Pesticide Program Dialogue Committee PRIA Process Improvement Workgroup

Minutes of November 2, 2006 Meeting

Attending:

Workgroup Members:

Sid Abel, Environmental Fate and Effects Division (EFED)/Office of Pesticide Programs (OPP)
Kate Bouve, Information Technology and Resources Management Division (ITRMD)/OPP
Ron Derbyshire, JohnsonDiversey, Representing CSPA and Biocides Panel
Dennis Edwards, Antimicrobial Division (AD), OPP
Ted Head, Nufarm America, Representing the Chemical Producers and Distributors Association (CPDA)
David Jones, Nice-Pack, Representing the International Sanitary Supply Association (ISSA)
Jim Kunstman, PBI/Gordon, Representing CPDA
Elizabeth Leovey, OPP
Ray McAllister, CropLife America (CLA)
Marty Monell, OPP
Kathy Monk, Registration Division (RD), OPP
Amy Roberts, Technology Sciences Group, Representing the BioPesticides Industry Alliance (BPIA)
Lois Rossi, RD/OPP
Julie Schlekau, MGK Company, Representing Responsible Industry for a Sound Environment (RISE)
Julie Spagnoli, Clorox, representing the Pesticide Program Dialogue Committee (PPDC)
Heather Taylor, Natural Resources Defense Counsel (NRCD)
Greg Watson, Syngenta, Representing CLA

Participants:

Kent Carlson BPPD/OPP
Michael Hardy, AD/OPP
Thomas Harris, RD/OPP
Karen Hicks, AD/OPP
John Jamula, ITRMD/OPP
Arnold Layne, ITRMD/OPP
Debbie McCall, RD/OPP
Dominique Rey-Carruth, ITRMD/OPP
Russ Schneider, Monsanto
Robert Schultz, ITRMD/OPP
Warren Stickle CPDA
Donald Stubbs, RD/OPP
Michele Thawly, EFED/OPP
Nelson Thurman, EFED/OPP
Pauline Wagner, RD/OPP
Arty Williams, EFED/OPP

Agenda:

I. Introductions

II. Labeling Committee Update

III. Product Chemistry and Inerts - Progress Report

IV. Environmental Fate and Effects Division Spatial Aquatic Model

V. Blue Book - Status Report

VI. E-label Review

VII. Information Technology/Information Management – Status of electronic submission/jackets/fee payments and other projects

VIII. Public Comment

IX. Future Activities/ Projects and Next Meeting of Workgroup

Minutes

Introduction

Marty Monell, Deputy Director, Office of Pesticide Programs, began the meeting with introductions.

Labeling Committee Update

Updates on the activities of the Labeling Committee were provided by Donald Stubbs, Associate Director, Registration Division. The Labeling Committee's charge is to serve as a clearing house for broad cross-cutting label issues, to revise and keep current the Label Review Manuel and to manage a web site (http://www.epa.gov/pesticides/regulating/labels/label_review.htm) devoted to labeling issues which has an e-mail box (OPP_labeling_consistency@epa.gov) for general questions on pesticide labeling. The Committee posts answers to these questions, general labeling information and policy options papers for comment on its web site. The web page received an average of 600 "hits" per month. As of September 30, 2006, 60 questions had been received through the web site and e-mail box. Answers for 30 were posted, 20 were being addressed, 3 were referred elsewhere in OPP and 7 were either addressed directly or were duplicates. The questions received covered topics such as antimicrobial claims, chemigation, distributors, establishment numbers, existing stocks, notifications, pictures and logos, pesticide exemptions, product names, and termiticides. The public is encouraged to use the web site and e-mail box to obtain answers to their labeling questions.

The Committee's Label Review Manuel Team is converting the Label Review Manuel (LRM) (http://www.epa.gov/oppfead1/labeling/lrm/) from WordPerfect to Word, making corrections, revising it for compliance with current policy, and making it more web friendly. The first three chapters were being reviewed by the Committee and have since then been posted. Chapters 4, 5 and 6, were next to be reviewed. Web posted chapters will contain the date of last revision. The Committee welcomes comments on the LRM from the public through its e-mail box.

Public comments were requested on an issue paper "For Use Only By …". Thirty were received: 14 states, 8 Pesticide Control Officials, 4 trade associations, and 4 industry. Following a review of the comments, the Committee had four findings: 1. The use of pesticide products can be enforceably limited to specific groups of applicators provided they are clearly identifiable. Such clearly identifiable persons include; applicators defined by statute or regulation, individuals licensed or holding another government issued credential, or individuals with demonstrated employment by an entity identified on the label, such as a vector control agency. 2. Use and user limitations required by the Agency as terms or conditions of registration in order to mitigate risk must be stated in enforceable, mandatory terms. 3. Advisory language such as "recommended (or not) for XXX use", is acceptable for marketing purposes, but is not enforceable and creates no obligations on sellers or enforcement agencies. 4. For non-restricted use products, specifying allowable or prohibited use sites is preferable to limiting user groups. The Committee anticipates reviewing the Worker Protection Standard, certification and training materials, and the LRM for possible changes.

The Agency reiterated its guidance on warranty statements, provided it along with examples of warranty statements to Agency staff and posted the guidance on the Labeling web site. Staff training was conducted in November to assure consistency among regulatory reviewers.

The next issues to be addressed by the Committee includes whether the statement "contains active ingredient X, the same active ingredient as in Product Y" will be allowed on labels and if allowed, whether allowed by notification or amendment and the guidance on its format. Any proposed guidance will be posted on the Committee's web site and distributed widely for comment. An issue paper on minimum use rates, i.e. whether to allow minimum use rates on a label in the absence of data showing harm to man or the environment, will also be posted. The public will be asked for input on specific questions. In response to a workgroup member's question, past comments will be considered. The PPDC Consumer Pesticide Label Improvement Workgroup recommendations on revisions to general environmental hazard statements for outdoor consumer products were being considered by the Committee with a focus on the procedure to adopt the recommendations. A PR Notice is an option.

One of the next issues to be considered by the Committee is chemigation. Current guidance (PR Notice 87-1) is obsolete and does not address current technologies and the increased use of subsurface drip irrigation. A notice with new guidance that is performance based and flexible to remain current with changes in technology is being considered. Any proposed guidance will be available for public comment.

In response to questions from Jim Kunstman and Julie Spagnoli, the issue on minimum use rates is whether they can be placed on a label for reasons other than risk and efficacy. A minimum use rate may restrict the pesticide from being tank mixed with other products. Under FIFRA section 2ee, a lower use rate can be used. The issue will be placed on the labeling committee's web site. Greg Watson commented that there may be warranty and liability issues with minimum use rates and asked how the Agency will make a decision on an efficacy basis if it no longer reviews efficacy data. Mr. Stubbs responded that the Agency can request submission of efficacy data on a case by cases basis and will consider these comments and those received after the issue paper has been posted on the Labeling Committee's web site.

Ted Head asked whether warranty statements may still be sent in by notification. He recently had a couple that became amendments. Don Stubbs responded that the guidance addresses what is or is not a good warranty statement and not whether changes in a warranty statement could be

made by notification or amendment. The Agency subsequently resolved Mr. Head's questions concerning his applications.

Greg Watson on behalf of the pesticide industry complimented the Committee on the success of its web site. The number of "hits" indicates that there was a "real need" for such a site. It is a success story for the PPDC PRIA Process Improvement Workgroup.

Product Chemistry and Inerts - Progress Report

Kathy Monk, Special Assistant to the Director, Registration Division introduced the work of the Office of Pesticide Programs' Product Chemistry Team. Product chemistry issues have been addressed in the past notably in the 1996 rejection rate analysis and in subsequent guideline revisions, in the 2002 workshop held by the Registration Division, in BPPD's 2001 workshop and in the Antimicrobial Division's workshops in 1996 to 2001, 2003, and 2005. The next AD workshop will be held in spring 2007. While submission errors have deceased, issues still remain. The Product Chemistry Team decided to take a more systematic approach to insure that it understood the issues and thereby could effectively target the solutions to the real problems. Issues were identified during the June PPDC Process Improvement Workgroup meeting and an analysis of the reasons why PRIA due dates were extended was used to further refine and effectively target the issues. Approximately one-third or more of due date extensions were the result of product chemistry and inert deficiencies. Smaller companies have greater difficulty meeting product chemistry data requirements. Each registering division's analysis was distributed during the meeting.

The Team's proposal for addressing the issues was to develop an addendum to the "Blue Book" on product chemistry since the "Blue Book" serves as reference source for many smaller registrants. These addendums will also be placed on the Agency's web site for easy access.

Deborah McCall, Branch Chief, Registration Division, provided additional details on the Registration Division's analysis of the reasons for extending PRIA due dates. Its analysis confirmed that product chemistry issues tended to involve smaller companies and companies new to the registration process. They were likely the result of a lack of complete understanding of the product chemistry data requirements resulting in submission of no data and incorrect Confidential Statements of Formula (CSF). Substantial time is spent by Agency staff explaining how to complete a CSF and finding cleared inerts. Delays in processing applications occurred as registrants required additional time to generate the data or to find an alternate product to cite once the Agency determine that the original product cited was not identical or substantially similar. There were also numerous issues with inert ingredients.

