical assistance, corrective action/preventive action report, individual lab result reports submitted and summary report for each round in accordance with internal record keeping policies of the lab.

During each round, the participating laboratory is responsible for:

1. Obtaining standard material (of known purity) so that analytical standards and extraction efficiency spikes may be prepared as needed.
2. Assigning personnel to prepare and analyze the samples who have been adequately trained by review of related documents (SOPs, protocols, methods) and shown proficient in the analytical technique used for the round. Participating lab personnel must also be trained in the firewall provisions that are to be maintained to keep the function separate from that of coordinating lab. Consequently, the personnel assigned to analyze the round would not have been involved with activities associated with preparing the round. Separate notebooks will be maintained for round participation and for round coordination.

3. Running the extraction efficiency spiking study by preparing and analyzing the internal QC spikes and thus determining the % extraction efficiency correction factor.
4. Analyzing the spike samples and correcting the results for media blank and extraction efficiency recovery.
5. Submitting results from both the extraction efficiency spiking study in units of % recovery and the spike samples, in units of ug/filter to the coordinating lab on or before the established due date for the round. If a replacement set is needed, it is the participating lab's responsibility to notify the coordinating lab in a manner that ensures timely replacement of the samples and allows for reporting of results on or before the established due date for the round. Data shall not be accepted after the scheduled close of a round. Reported spike sample results should be 1) corrected for recovery, 2) media blank corrected, and 3) reported as total ug/filter.
6. Including a detailed description of all deviations made to the method when reporting results.
7. Maintaining a copy of the analytical method, lab notebook and lab result report for each round in accordance with internal record keeping policies of the lab.

During each round, the Pharmaceutical Round Robin Committee is responsible for:

1. Designating a committee member to be responsible for:
 - a. Collating the data for the round,
 - b. Conducting the statistical analysis as detailed below for both round and lab performance,
 - c. Determining each participating laboratory's proficiency rating,
 - d. Communicating the proficiency rating to each participating laboratory, and
 - e. Providing a report of PT sample results to AIHA.
2. The Pharmaceutical Round Robin Committee will meet routinely via email, teleconference, site visits and/or at the AIHce to discuss issues concerning round performance, lab proficiencies, corrective actions, correspondence with AIHA, and other program issues. All decisions will be documented and shared with members.
3. Copies of summary reports and corrective action reports generated by the committee will be maintained by the designated committee member responsible for generating the performance statistics, and additionally maintained as per internal record retention guidelines.

5.4 Proficiency Testing Performance

5.4.1 Round Performance

- a) The sample spike results reported from the participating laboratories will be compared to the theoretical spike amount from the coordinating lab for each concentration level to determine percent recovery for each reported result.
- b) Only results reported by the established due date for the round will be included in determining the round performance.
- c) An overall RSD for the percent recoveries will be calculated for the round.
- d) The validity of the round will be determined. A round will be considered invalid if 1) overall RSD is greater than 20%, and 2) more than 50% of the reported results fall outside the performance limit range.
- e) Both criteria must be met to invalidate the round. In the event of an invalid round, the coordinating laboratory will work together with the internal QA management for the lab and the Pharmaceutical Round Robin Committee to immediately investigate the cause(s) of the invalid round and determine appropriate corrective action and

preventive action. The committee will notify all participating laboratories of the invalid round and the round will be repeated using the same compound.

