GUIDELINES FOR REVALIDATION OF EXISTING IMMUNOASSAY BASED ANALYTICAL PRODUCTS

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Revisions Included to December 13, 1996

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INTRODUCTION

Analytical products provide information to those using the product. Product manufacturers strive for uniformity so that a given test product produces results that end users can obtain and interpret in a consistent manner. EPA OSW has initiated a program to assign method numbers to analytical procedures performed with commercial immunoassay products. Product manufacturers provide laboratory data, field data, and product information that supports their request for a new method number or inclusion under an existing method. After a test product receives a method number, certain changes in the format (i.e, type or substrate of product, e.g., tube kit, coated microtiter plate kit, magnetic particles, etc.), performance or claims of the product will require the manufacturer to notify the EPA OSW and possibly the end users of that change. It is the intent of the manufacturers to minimize the occurrence of changes which would be detrimental to the performance or applications of the products and it is noted that detrimental changes are expected to be a rare occurrence. Changes often occur because improvements in performance or claims are achieved. This document specifies those modifications that would require the manufacturer to notify the EPA OSW and possibly submit performance data or other information to document the changes in format, performance or claims.

I. SUMMARY OF GUIDELINES

This document establishes that the requirement for notification of EPA OSW of changes in analytical products be based on whether there are changes in:

1) the critical performance characteristics
2) in the claims of the product, or
3) in the format of the product.

Any change which significantly (as defined below) affects the manufacturer's claims or performance characteristics of the product would require that the manufacturer notify the EPA OSW and submit appropriate data documenting that change to the EPA OSW for their review. The EPA OSW would 1) accept these data and agree to the change(s) in the manufacturer's claims or performance characteristics of the product or 2) request that additional data be generated and submitted to document the claims and/or performance change(s). Some claims or performance changes might require the manufacturer to generate some additional data or complete a partial revalidation but not require a complete external revalidation study. The response from EPA OSW would be generated within a flexible time frame consistent with the best interest of the Agency, the user community, and the operational need of the manufacturer. Any "format change" (as described below) would also require the manufacturer to notify EPA

OSW and to submit data to the EPA OSW for review. The EPA OSW could then determine whether this information was sufficient or whether an external revalidation study was required in the new product format.

The manufacturer would be responsible for documenting internally all changes in lots, materials or reagents (including antibodies) whether or not they change the format or alter the critical performance characteristics or the claims of a product. This documentation of changes that do not alter the format or the critical performance characteristics or claims of a product would not be submitted for review by the EPA OSW but should be available if requested for a specified purpose by the EPA OSW. These routine studies associated with changes in reagent lots or other materials must show that the performance of the product is not changed significantly (it must still pass the same routine quality control criteria). We propose that all manufacturers voluntarily agree to have data and any other relevant information available for confidential review by the agency that document lot changes, changes in reagents, and other manufacturing quality control procedures.

II. DEFINITION OF PERFORMANCE, CLAIMS AND FORMAT CHANGES

The definition of changes that requires the product manufacturer to notify EPA OSW are " 1) any change or modification in the materials, reagents or procedures that significantly alter the safety or effectiveness of the product or 2) a major change or modification in the intended use of the product, 3) any alteration of performance or claims that exceed the margin of error specified on the original claim, or 4) any significant change in the format or operating instructions of the product".

A. CRITICAL PERFORMANCE CHARACTERISTICS AND CLAIMS CHANGES

All quantitative performance claims such as sensitivity, specificity, precision and accuracy should be stated in the product insert along with corresponding statistical margins of error. Significant changes are those that result in product performance that is no longer within the stated margins of error for any of the claims. The claims can be narrow or broad and do not necessarily guarantee that the product is useful but the product must always operate within the stated margin of error of the claims. The ACS book chapter Rittenburg and Dautlick of AEIC "Quality Standards for Immunoassay Products" (ACS Symposium Series 586, Immunoanalysis of Agrochemicals; Emerging Technologies, Chapter 21, pp 301-307, 1995) was used as a starting reference for the list of parameters and should generally be followed to develop the product insert claims. Performance information and claims that are disclosed in the package insert will provide examples of changes based on this approach. This will require better standardization and some auditing of the product inserts by the AEIC and/or the EPA OSW. The following changes require the manufacturer to notify EPA OSW:

1. Inclusion of additional claims regarding new sample matrices (media)-For example, extending a water application to soil or food.

2. New assay workflow- For example changing sequence of reagent addition, volumes, incubation times.

3. Claims which alter the stability (shelf life) of entire product or any specific components. For example, as more data is collected over time the manufacturer may extend the time that a product can be stored at ambient or elevated storage temperatures.

4. Interferences. Effects on the analytical performance of an assay caused by substances other than the analyte of interest. Experience with new site situations may identify new potential interferences.

5. Sensitivity. Detection Sensitivity (Limit of Detection), Limit of Quantitation and Range of concentrations detected.

6. Accuracy. Bias (systematic error) and precision (random error).

7. Precision. Reproducibility in quantitative assays. False positive and false negative rates in semi-quantitative or qualitative assays.

8. New standard levels

9. Interpretation of data including changes in data reduction algorithms

B. FORMAT CHANGES

Immunoassay product performance may change when critical components of the method are altered. Product manufacturers must notify EPA OSW and document performance when one or more of the following change:

1. Changes in solid phase, e.g., changing from a coated microwell to magnetic beads or other solid support matrix; liquid assay to lateral flow device.

2. Changes in detector (enzyme or label) system. For example, changing from HRP to acridimium ester tag or colloidal gold.

3. Changes in physical preparation of sample. For example, extraction or filtration equipment (if included as part of the product) or solvent.

4. Changes in instrumentation that alters the interpretation of the assay.

5. Change in immunoassay format. For example, from competitive to capture (sandwich) format.

III. EXAMPLES OF CHANGES THAT WOULD REQUIRE NOTIFICATION OF EPA OSW AND REVALIDATION OF THE PRODUCT

A change in "critical chemistry" that causes a performance change is the main criteria that triggers some level of immunoassay validation. Examples of changes in the "critical chemistry" include:

1. Antibody change that results in the assay now detecting only one compound in a family of compounds when before it would detect several compounds in a family of compounds.

2. Changes in solid phase, e.g., changing from a coated microwell to magnetic beads.

3. Changes in detector (enzyme or label) system. For example, changing from HRP acridimium ester tag or colloidal gold.

4. A change from lyophilized to stabilized liquid conjugate.

IV. EXAMPLES OF CHANGES THAT DO NOT REQUIRE NOTIFICATION OF EPA OSW

1. New lots of materials, such as a new lot of antibody (monoclonal antibody line or polyclonal), standard, a new lot of buffer salts, a new lot of protein component such as BSA, a new lot of enzyme, a new lot of the same type of solid phase do not automatically constitute a change. The manufacturer's established QC acceptance testing criteria should govern the inclusion of these new lots in the product. These data should be available for confidential review if requested by EPA OSW, but will not be automatically submitted if there are no changes in performance of the assay or the associated claims.

2. New packaging. The manufacturer should, however, generate new stability data to support existing expiration dates. No notification will be required, but data should be available for review.

3. Performance changes that are "improvements", such as increased shelf life is an example of a change that the manufacturer wouldn't have to change claims to reflect the improvement. An "improvement" such as a more sensitive test however, would have to be disclosed due to the potential effects on the end user.