Issues resulting in an extension of the PRIA due date in order of the number of decisions or applications affected include; insufficient or no data submitted, inert ingredients, CSF errors and citation of cancelled products or other problems. A problem with "me-too" (identical or substantially similar) product applications is that data could not be located for the cited product. One of the documents prepared to address these issues is the Standard Operating Procedure for Product Properties available on the web (http://www.epa.gov/oppfead1/guidance/product-sop.htm). This SOP was prepared for the Agency's product chemistry reviewers and also serves as a source of information for pesticide applicants. It is being reviewed to determine if additional information would benefit registrants. The Antimicrobial Division and the BPPD are preparing addendums to the SOP noting aspects that are specific to the applications and data reviewed within these divisions. Supplements to this SOP such as general and product chemistry specific tips to help avoid product chemistry issues and additional guidance on completing CSFs

were distributed during the meeting. These will be placed on the web. Inerts will be addressed separately and specifically.

The Antimicrobial Division's analysis of its PRIA due date extensions presented by Karen Hicks, Team Leader, Antimicrobial Division also revealed that a greater number of extensions were for applications from smaller companies. These companies tend neither to request pre-registration meetings nor attend AD's workshops. In order of importance or frequency of occurrence, the reasons for AD due date extensions were due to data deficiencies, missing data, CSF errors, unmet GLP requirements, and uncleared inert ingredients. AD and industry have held workshops yearly from 1996 to 2001, in 2003, 2005. The next one is scheduled for spring 2007 in which product chemistry issues will be discussed. Registrants are encouraged to participate in these workshops and obtain answers to their questions. Guidance on avoiding common errors, e.g. "tip sheets" was distributed during the meeting, is attached and will be available on the web. Topics addressed during the AD/industry workshops were registering an Antimicrobial product, products requiring registration, inerts requiring clearance, formatting a scientific study, and how to complete the CSF. Electronic copies of how to complete a CSF are available by contacting Ms. Hicks (hicks.karen@epa.gov).

The results of a detailed analysis conducted by BPPD were discussed by Kent Carlson. Of the due date extensions examined, approximately 73% involved product chemistry and CSF issues. The majority of the due date extensions, 89%, were for microbial/biochemical products reviewed by the Biochemical Pesticides Branch while 11% were for applications reviewed by the Microbial Pesticides Branch which assesses primarily plant incorporated protectants. Among the reasons for extensions due to product chemistry were: the formulation or manufacturing process, 43%; submission of physio-chemical study data, 35%; product identity, composition, or starting materials, 32%; analytical method including enforcement method, 28%; preliminary analysis, 15%; discussion of the formation of impurities, 8%; and certified limits, 4%. Approximately 79% of the extensions also involved errors in the CSF. The frequency of the CSF issues were: inadequate identification of the active ingredient (Name, CAS number, and/or supplier), 67%; discrepancies between the CSF and label or product chemistry data, 33%; certified limits, 27%; nominal concentration or percentages of the ai, 25%; inert ingredients, 23%; pH or bulk density, 9%; and calculation errors (other than the certified limits), 6%. The detailed analysis was distributed and is attached. "Tips for Avoiding SCF or Product Chemistry Issues" will be in an appendix for the EPA "Blue Book" and is available on the internet (http://www.epa.gov/pesticides/biopesticides/regtools/product_chem_csf.htm). In response to Russ Schneider's question, in BPPD's analysis, inerts were not a major reason for BPPD due date extensions.

Improvements in inert clearance that will benefit applicants and plans for future improvements were summarized by Pauline Wagner, Chief, Inerts Assessment Branch, Registration Division. By the end of 2006, a complete list of inert ingredients will be placed on the inerts website with names and CAS number. It will include food and non-food use inerts, limitations placed on food use inerts, and a PDF of a Microsoft excel spreadsheet. Comments will be invited. A tip sheet for new petitioners on avoiding common problems is available on the internet (http://www.epa.gov/opprd001/inerts/). A streamlined fragrance approval process is being piloted. The fragrance industry provided EPA with a list of all fragrance components used in pesticide products. The list is being reviewed. If the Agency has no concerns for any chemical as used in a fragrance, a pilot certification process will be put in place for fragrance changes. If the pilot successful, the process will become permanent.

A process is being developed for non-food use inert approvals to assure consistency. Schedules for new inert petitions will be placed on the inerts web site (http://www.epa.gov/opprd001/inerts/). Decision documents will be developed for all new inert petitions and will be placed in the docket and if approved, placed on the web. Decision documents for non-food use approvals will be included in the approval package sent to the requester and then placed on the inerts web site. Consultation with the Office of General Counsel will be undertaken to discuss data compensation issues raised by stakeholders.

Regarding the inerts tip sheet, information will be provided on where to find food use inert ingredients approved for growing crops and raw agricultural commodities, for growing crops only, and for animal uses; approved non-food use inert ingredients; the information needed on a CSF and other sources of information such as the web site for food use inerts and the inerts web site itself. The current list of food use inerts in the CFR is incorrect and for accurate information, the eCFR should be consulted.

Training is being developed for Agency staff on the information sources available on the status of food use inerts, the use of eCFR, and how to access the mixtures database in OPPIN. The website will be streamlined, routinely updated and become a "one stop shopping" source of inerts information. More efficient electronic storage of inert decision documents is under development.

Ron Derbyshire inquired whether the BPPD and AD web sites will have links to the inerts website. The Agency will follow-up on this suggestion.

Greg Watson observed that many of the same inerts are used in conventional, antimicrobial and biopesticide products. Addressing the data compensation issue is urgent and a process has yet to be established although FQPA was passed over 10 years ago. An industry inerts task force has been established. In response, to provide some relief for pesticide applicants, the Agency is trying to pilot a process in conformance with rule making.

Julie Schlekau, MGK, asked whether the mixtures database in OPPIN could be available to registrants. The database is confidential at this time. Greg Watson observed that brand names for some mixtures have changed and this has led to CSF problems. Registrants would like some way to keep track of these name changes.

Environmental Fate and Effects Division Spatial Aquatic Model

Nelson Thurman and Shelly Thawley, Environmental Fate and Effects Division, described recent efforts to integrate geospatial data, tools, and models to enable the Agency to conduct improved aquatic risk assessments and thereby enhance the Agency's regulatory decision making process. Spatially explicit risk assessments consider the relative spatial distributions of the stressor (pesticide) and the receptor (nontarget organism, i.e. human, other animal, vegetable) to identify areas where the receptor will be exposed to the stressor. While screening models assume "uniform and random" access of the receptor to the stressor, a spatially-explicit assessment considers heterogeneous, non-uniform distribution of the receptors and contaminant. The tools support each phase of a risk assessment from problem formulation through analysis and risk characterization and allow the Agency to go beyond a screening level assessment or level of concern approach to further characterize the risk on an area basis.

Three recent assessments illustrate the use of this technology in different phases of pesticide risk assessments and to show the progress made by the Agency:

1) Defining the stressor range (areas of potential high exposure) for an Atrazine water monitoring study;
2) Defining the intersection of stressor and receptor for an endangered species assessment for the Pacific Northwest salmonid and
3) Characterizing the extent of the overlap of the areas of the stressor and the receptor for the N-methyl carbamate cumulative assessment.

The first example used a combination of Geographical Informational Systems (GIS) data and the water model, WARP (Watershed Regression for Pesticides) to identify watersheds with areas of potential high exposure for targeted Atrazine monitoring. The second example used GIS overlays of cropland information with species-specific location data (areas of spawning, etc) to identify the potential action area for an endangered species assessment. Agricultural census and national land cover (NLCD) data were used to identify the cropped areas where the pesticide could be used. Maps showing the extent of Evolutionary Significant Units (ESUs) and stream segments associated with salmonid migration, spawning, and rearing defined the receptor range.

The third example illustrated the use of GIS spatial analysis throughout the risk assessment process, from problem formulation (identifying high potential exposure conditions and defining scenarios to include in regional assessments) to analysis and risk characterization (delineating the spatial extent of potential high exposure areas) for the N-methyl carbamate cumulative drinking water assessment. The Agency used monitoring data available for private wells in Florida to identify conditions that contribute to high exposure and then used spatial data to identify other areas of the country with similar soil types, cropping, rainfall and hydrologic conditions associated with N-methyl carbamate use.

For this later illustration, aquatic monitoring data was available. Such data would not be available for a new pesticide. The Agency is developing spatial and modeling tools that will allow it to conduct similar assessments in the absence of monitoring data. The tools include currently available models, the National Hydrographic Plus Dataset (NHD+) containing hydrographic and watershed attributes, currently available national data sets and desktop applications and tools that are currently being adopted. The Agency is moving from a scenario-driven assessment to one with a spatial component. To demonstrate the power of a spatial analysis, a proof of concept was shown in which GIS was coupled with the PRZM/EXAMS water model to specifically identify areas of potential high exposure. Tools such as these will allow the Agency to pull modeling inputs from spatial data layers and to generate an exposure map that identifies specific geographical areas that can be predicted to result in high exposure if a pesticide were applied.