5.4.2 Lab Performance

- a) Only results submitted by the established due date will be considered in determining laboratory performance, unless otherwise pre-approved by the Pharmaceutical Round Robin Committee as temporary non-participation in accordance with Section 5.6 below.
- b) The % recovery determined for each sample spike result reported by the participating laboratories will be compared to the established performance limits for % recovery of theory to determine whether the results are acceptable. An unacceptable result is defined as a result outside of the established performance limits. The performance limits for % recovery of theory, based on a statistical analysis of the historical Pharmaceutical Lab Round Robin data, 1991 – 2000¹, were determined to be 78 to 121 percent recovery (based on mcg added). The performance limits may be revised/reevaluated as additional Pharmaceutical Round Robin Proficiency Testing Program data are obtained, and/or the statistical methods used to define the limits are changed.
- c) For the Pharmaceutical Round Robin Proficiency Testing Program, a lab's performance rating will be based on accumulated results over two consecutive rounds (one year).
- d) A lab will be rated proficient if three-fourths (75%) or more of the accumulated results over two consecutive rounds are acceptable.
- e) The committee member responsible for generating the overall performance statistics will calculate the ratio of the number of acceptable results to the total number of samples to be analyzed and determine the % acceptable over the last 2 consecutive rounds for each participating lab.
- f) If a laboratory receives samples and does not report the data by the established due date for the round, all results for that round will be considered unacceptable, unless otherwise pre-approved by the Pharmaceutical Round Robin Committee as temporary non-participation in accordance with Section 5.6 below.
- g) A lab must have a current rating of proficient in order to be a coordinating lab for the Pharmaceutical Round Robin Proficiency Testing Program.
- h) The participating labs will be notified in writing of round performance and lab proficiency ratings. Included in the report will be the assigned values and range of acceptable results, along with the participants' results, % acceptable for last 2 consecutive rounds and proficiency status.
- i) The confidentiality of the participating laboratories will be maintained.
- j) Any issues or concerns that a participating laboratory may have regarding their proficiency rating will be handled by the Pharmaceutical Round Robin Committee and AIHA.
- k) Decisions will be based on sound scientific judgment without bias and pressures from employer, or other outside influences.

5.5 Requirements for Initial Accreditation

Laboratories must comply with the requirements of Module 3 for this section. In addition, laboratories applying for initial accreditation shall be enrolled in the Pharmaceutical Round Robin Proficiency Testing Program in order to be considered for initial accreditation.

5.6 Changes in Pharmaceutical RRP Testing Program Participation

Laboratories must comply with the requirements of Module 3 for this section. In addition, laboratories shall request changes to their participation in the Pharmaceutical Round Robin Proficiency Testing Program in writing to the Pharmaceutical Round Robin Committee. If

revocation procedures have been initiated for a FoT applicable to the Pharmaceutical Round Robin Proficiency Testing Program due to poor proficiency testing program performance, then the laboratory shall not be permitted to alter its proficiency testing program participation to avert revocation procedures. Acceptable reasons for PT participation changes include the following:

5.6.1 Temporary Non-Participation

A laboratory may temporarily stop participation in the Pharmaceutical Round Robin Proficiency Testing Program if their laboratory is undergoing renovations, if equipment is being serviced or new equipment is on order, or if they have a short-term personnel issue that prevents them from completing the required analyses. The laboratory must obtain permission from the Pharmaceutical Round Robin Committee, prior to the round closure date, to be excused from the PT round(s) in order for the laboratory's proficiency status and/or laboratory accreditation to be unaffected. Any unexcused non-participation shall result in outliers as described above that will, ultimately, impact the laboratory's accreditation status. Excused non-participation shall not exceed two consecutive PT rounds.

5.6.2 Practice Rounds

Due to the nature of the samples and the lack of long-term stability data, sample sets left over from the current round may be available for a reasonable time period after the close of the round.

5.6.3 Addition of a Field of Testing

Refer to Module 3.

6. MAINTENANCE OF ACCREDITATION

6.1 Maintenance of Pharmaceutical Round Robin Proficiency

Laboratories must comply with the requirements of Module 3 for this section.

7. ACCEPTABLE ADVERTISING FOR LABORATORIES ACCREDITED IN THE PHARMACEUTICAL ROUND ROBIN PROFICIENCY TESTING PROGRAM

Laboratories must comply with the requirements of Module 7 for this section.

¹Reference: *“Statistical Analysis of Historical Pharmaceutical Lab Round Robin Data”, a compilation and statistical analysis of round robin data from 1991 to 2000.*

Figure 5-1

Pharmaceutical Round Robin Proficiency Testing Program