The availability of NHD Plus (NHD+) provides the Agency with a framework for developing spatial methodologies. The NHD+ includes stream segments at a 1:100K scale as well as delineations of the associated catchment drainage areas. The NHD+ includes additional attributes for the catchment area including the extent of agricultural land, stream flow direction and volume, elevation and slope, among other attributes. The NHD data framework allows the Agency to predict the movement of a stressor throughout a landscape or to analyze the landscape features of the drainage area flowing to a drinking water intake.

The Division is tapping into the Agency's geospatial infrastructure contained in different Agency program and regional offices. The Office of Environmental Information and the Office of Pesticide Programs have embarked on a "Big Decisions" project through which national and regional databases and desktop modeling applications are being developed. The Agency GIS

data services are housed in Research Triangle Park (RTP), North Carolina, the GIS hub for the Agency, which will host all of the applications and data used in these assessments.

In response to Jim Kunstman 's question on how often the GIS data is updated and its availability, Ms. Thawley noted that schedules are being developed to refresh data that will need it and RTP is in the process of accumulating the data. Greg Watson observed that the Agency has made progress and particularly in anticipation of upcoming endangered species risk assessments. Russ Schniedler inquired whether GIS data was available on ground water. In response, the Agency's carbamate cumulate assessment was a ground water assessment and currently the Agency has both surface and ground water data although the ground water data tends to be regionally available. Ms. Thawley commented that the long term goal of these efforts is a web based application that does not require a knowledge of GIS so that everyone will be able to use the information.

Blue Book - Status Report

The last version of the Blue Book, "General Information on Applying for a Pesticide Registration in the United States," was originally developed in 1992. Michael Hardy, Antimicrobial Division, reported on the Agency's progress begun a year ago in revising the document to reflect current regulations and procedures. Many aspects have changed since 1992 such as mailing addresses, in-processing procedures, and requirements resulting from the Food Quality Protection Act and PRIA. A focus group of potential users provided comments and ideas on improving it. A suggestion was to include a decision tree. The focus group's comments were incorporated and included are tips on improving applications and a decision tree of the questions that need to be considered when developing an application. The long term goal is a web based application which will walk the applicant through completing an application.

At the time of the meeting, representative from AD, BPPD and RD finalized the draft incorporating the industry comments in October, 2006, then "fresh eyes" reviewed it to assure its "readability" and accuracy. This included as review by staff conducting 86-5 reviews for compliance with the PR Notice. The next step is a review by the Office of General Counsel (OGC) which was expected to begin in November 2006. Once revised per OGC comments, the final draft will undergo Division Director concurrence and the Agency "product review process". Contingent on OGC review, the target date is December 2006 for a "hard copy" version" and the electronic version for web posting would follow a couple of months thereafter, possibly February 2007.

In response to questions, the new version will include the pay.gov information and guidance on applying for a small business fee waiver. A challenge facing the Agency is to provide guidance to small business applicants. Some do not know how to begin the application process. One suggestion is to develop a CD containing detailed guidance that could be sent to these applicants when they request application materials. In response to a question, the Agency will announce the Blue Book's availability through an "OPP update", informing trade associations, and possibly a FEDERAL REGISTER notice.

E-label Review

The Agency's Electronic Label Review initiative was described by Thomas Harris, Registration Division. The Agency is pursuing E-Label Review to improve the efficiency and accuracy of the label review process. The E-Label Review process uses the compare function in Adobe Acrobat 7 to quickly and thoroughly identify proposed label changes. The reviewer can then use

Acrobat's commenting tools to indicate any required corrections to the proposed label text. Labels with EPA comments and labels revised by the registrant can be traded via email until an acceptable label is reached. An electronic label library database will store these labels along with the Agency's review of the label. An example of a label review using the software was demonstrated.

Mr. Harris noted that: 1) The current E-Label Review initiative does not involve electronic transmission of an entire registration application. Electronic transmission will only be possible after procedures are adopted for electronic signatures, security, and electronic processing. The Agency is heading in this direction and is developing these aspects. 2) This initiative also does not involve electronic distribution of labels approved by EPA since marketplace labels must be approved by each state, labeling must be done at registered establishments, and there are potential enforcement issues.

To take advantage of E-Label Review, the initial e-label for an action (new product or label amendment) must be submitted on a CD along with the usual application paperwork. Any necessary revised labels for the same action can then be submitted by e-mail directly to the EPA reviewer. Registrant guidance is posted at:
http://www.epa.gov/oppfead1/eds/esr_guidance.htm#pilots .
The application with a CD should be sent by courier and not US Mail since the Agency's mail is x-rayed. Text .PDF is critical as scanned images can not be compared. All fonts should be embedded, the file name convention on the web site must be closely followed, and the label should be "clean" (i.e. without any registrant comments or change markups). Registrants must follow the file name convention indicated in the guidance since this will allow the Agency to store and then retrieve the label electronically and track the label in its databases. The entire process is voluntary although it is suggested that once a registrant submits an e-label that future submissions should also include an e-label in order to maintain the efficiencies of this process.

In response to questions, electronic labels are currently being reviewed using this technology and approximately 900 labels have been stored in a Lotus Notes database with an additional 300 labels located in a DOS directory. As a result of "seat management" all employees in the Office of Pesticide Programs can now access the required Acrobat Professional version 7 software. Employee training is a high priority and the Agency is ready to move from "pilot" into "production". If an electronic label is submitted, the Agency's expectation is that it will be reviewed electronically according to Don Stubbs. This effort is being coordinated with other electronic submission efforts. Ron Derbyshire would like to submit electronic copies of all of his company's master labels for the Agency's label library to facilitate the electronic review of future submissions.

For questions on this project, Mr. Harris may be contacted at 703-308-9423 (harris.thomas@epa.gov) . Questions on electronic submission in general should be directed to Steve Robbins, 703-305-6439 (robbins.steve@epa.gov).

Information Technology/Information Management

On-line payment of PRIA fees was described by John Jamula, Information Technology and Resource Management Division. As of November 1, 2006, applicants can pay their PRIA fees by credit card or wire transfer through pay.gov. Pay.gov is a service provided the Department of Treasury that has been in operation for close to 6 years. The Agency recently made use of this mechanism to receive fee payments. Pay.gov currently collects payments for approximately 40 government offices, is secure (132 bit encryption), available 24/7, and free to the user. There are

no credit card or wire transfer fees levied on users. Mr. Jamula walked participants through a credit card payment. The payment form may be accessed through pay.gov, forms, selecting P and the Pesticide Registration Improvement Act Fee. Completion of the form requires a company name, telephone number, contact name with e-mail address, decision number, registration number, and amount. The decision number and registration number should be identical to that on the EPA invoice. After submitting this information, the user can then select the form of payment (Bank Account Debit) or Plastic Card (credit card) and complete the appropriate fields. A copy of the transaction may be printed and an e-mail confirmation of payment requested for the applicant's records. An e-mail confirmation is also sent when the payment is posted to OPPIN, the pesticide tracking database. Users of pay.gov can also establish a password protected account to maintain records of their transactions in pay.gov. Questions and help on pay.gov should be directed to the customer service number on the pay.gov web site.

Arnold Layne, Director, Information Technology and Resource Management Division summarized the status of electronic jackets and progress on the Pesticide Registration Information System (PRISM) and electronic submission. In October, 2006, 100% of the over 25,500 regulatory files or jackets consisting of over 5.2 million pages had been imaged. The scanning process was complicated since some old documents were on "carbon" copies. A process is in place to image new product jackets and to add subsequent information and documents to existing e-jackets. Regulatory information can now be accessed by a number of individuals at their desks instead of a succession of individuals handling a paper file. The next step is to index each electronic jacket.

The Office of Pesticide Programs is creating PRISM, the next generation of its information management system. PRISM is envisioned to lead to further efficiencies in making regulatory decisions. Under PRISM, there will be one web portal for all regulatory documents and information and a central system to store, move and access routine documents. During FY06, requirements analyses were completed for the Label Use Information System (LUIS) and systems supporting Endangered Species, Document Management, electronic submission, registration review, the Office of Enforcement and Compliance Assistance's Section Seven Tracking System and a system for Notice of Arrivals (NOAs). A production version of LUIS is expected in November, 2006 and a demonstration application of the first phase of the Document Management system is expected in the first quarter of FY07. Data in the current system is being improved for migration into PRISM. This includes such information as company history and Section 18s.

In response to an observation from Greg Watson that there were errors in the LUIS section summaries, the Office of Pesticide Programs is internally discussing whether quality assurance staff would be willing to take on a number of resource intensive data correction projects.

The long term vision for electronic submission is that documents will be submitted and reviewed electronically and the status of a submission will be reported to an applicant electronically. Electronic submission will support the Agency's international harmonization and joint review goals. Registrants would submit all application materials, including data and labels via EPA's e-PRISM utility or by a XML generator, web interface, paper or CD or DVD and all will be stored and transmitted and reviewed electronically. The e-PRISM utility will be the same as PMRA's e-Index and the EPA is working closely with Canada on this project, e.g. sharing the program code. The Agency has been impressed with Canada's ability to reduce the amount of "paper" it receives. Requirements for electronic submission are expected to be gathered by October, 2006 with the XML schema in November. Industry input will be requested on the

schema and a pilot is expected in January 2007 with a focus on creation and receipt of XML files and attached documents. Registrants can expect a full production version in May 2007.

For the future and based on available funds, a web interface for submission of data identified in the schema will be developed. Subsequent expansion will include other documents such as CSFs and labels. Eventually a secure status tracking system will be available as an "Individual Bank Account Concept" to allow registrants to obtain information via the web on the status of their application. To help registrants develop a complete application that the Agency can efficiently process, an interactive web based application program is envisioned that will identify errors as they are being made.

Public Comment

Ray McAllister, CropLife America, suggested that the Labeling Committee also post questions that the Committee has received and is in the process of addressing to avoid duplicate questions from the public. He recommended that the current list of approved inerts be cross-referenced with past lists and asked whether the eCFR listed those inerts with revocations that had been delayed for two years. In addition, to help registrants find out whether an inert had a name change, he suggested that the name be listed when inerts are listed. Marty Monell responded that the program would provide an answer to his question. In response to Mr. McAllister's question on the legal requirement for a paper record, Tom Harris responded that paper records were retained for even 15 years after a product was cancelled and that the official record is the paper record.

Ron Derbyshire noted that the positive achievements under PRIA were appreciated. Marty Monell observed that through the stakeholder workgroup, communication had improved.

Future Activities/ Projects and Next Meeting of Workgroup

Marty Monell announced that due to a change in the format for the next meeting of the full PPDC, there would not be a workgroup report. For the next meeting of the workgroup in approximately four to five months, members should forward their topics to Elizabeth Leovey (leovey.elizabeth@epa.gov), 703-305-7328. Greg Watson suggested that since E-label review would result in substantial resources savings by both industry and the Agency, there needed to be a mechanism to track its progress.

ADDENDUM PER ANTIMICROBIALS DIVISION (AD)

1. **Supplier Name & Address (Column 11 on CSF) -** The names and addresses of the suppliers should always be provided. The term "commodity chemical" is not acceptable as a replacement for names and addresses of suppliers. There is no statutory definition for this term. There is no Agency derived list for recognized "commodity chemicals". All end-use products (registered or not) must have chemistry data. Therefore, the term "commodity chemical" is not an acceptable term.

AD Interim Policy

The following is an interim policy established by the Antimicrobials Division. This policy is applicable to notifications, amendments and registrations. These procedures will be effective immediately until further notice.

1. The names and addresses of the suppliers of List 4 inerts are not required. The term "List 4" should be placed in column 11.
2. Registrants must provide the names and addresses of all possible suppliers of List 1, 2, and 3 inerts included in an attachment to the CSF, to be used without further notification to the Agency.
3. Registrants may purchase List 1, 2, and 3 inerts from suppliers not currently listed as a source if names and addresses of the new suppliers are submitted by notification to the Agency immediately upon purchase.
4. If the names and addresses of the suppliers (for List 1, 2, and 3 inerts) or the term "list 4" are not present, the data submission is not rejected solely on this deficit. The registrant is given thirty (30) days to submit that which is needed. If not submitted within thirty (30) days, the submission will be rejected at the next amendment.

2. **Submission of an Alternate AI Source -** An alternate source may be used if it is the same chemical, registered and cleared for use in a pesticide product. If the active is not registered, the chemical specifications as well as all chemical data required under 40 CFR Part 158 must be submitted before the ingredient may be used in a pesticide product. If the active is not registered, but is the same chemical with same inerts, a five batch analysis may be acceptable in lieu of complete chemistry data.

3. The **21 CFR** needs to be checked for clearance (active and inert) for sanitizers, pulp and paper use, coatings, adhesives and any other direct or indirect food contact materials for which FDA has established food additive regulations. * Note that for sanitizers, the formulation must exactly match the existing 21 CFR 178.1010 citation. If the Agency is not certain whether an inert ingredient is cleared under 21 CFR for uses other than sanitizers, then the Agency will ask the registrant to provide additional information or get an opinion letter from FDA. Finally, should the Agency find that an inert under EPA's jurisdiction is not cleared, the registrant must be directed to the "Inerts Team" in RD to start discussion regarding data/information needed to start the clearance process. * The procedure of exactly matching sanitizers to 21 CFR 178.1010 may change in the future. This is dependant upon the outcome of ongoing discussions with OGC.

4. **Interim Product Chemistry Policy Regarding the Registration of Towelettes (Wipes, Cloths, Blotters, etc.)**

Since towelettes were first registered, approximately twenty-seven years ago, there has been no policy which regulates the registration of these products. Much of what has been submitted has been registered without question. The universe of towelettes is still very small. There are currently approximately twenty-one active products on the market. However, as this universe grows, the demand for a written-working policy is becoming increasingly heightened.

Due to the varying factors that are apparent with the registration of towelettes, each submission must be handled on a case-by-case basis. Differing fabric compositions and sizes and pre-moistened verses dry are some of the factors which will account for many of the major variations.

There appears to be several issues that must be addressed which concern the **chemical** aspect of towelettes:

a. Company Submitted Manufacturing Process (Methods)
A certified method (preliminary batch analysis) for the end-use product, which describes how the product is formulated, must be submitted with each new registration. Two copies should be sent directly to front-end processing in order to receive MRID numbers. One copy should be addressed to the lab in Fort Meade, the other copy should be addressed to the appropriate Product Manager team. The method submitted must represent the label claim and agree with the CSF. Since the method may be reviewed by the states it, therefore, can not be considered as CBI. **Note:** The use of different fabric type and size will require a different method or a five batch analysis may be used.

b. Label Claim Active Ingredient
The amount of active included on the label, should represent the original amount as well as the expressed amount. This same amount should also be listed on the CSF. Over formulating to account for the amount of active which may bind to the cloth will not be acceptable. The method should allow for the amount of active that is bound by the towelette cloth.

c. Fabric of Towelette
Each type (components) and size of fabric will need to be identified and the differences (such as amount of AI per towelette, binding properties per towelette, etc...) between each must be accounted for on the label and/or CSF. All individual components of the towelette are required to be cleared for use in pesticide products. (See attached*) The registrant will determine whether or not the weight of the towelette is included in the formulation. However, any method used must be submitted by the registrant (see #1).

The policy on antimicrobial towelettes and wipes is under consideration by the Antimicrobial Division. Once the policy has been finalized, registrants will be informed if there are changes that need to be made regarding the registration process and if there are any additional data that must be submitted to the Division for review.

*** Attachment**

In order to reduce the confusion regarding the type of compositional information needed and format for presenting antimicrobial wipe information, the following recommendations have been recommended:

At the time of initial application, the registrant may, in lieu of listing a specific wipe material with a specific trade name and specific supplier, list a generic descriptor along the lines of "adsorbent wipe material" (in column 10 of the CSF). Directly beneath this listing, the registrant shall list (in aggregate fashion) **all** the individual components (by chemical name and CAS Registry Number) that would be found in any of the different wipes proposed to be used by the registrant. Column 11 would then have an associated entry that would list the specific suppliers of the proposed wipe materials.

OPP would then review the CSF to determine if each individually listed wipe component is acceptable for use as an inert ingredient in such a formulation. If all the components are acceptable, then the registrant could utilize any specific wipe material from any of the listed suppliers that consists solely of the specifically listed materials, regardless of proportion. The use of wipe materials with components not listed on the CSF would need to be reviewed by OPP via amendment and the utilization of different suppliers would need to be effectuated by either notification or amendment. This format would eliminate the need for a registrant to submit numerous CSFs for formulations differing only in the name of the wipe material and would also eliminate the need for EPA to separately review the composition of each wipe material provided it was formulated from the established list of wipe material components specified in the CSF.

The policy on antimicrobial towelettes and wipes is under consideration by the Antimicrobial Division. Once the policy has been finalized, registrants will be informed if there are changes that need to be made regarding the registration process and if there are any additional data that must be submitted to the Division for review

STEP BY STEP GUIDANCE FOR PRODUCT CHEMISTRY SUBMISSIONS (INCLUDING TIPS ON PREVENTING COMMON ERRORS)

1. Complete form 8570-1 (Application for Pesticide Product). Make sure this form is signed and dated.

2. Include a transmittal document (cover letter) that details the purpose for submission.

3. Follow PR Notice 86-5 (Standard Format for Data Submitted Under FIFRA).

4. Complete form 8570-4 (Confidential Statement of Formula). Follow the instructions on the back of the form.
   - A. Make sure a box is checked for the basic or alternative formulation. If there is more than one alternative formulation, include a special designation or identification such as; alt #1, alt a,b,c, etc… In reference to alternate formulations, the following must apply:
     1. The identity of the active ingredients must be the same.
     2. The alternate formulation should not have a toxic inert or impurity of toxicological significance that is not present in the basic formulation.
     3. The certified limits of the active ingredients must be the same as the basic formulation.
     4. Inerts must also be the same between the alternate and basic formulations. (i.e., same chemicals, certified limits should be within the prescribed limits, as well as same physical state, etc...)
     5. The flammability, pH and density must be the same as the basic formulation.
     6. The label claim and label text of an alternate formulation must be the same as the basic formulation.
     7. Any precautionary statement must be the same.
   - B. Cleared inerts should be identified in the transmittal document.
   - C. If inerts are not cleared for use in pesticide formulations, registrants must request that suppliers submit the complete chemical identification of all components in the ingredient, CAS numbers of each component and the percentage of each component used in the formulation directly to the Agency. Registrants should provide suppliers with associated EPA Reg. No., barcode number and PM to enable ease in location of the associated submission.
   - D. To avoid delays in review, the exact name must be entered for a chemical (e.g. fragrance, dye) for each entry; otherwise a new CAS number is associated (which may delay time).
   - E. The AI should be the ingredient that causes the product to be efficacious.
   - F. The names and addresses of the suppliers should always be provided. The term “commodity chemical” is not acceptable as a replacement for names and addresses of suppliers. There is no statutory definition for this term. There is no Agency derived list for recognized “commodity chemicals”. Therefore, the term “commodity chemical” is not an acceptable term.
   - G. The following is an interim policy established by the Antimicrobials Division. This policy is applicable to notifications, amendments and registrations. These procedures will be effective immediately until further notice.

1. The names and addresses of the suppliers of List 4 inerts are not required. The term “List 4" should be placed in column 11.

2. Registrants must provide the names and addresses of all possible suppliers of List 1, 2, and 3 inerts included in an attachment to the CSF, to be used without further notification to the Agency.

3. Registrants may purchase List 1, 2, and 3 inerts from suppliers not currently listed as a source if names and addresses of the new suppliers are submitted by notification to the Agency immediately upon purchase.

4. If the names and addresses of the suppliers (for List 1, 2, and 3 inerts) or the term “list 4" are not present, the data submission is not rejected solely on this deficit. The registrant is given thirty (30) days to submit that which is needed. If not submitted within thirty (30) days, the submission will be rejected.

H. Verify the weight percentage of each component. Note that the weight percentage in formulated products when multiplied by chemical purity would result in the label claim nominal concentration. The nominal of the AI on the CSF must exactly match that on the label (per PR Notice 91-2). CSFs will be rejected if PR Notice 91-2 is not followed. It is quite common and recommended (however, not mandatory) that the registrant include the nominal concentration of the AI between parenthesis below the percentage by weight in column 13b and the corresponding certified upper/lower limits in columns 14(a) and 14(b), respectively.

I. Upper and lower certified limits are required for each active and inert ingredient of a pesticide product. The certified limit for the AI should be based on the nominal concentration in pure form, not on the percentages by weight. The certified limits are calculated according to “The Table of Standard Certified Limits.” See 40CFR §158.175(b)(2). The applicant may propose a certified limit for an active or inert ingredient that differs from the standard certified limit, with a justification. The certified lower limits may not be lower than the minimum level to achieve efficacy. Therefore, zero is not acceptable as a lower limit.

J. The CSF must be signed and dated.

5. All required studies must be addressed per 40 CFR 158. If a guideline study is not applicable, the registrant must indicate such by adding “N/A” next to the guideline number.

6. Product Chemistry Data (Master Record Identification Document (MRIDs) - guideline studies - Refer to the OPPTS Test Guideline Series 830. Each study should have a MRID number and a date pin-punched by the front end processing center.

7. In reference to GLP, registrants are advised to refer to CFR 160.135. GLP applies totally to those studies listed in (a) and partially to the remaining physical and chemical characterizations studies listed in (b).

Tips for Avoiding CSF or Product Chemistry Issues with Biopesticides (v. 11/01/06)

The Biopesticides and Pollution Prevention Division (BPPD) has compiled recommendations that may assist registrants in reducing common mistakes associated with the Confidential Statement of Formula or product chemistry submissions for biopesticides. These are discussed below in general terms and in terms of specific product types.

General Tips

BPPD has four general recommendations that the registrant should consider when registering a biopesticide.

The first recommendation is to contact BPPD to determine whether the pesticide is a biopesticide, an antimicrobial, or a conventional pesticide. BPPD has organized a Biochemical Classification Committee (BCC) to perform this function and the BCC representative (jones.russell@epa.gov) can provide more information on this process. A good overview of what constitutes a biopesticide is also available on the internet [1]. In general, the BCC asks for the following information to support a "Biochemical Classification Determination".

1) Evidence of the pesticide's natural occurrence, or evidence that the pesticide is structurally similar and functionally identical to naturally-occurring compounds.
2) Evidence for a non-toxic mode of action against the target pest. A non-toxic mode of action may include such pest control methods as attraction, repellency, growth regulation, induction of systemic acquired resistance, desiccation, smothering, etc.
3) Product chemistry information (structure(s), CAS #, source(s), physical/chemical properties, etc) for each proposed active and other ingredients in the formulated product.
4) Rate and timing of application.
5) Any available information regarding toxicity of the product (acute, subchronic, chronic, developmental, carcinogenicity, mutagenicity, etc).
6) Efficacy data, if products are to be used specifically against a public health pest (e.g., mosquitos, flies, cockroaches, fireants, termites, rodents; PR notice [2]).

Once information is submitted, registrants will be contacted with the decision within 30 days.

The second recommendation is to schedule a pre-registration meeting with BPPD regulatory action leaders and scientists. Contact the appropriate BPPD Branch Chief [3] for more details. Schedule this meeting far in advance of performing studies or submitting a registration package. Submit an agenda with the proposed product and identify if a Section 3 registration, tolerance exemption, or EUP is desired. Also be prepared to discuss potential data waiver justifications. Many of the "case-by-case" requirements associated with product chemistry and toxicology can typically be resolved at these meetings.

The third recommendation is to follow the tips below and the weblinks provided in this appendix for additional information. Complex biopesticide applications should also consider hiring a regulatory consultant to facilitate registration [4].

The fourth recommendation is to submit the entire registration package at one time. If a package/application is incomplete, under 40CFR §152.105, the applicant will be informed by a

letter that they have 75 days from the date of the letter to correct the problem or the application will be withdrawn. It is also possible to ask for additional time to correct the deficiencies. In either case, EPA will ask for the time lost for this correction to be added on to the PRIA due date, if the action is subject to PRIA.

General Tips for the CSF:

When organizing the CSF for biochemical and microbial pesticides, first refer to the CSF preparation guide [5]. This step-by-step guide provides most of the detailed information necessary to successfully prepare biochemical and microbial pesticides CSF's for submission.

A CSF guide for plant-incorporated protectants (PIPs) has not yet been prepared by BPPD. A few specific tips on PIPS can be seen below. Registrants for PIPs are also encouraged to contact the BPPD Microbial Pesticides Branch Chief [3] for more details on PIP CSF preparation.

Even though BPPD's guidance addresses most CSF issues, many submitted CSFs still contain problematic areas. In order to avoid delays in registration due to the CSF, the registrant should be sure to:

- Match the Brand name on the label to the name on the CSF
- Match the active ingredient name and percentage on the label to that on the CSF
- Provide CAS numbers for all ingredients (except perhaps for PIPs and microbials)
- Provide inert ingredients that are cleared for the products potential uses
- If an inert component is an attractant for the target pest, re-consider it as an active ingredient
- List active and inert components by their chemical name (not brand name)
- Provide nominal concentration and upper and lower certified limits for the active ingredient(s)
- If the active ingredient(s) are not 100% pure, provide the concentration and upper and lower certified limits for the pure active ingredient
- Do not exceed the upper certified limit of 100% for the technical grade active ingredients, pure active ingredients, or manufacturing products
- The upper certified limit for end-use product ingredients can exceed 100%
- Provide justification when certified limits are beyond that recommended in 40 CFR §158.175
- Provide an original signature and date on the CSF
- List ingredient sources with complete addresses (not the phrase "commodity")
- Provide a separate CSF for each alternate formulation
- When water is used as an inert, provide a complete address for the source.
- Insert physical characteristics from the product chemistry into blocks 7, 8, and 9
- Leave block 4 blank if an EPA registration number is unavailable or insert the company number (EPA will then assign a product number)
- Provide a "Purpose in Formulation" (block 15) for each ingredient (e.g. diluent, preservative, surfactant, impurity)
- Ensure that the nominal percentages in column 13b total up to 100%

General Tips for Product Chemistry:

Unlike the CSF guidance, a universal product chemistry preparation guide has not yet been prepared by BPPD. Product chemistry guidance is provided on the internet, however.

Microbial guidance is available for product identity [6], manufacturing process [7], discussion of formation of unintentional ingredients [8], analysis of samples [9], and the certification of limits [10]. Product characterization guidance is also available for pesticides derived from biotechnology [11].

Even with the available guidance, many submitted packages still contain a variety of problematic issues. In order to avoid delays in registration due to product chemistry, the registrant should be sure to:

- Present the ingredients at a single concentration (ie, not 30-70% pure)
- Address each product chemistry data requirement with a rationale or statement, even if the requirement does not apply (ie cite the 40CFR footnote)
- Provide summaries AND copies of literature when waiver rationales cite published or unpublished literature
- Do not cite the FDA determination of Generally Regarded as Safe (GRAS) as a sole waiver rationale
- In the pre-registration meeting, discuss whether the certified limits recommended in 40 CFR §158.175 apply to the product
- Do not use Material Safety Data Sheets as a sole support for product chemistry requirements
- When MSDS's are used as support, ensure that the supplier, % purity, and impurities of toxicological concern are identified appropriately
- Manufacturing processes can best be followed when presented in conjunction with a flow chart
- Provide data for the end-use product, even if the manufacturing product comes from a registered source

Tips for Biochemical Pesticides

General

Guideline requirements for biochemical pesticides are similar to conventional pesticides. Specific testing guidelines can be found on the internet [12].

Pheromones/Allelochemicals

Product chemistry is the primary data requirement for pheromones and allelochemicals. A good overview of what factors should be considered is available from OECD [13]. In general, identity data demonstrating allomonal, kairomonal, synomonal, or pheromonal activity should be submitted. Straight chain lepidopteran pheromone registrations should also submit data demonstrating similarity to unbranched aliphatic compounds having 9-18 carbons, up to 3 double bonds, and a terminal alcohol, acetate, or aldehyde functional group. Formulated products using microencapsulation should also provide information on the size of the carrier bead.

Clays/inorganics/ash

Registration of inorganic pesticides should consider both solid matrices and potentially soluble components when being described via product chemistry. Descriptions of the matrix

should include the percent carbon, percent crystalline silica, and a particle size analysis. Quantification of asbestos fibers is also encouraged for some products having vermiculite as a component. Potentially soluble components such as metals and metalloids must also be described in order to capture the potential for soluble leachates. Finally, since mined or waste ash products are compositionally heterogeneous, discussion of mining or production methods that ensure product consistency should also be included in the submission.

Plant Extracts

Plant extracts are oily heterogeneous mixtures of terpinoid molecules that have been pressed or processed from plants. Submissions should identify the species and variety of the plant. The active components (and/or surrogate analytical markers) in the extract should also be identified, quantified, and have certified limits. If the identity of any ingredient or impurity can not be specified as a discrete chemical substance, sufficient information must be provided for EPA review (40 CFR 158.155 (f)). Blending, batch deletion, enrichment with purified components may be used to maintain product consistency. Nominal concentrations will be used for enforcement purposes and must be listed on the product label and CSF. Impurities >0.1% composition should also be identified, quantified, and listed on the CSF (40 CFR 158.155 (d)(1), (2), (3)).

Peroxides/Oxidative reaction products

Peroxide products are characterized by having strong chemical reactivity. For this reason, submissions with multiple components should identify secondary byproducts from the reaction and identify the relative component equilibriums in storage over time and at relevant temperatures.

Animal Byproducts

Animal byproducts include such pesticides as urine, blood, and egg solids. Animal byproduct pesticides have the unique potential to transfer viruses, bacteria, fungi, and parasites to humans or other animals. Because of this potential, registrants should submit information regarding the lack of such contaminants. Detailed information on the manufacturing process, analytical methods, and quality assurance/quality control (QA/QC) should be provided to demonstrate that the product is free of all potential mammalian pathogens. Justifications for acceptable levels of microbial contaminants and control methods when such levels are exceeded must be included in the QA/QC discussion. These protocols should be submitted to EPA prior to use in a study.

Volatile Compounds

Products with volatile components should provide adequate characterization of the volatile components, including the rate of production in different environmental scenarios, and growth media or chemicals used to produce the volatiles. A discussion of the predicted variability of volatile production is also important to include in product submissions.

Repellents/Attractants in Traps

Products to be dispensed within a trap or dispenser should include a detailed description of the dispensing/trapping device, including anticipated propellents or additional conventional

pesticides. Biopesticide submissions conjoined with conventional pesticides are reminded to contact the Registration Division of OPP for additional registration information.

Plant/Insect Regulators

Products that are plant or insect regulators should include a discussion of the mechanism of action. The discussion can be supported by data and/or published literature. Activity related to a particular chemical isomer should also be described.

Tips for Microbial Pest Control Agents (MCPA)

General

Detailed guidance for product chemistry has been provided in the web-links above and in a guideline overview [14]. In general, MCPAs should be expressed as viable organisms per unit weight or volume (e.g. cfu/g) or international units of potency per unit weight. Methods might need to be combined to verify certified limits and impurities. Specific testing guidelines can also be found on the internet [15].

Bacteria/Fungi/Protozoans/Phages/Viruses

In general, adequate identification of microbes, microbial contaminants, and/or impurities is important for these pesticides. Each microbe should be identified by taxonomic position, serotype, and/or strain utilizing the best methods currently available and have an assigned or nationally recognized collection number (ie *Bacillus thuringensis* subsp *kustaki* AA1234; *Beauveria bassiana* strain 123). Alternate names are also important to provide a link to the older literature on the microbe. Identification of relevant genetic alterations (plasmids or extrachromosomal genetic elements), the phenotype coded for, and its stability (and rate or exchange with other organisms), and method used to alter the genetics is also necessary. Identification should also include information on the natural occurrence of the microbe, its relationship to other species, and its life cycle and mode of action with respect to target species and known host range.

A detailed description of the manufacturing process and QA/QC methods should also be submitted. This description must include methods taken to prevent contamination, ensure a uniform product, and identify the MCPA. Impurities such as microbial toxins, allergens, metabolic products, mutant strains, microbial contaminants (especially mammalian pathogens or antagonistic microbes), side products from chemical reactions, growth fermentation residues, extraneous host residues from produced viruses, contaminants from purification or extraction, and chemical impurities should also be described. If hazardous contaminants are detected during production or purification, mitigation measures may be proposed in order to ensure that these are present in the final product in non-hazardous quantities. Storage stability should also be submitted to establish expiration dates for the claimed label rates of live microbial active ingredient.

Microbial Products which Produce Volatiles

Microbial products which produce volatile fumigants should fulfill standard microbial guideline requirement for product chemistry (as described above). Registrants for these products

should also provide adequate characterization of the volatile components, including the rate of production in different environmental scenarios, and growth media (nutrient sources/solid carriers) used to produce the volatiles. A discussion of the predicted variability of volatile production is also important to include in product characterization submissions.

Microbial Consortia or Mixtures and Composted Materials

Microbial consortia and composted material pesticides are inherently difficult to describe using standard product chemistry guidance because of the complexity of components. The BPPD Microbial Pesticides Branch Chief [3] should be contacted for further information regarding these types of pesticide products.

Tips for Plant Incorporated Protectants (PIPs)

General

In general, PIP's and their associated marker proteins require much of the same CSF information as biochemicals and microbials. They differ, however, in that bulk density, pH, and flash point, (blocks 7, 8, 9) are typically not applicable (n/a). PIP CSFs also differ in that the "Components in Formulation" (block 10) do not have CAS numbers, but instead identify the protein, the genetic material necessary for its production, and the plant into which it was incorporated. Useful examples of PIP nomenclature can be seen on the internet [16]. It is also recommended that registrants express "Each Component in Formulation" (block 13) in terms of plant parts (Whole plant, leaf, root, pollen, seed), in order to provide satisfactory information for Insect Resistance Management and human and ecological risk assessments. Quantitative determinations of the amount of pesticidal protein produced by each plant part should also be presented on a % dry weight basis.

Single Protein PIPs

Product characterization for single protein PIPs has been described in detail in Science Advisory Panel (SAP) meetings [17, 18]. In general, single protein PIPs should include details of the inserted DNA, transgenic protein production and RNA expression, the transformation system, the inheritance and stability of functionally induced traits. Useful examples of molecular and genetic characterization of transgenic plants can be seen on the internet [19].

Stacked Protein PIPs

Product characterization for multiple or "stacked" protein PIPs should include relevant information on the registered single protein PIP components as well as discussion of any potential antagonistic, synergistic, or potentiating toxicological interactions. Registrants are encouraged to contact the BPPD Microbial Pesticides Branch Chief [3] for more details.

Plant Virus Coat Protein (PVCP) PIPs

These products include PIPs whose inserted genetic material is derived from a plant virus sequence encoding a coat protein. Informational requirements for PVCP registration are

currently being determined, and registrants are encouraged to contact the BPPD Microbial Pesticides Branch Chief [3] for more details.

1. http://www.epa.gov/pesticides/biopesticides/whatarebiopesticides.htm
2. http://www.epa.gov/opppmsd1/PR_Notices/pr2002-1.pdf
3. http://www.epa.gov/pesticides/biopesticides/bppd_contacts.htm
4. http://www.epa.gov/pesticides/biopesticides/regtools/biopesticide_consultants.htm
5. http://www.epa.gov/pesticides/biopesticides/regtools/biopest_csf.pdf
6. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/oppts_885_1100.htm
7. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/oppts_885_1200.htm
8. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/oppts_885_1300.htm
9. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/oppts_885_1400.htm
10. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/oppts_885_1500.htm
11. http://www.epa.gov/ pesticides/biopesticides/regtools/biotech-reg-prod.htm
12. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/biochem_gdlns.htm
13 http://www.olis.oecd.org/olis/2001doc.nsf/43bb6130e5e86e5fc12569fa005d004c/bf8feefe7a272650c1256b0600364359/$file/jt00121481.pdf
14. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/oppts_885_0001.htm
15. http://www.epa.gov/pesticides/biopesticides/regtools/guidelines/microbial_gdlns.htm
16. http://www.lifesci.sussex.ac.uk/home/Neil_Crickmore/Bt/intro.html
17. http://www.epa.gov/scipoly/sap/meetings/1999/index.htm
18. http://www.epa.gov/oscpmont/sap/meetings/2004/june/agenda.htm
19. http://www.aphis.usda.gov/brs/international_coord.html

Biopesticides and Pollution Prevention Division (BPPD)

Product chemistry and CSF issues (PCCI) were involved in approximately 73% of the renegotiations in BPPD. The Biochemical Pesticides and Microbial Pesticides branches accounted for 89% and 11%, respectively of these renegotiations.

In the majority of renegotiations, PCCI were clearly the primary motivating factor. For other renegotiations involving multiple causative factors, however, it was unclear if the PCCI-alone would have resulted in renegotiations. This lack of clarity is because renegotiations are dependent on the timing, severity, and the type of deficiencies.

Renegotiation due to PCCI delayed product registration substantially. The average "time added to registration" by first-time renegotiations was approximately 18 weeks (2-85 weeks, n=63). The time added by second renegotiations was also approximately 18 weeks (4-36 weeks, n=12). Time added statistics were not calculated for third and fourth time renegotiations because of few available cases.

A **screening level** analysis demonstrated that:

- Of the renegotiations due to product chemistry alone, approximately,
    - 43% involved issues with the formulation or manufacturing process
    - 35% involved issues with the submission of physico-chemical study data
    - 32% involved issues with product identity, composition, or starting materials
    - 28% involved issues with analytical methodology (including those for enforcement)
    - 15% involved issues with the preliminary analysis
    - 8% involved issues with the discussion of the formation of impurities
    - 4% involved issues with certified limits
- CSF completeness was dependent on product chemistry submissions
- Approximately 79% of the PCCI involved the CSF. Of these, approximately,
    - 67% involved inadequate identification of the active ingredients (Name, CAS #, Supplier)
    - 33% involved discrepancies between the CSF and label or product chemistry data
    - 27% involved issues with certified limits
    - 25% involved issues with nominal concentration or percentages of the active ingredients
    - 23% involved issues with inert ingredients
    - 9% involved issues with pH or bulk density
    - 6% involved calculation errors (other than those in certified limits)
- Few packages were renegotiated due to a total lack of submitted data
- While storage stability and corrosion characteristics were often cited as data deficiencies (50% of product chemistry cases), the lack of these studies alone were not responsible for renegotiations

Product Chemistry Team Proposal to the PPDC Workgroup on Process Improvements

Background

Issues with product chemistry have been addressed by the Agency in many ways and through several means in the past. This includes a thorough review which was done in 1998 with the rejection rate analysis and resulting changes in the guidelines. Workshops have been conducted by RD in 2002, AD in 1996 – 2001, 2003, and 2005 (and scheduled for spring 2007) and by BPPD in 2001 (in conjunction with IR-4, PMRA, and CalEPA). The results of these efforts were to decrease the number of errors occurring in the submissions to the Agency.

Nevertheless product chemistry issues continue to be a problem for both the Agency and registrants. Most recently they have become a key area being addressed by the PRIA Process Improvement Workgroup. As a result the Agency has formed an internal Product Chemistry Team to address these issues.

At the last meeting of the PRIA Process Improvement Workgroup on June 14, 2006, each of the registering Divisions presented answers to questions and addressed issues that were brought up by industry concerning product chemistry. In attempting to find a format for providing this information to the general public, the Agency's Product Chemistry Team was faced with a wide array of material that did not lend itself to easy presentation to the general public in the format that it had been presented to the PRIA workgroup.

The Agency's Product Chemistry Team decided that a more systematic method was needed to ensure that we understood what the exact issues are and how to best address these issues by effectively targeting the real problems. As a result the Agency's Product Chemistry Team has reanalyzed not only the questions that have been recently presented by the PPDC Workgroup but also information on the reasons for re-negotiations of PRIA submission due dates.

The Agency's Product Chemistry Team's detailed analysis of the reasons for re-negotiations of PRIA due dates is included on the attached spreadsheets. In summary, the team found that in each of the Divisions, product chemistry issues (including issues with inert ingredients) accounted for over one-third of the re-negotiations of PRIA due dates. This analysis was conducted on all re-negotiations since the beginning of PRIA through mid- August 2006. The count included those cases where there were multiple issues (in addition to product chemistry). The analysis of this information revealed that the renegotiations for product chemistry:

- Mainly involved small registrants
- Likely resulted from a lack of complete understanding of the requirements for product chemistry
  - Data requirements
  - How to correctly complete CSFs
  - For BPPD, issues with the manufacturing process; and product identity, composition or starting ingredients
- Likely included registrants looking for help in finding a product to "me-too"
  - Extra time was needed to find an alternate product to cite
  - Extra time was needed to generate data

- Often involved issues with inert ingredient

As a result of this analysis the Agency's Product Chemistry Team concluded that the best approach to address these issues was to develop a detailed addendum to the Blue Book that more systematically addresses product chemistry issues (including inert ingredient issues). The Blue Book has been a primary source of information for registrants who are less knowledgeable about the registration process and requirements. In addition, these addendums will be placed on the website so that people looking for additional information on product chemistry can easily access it there as well.

Analysis of Renegotiated PRIA Due Dates

Registration Division

The reasons for renegotiation of PRIA due dates as the result of product chemistry issues are detailed in the attached file "Analysis of Product Chemistry Issues in RD Resulting in Renegotiated PRIA Due Dates" which contains information as of August 2006. The analysis demonstrates:

- The issues are mainly with smaller registrants
- In order of importance by number of times they occur, the problems are related to:
  - Insufficient or no data submitted
  - Inert ingredients
  - CSF errors
  - Citation of cancelled products or other problems with the citations for "me-too" products

Antimicrobials Division

The reasons for renegotiation of PRIA due dates as the result of product chemistry issues are mainly due to the following:

- The issues are mainly with smaller registrants
- In order of importance by number of times they occur, the problems are related to:
  - Data deficiencies
  - Data not submitted
  - CSF errors
  - GLP not met
  - Inert ingredients not cleared

Biopesticides and Pollution Prevention Division (BPPD)

Product chemistry and CSF issues (PCCI) were involved in approximately 73% of the renegotiations in BPPD. The Biochemical Pesticides and Microbial Pesticides branches accounted for 89% and 11%, respectively of these renegotiations.

In the majority of renegotiations, PCCI were clearly the primary motivating factor. For other renegotiations involving multiple causative factors, however, it was unclear if the PCCI-alone would have resulted in renegotiations. This lack of clarity is because renegotiations are dependent on the timing, severity, and type of deficiencies.

Renegotiation due to PCCI delayed product registration substantially. The average "time added to registration" by first-time renegotiations was approximately 18 weeks (2-85 weeks,

n=63). The time added by second renegotiations was also approximately 18 weeks (4-36 weeks, n=12). Time added statistics were not calculated for third and fourth time renegotiations because of few available cases.

A screening level analysis demonstrated that:

- Of the renegotiations due to product chemistry alone, approximately,
  - 43% involved issues with the formulation or manufacturing process
  - 35% involved submission of physico-chemical study data
  - 32% involved product identity, composition, or starting materials
  - 28% involved analytical methodology deficiencies (including those for enforcement)
  - 15% involved issues with the preliminary analysis
  - 8% involved deficiencies in the discussion of the formation of impurities
  - 4% involved issues with certified limits

- CSF completeness was dependent on product chemistry submissions
- Approximately 79% of the PCCI involved the CSF. Of these, approximately,
  - 67% involved inadequate identification of the active ingredients (Name, CAS #, Supplier)
  - 33% involved discrepancies between the CSF and label or product chemistry data
  - 27% involved deficiencies with certified limits
  - 25% involved issues with the nominal concentration or percentages of the active ingredients
  - 23% involved inert ingredients
  - 9% involved pH or bulk density deficiencies
  - 6% involved totaling or calculation errors (other than those in certified limits)

- Few packages were renegotiated due to a total lack of submitted data
- While storage stability and corrosion characteristics were often cited as data deficiencies (50% of product chemistry cases), the lack of these studies alone were not responsible for renegotiations

DATE: 23/OCT/2006

How Registrants / Applicants can Avoid Common Errors in Product Chemistry Submissions for Registration and Re-registration of Pesticide Chemicals

General Tips:

- When in doubt, consult with the Product Chemistry Team Leader.
- Follow the table of data requirements, page 16 in the guidelines and chapter IV in the SOP (Reference #10 Need Link).
- Cover letter to Agency should explain briefly what action is being requested. [Do not provide superfluous information that can be obtained from the data or label and CSF, e.g. product safety, efficacy, uses, clearance of ingredients, etc.]
- Ensure application is complete, Form, 8570-1 is filled out completely. In "R-30" application requests, it is important to cite the name and registration number of the product claimed to be substantially similar to the pending product.
- Alternate formulation should be identified by a number or a letter in Box A of the CSF.
- A Microsoft ® Excel worksheet has been placed on the Registration Division's website as an aid for submitters in calculating the correct nominal concentrations Need Link.

[A.] Product Chemistry Data:

1. Follow PR Notice 86-5 for organizing and formatting the submission.

2. Follow the specific requirements for each type of product whether it is EP or MP. Also, solubility in organic solvents is required along with solubility in water. Further, the storage stability and corrosion characteristics are required for all EPs and MPs (refer to Chapter V in the SOP Need Link). However, the Agency may grant "conditional registration" if the data is stated to be in progress. An accelerated stability study may be submitted for MP, but it does not exempt applicants from the one year storage stability requirement.

3. The GLP requirements are listed in 40CFR160. Some studies require full compliance, others partial, and the remaining no compliance (refer to chapter X of the SOP Need Link). And include a Statement of Data Confidentiality and GLP/Quality Assurance Statements.

4. If the applications for EP's/MPs are formulated using registered sources, take advantage of the self certification process found in PR Notice 98-1. The registrant need only submit four pages (a Statement of Data Confidentiality, GLP statement, Form 8570-36 (abstract summary of the physical/chemical properties), and Form 8570-37 (a self-certification statement) in lieu of a volume of information, Reference #7 in this document).

5. Data is reflected on the product's label and CSF so they must match. [Examples: the pH, density, and flammability cited in boxes 7, 8 & 9, respectively, of the CSF must be consistent with values in the submitted data. Also, the ingredient statement, sub-statements, the physical or chemical hazards statements, and storage and disposal statements in the label must be consistent with the data submitted. There must be a consistency between the label

and CSF in citing the ingredient statement and whether the product is flammable or extremely flammable as shown in the data and box 9 of the CSF].

6. If registration is <u>not</u> requested for a new technical source, it must be supported with Groups A & B of product chemistry data. No need to submit a label or CSF.

7. Import tolerances, no need to submit a label or CSF, but supporting Groups A & B product chemistry data must be submitted along with a petition seeking tolerances for a product registered abroad. References must be made to the MRID's previously submitted when using a non-registered source that was approved by the EPA.

8. Production of a TGAI in a different facility and/or using different methods of manufacturing or different starting materials must be supported with five batch analysis. The new TGAI may be claimed in an alternate CSF to a currently registered TGAI approved in a basic or alternate CSF.

9. The enforcement analytical method must be submitted/referenced for a new MP/TGAI. Copies of the method and samples of the product must be submitted to EPA's laboratory for validation. If applicable, the method can be referenced for a TGAI produced in a different facility or an EP/MP formulated using a registered TGAI source. Otherwise, a modified or a new method must be developed and submitted for review and validation by the EPA's laboratory. If using a non-registered source to formulate a product, reference the MRID number of that source citing the analytical method, or resubmit the method indicating it was previously submitted in MRID (number).

[B.] <u>Confidential Statements of Formula (CSF)</u>:

1. Table 1 below provides an example of how to complete the label and CSF assuming a formulated product using 50 pounds from a non-registered TGAI, 96% pure containing impurity A at 2.4% and B at 1.6%: CSF (1) if the data on the TGAI was previously approved by the EPA, and CSF (2) if the data on the TGAI was not submitted, not reviewed, or found inadequate by the EPA. In situation 2, referral to the Health Effects Division will be necessary for their assessment as to the toxicological significance of carryover impurities, noting that the chemical name and CAS registry number of each impurity must be listed in column 10 of the CSF.

Table 1: Expressing values in pesticide labels and Confidential Statements of Formula (CSFs) when using non-registered technical sources in Formulating products

Label	CSF (1)			CSF (2)		
	13(a) Lbs	13(b) %	15 Purpose	13(a) lbs	13(b) %	15 Purpose
Active Ingredient…… 48%	50	50 (48) (2)	Active Ing. Nominal Impurities	50	50 (48) (1.2) (0.8)	Active Ing. Nominal Impurity A Impurity B
Other Ingredients…… <u>52%</u> Total…….. 100%	50	50	Inert Ing.	50	50	Inert Ing.

- Note: Nominal concentration = % w/w X TGAI purity [50% x 0.96%] = 48%.

2. Errors occur when calculating the nominal concentrations using a salt factor. This example may also be fund in Chapter XI of the SOP):

Example 2: when cupric hydroxide reacts with naphthenic acid to form copper naphthenate); the nominal concentration of the salt complex that should be declared on the label. It can be calculated by multiplying the salt factor by the nominal concentration of free acid. The salt factor is calculated by dividing the molecular weight of copper naphthenate by that of naphthenic acid. The metallic equivalent is calculated by dividing the molecular weight of copper by the molecular weight of copper naphthenate X 100. This percentage should be indicated as a sub-statement to the ingredient statement.

This can be represented by the following equations:

$2C_5H_9COOH + Cu(OH)_2 \rightarrow CuC_5H_9(COOH)_2 + 2H_2O$

Naphthenic acid, MW = 113 + Cupric hydroxide → Copper naphthenate, MW = 287.55

Salt Factor = MW of Cu Naphthenate ÷ (2) MW of naphthenic acid = 287.55 ÷ (113 x 2) = 1.27

% of the PAI on the label = the nominal concentration of the free acid x 1.27 [the nominal concentration of Naphthenic acid = % w/w X its purity].

% Cu in the formulation = MW of Cu ÷ MW of complex x 100 = 63.55 ÷ 287.55 = 22.1%

Metallic Cu equivalent = % PAI on label x 0.221

3. Take advantage of the Microsoft ® Excel worksheet placed on the Registration Division's website to aid submitters in calculating the correct nominal concentration.

4. Errors occur with the inert ingredients when not enough information has been provided and the Agency can not discern if it has been "cleared" for us or not. See section on inert ingredients.

5. The certified limits of active ingredients should comply with 40 CFR §158.175(b)(2) and (c). However, in some cases, a wider certified limit range is acceptable if a written justification is provided and is supported by data.

6. Inert ingredients common errors (Food or Non-food) will be addressed under a separate heading. However, one tip bears repeating--if the certified limit is zero for an inert ingredient the Agency will assume that the registrant is not adding that inert ingredient(s) in the formulation. An alternate CSF stating the lowest detectable limit should be used in cases where the inert is present in trace amounts.

7. Fertilizer Components have caused errors because:

- All fertilizer materials used in pesticide products, whether generated or premixed,

must be identified on the CSF (per 40 CFR §158.155, 158.160 and 158.175). Registrants must list out the individual components of the fertilizer on the CSF, and must include N-P-K ratios, CAS numbers, chemical composition (% by weight), and upper and lower certified limits and the name and address of the fertilizer source.

- All possible variations in fertilizer components or alternate fertilizer materials used for a product must be presented on the CSF or in a separate confidential attachment to the CSF and must include the supplier's name and address.

- In cases where a fertilizer product contain non-fertilizer components such as limestone, corn cobs, paraffin oil, etc, the non-fertilizer components must also be identified on the CSF and must include CAS numbers, % by weight and certified limits of each component.

References:

1. Code of Federal Regulations, Title 21.
2. Code of Federal Regulations, Title 40, Parts 158.150 to 158-190.
3. Code of Federal Regulations, Title 40, Parts 766.27.
4. Federal Register Notice: 49(207) FR42863,24/OCT/1998.
5. OPPTS Test Guidelines, Series 830, Product Properties, EPA 712-C- 96, August, 1996.
6. PR Notice 91-2 Accuracy of stated percentages for ingredients statement.
7. Pesticide Regulations 98-1, entitled "Self-Certification of Product Chemistry Data."
8. Pesticide Registration (PR) Notice 98-10, "Notifications, Non-Notifications and Minor Formulation Amendments."
9. The Federal Insecticide, Fungicide, and Rodenticide ACT (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA) As Amended by the Food Quality Protection Act (FQPA) of August 3, 1996.
10. Malak, S. and Betsy Grim (2003). Standard Operating Procedure 2002-1 on Product Properties Data Requirements For Registration and Reregistration of Pesticides, National Conference on Managing Environmental Quality Systems, Division on Information Quality Policies and Standards, New Orleans, Louisiana (54 pages). Internet Address: http://www.epa.gov/oppfead1/guidance/product-sop.htm

Analysis of Product Chemistry Issues in BPPD Resulting in Renegotiated PRIA Due Date

PRIA Code	Date	General Reason for Renegotiation (from Renegotiation Form)	Detailed Product Chemistry or CSF-related Reasons for Renegotiation
B67	4/5/2005	Data deficiencies	Nominal concentration for the ai not provided, upper and lower cert limits need to be provided for the ai only, alternate formulation did not provide a CSF
B67	4/5/2005	Data deficiencies	Nominal concentration for the ai not provided, upper and lower cert limits need to be provided for the ai only, alternate formulation did not provide a CSF
B77	1/9/2006	Nomenclature of BT ai	Microbial identity inadequate (trade name). Need to identify as per the Crickmore nomenclature system for Bt proteins to the tertiary level
B68	8/9/2006	Data not submitted - product chemistry, Issues - CSF, label	Manufacturing process not provided for alternate source producer, the preliminary analysis of the TGAI not performed by a validated GLP method, nominal percentages of individual components did not fall within certified limits
B67	6/30/2005	Data not submitted - efficacy	Selective citation of data for product chemistry and acute toxicity not acceptable because of substantial differences in products, enforcement analytical method, storage stability, and corrosion characteristics data not submitted, CAS numbers missing on CSF, MSDSs provided for two suppliers but no alternate supplier identified on CSF, no information on active ingredients provided under "Description of the Starting Materials", incomplete discussion of reactant products in "Discussion of Formation of Impurities"
B67	10/11/2006	Inert data	Selective citation of data for product chemistry and acute toxicity not acceptable because of substantial differences in products, enforcement analytical method, storage stability, and corrosion characteristics data not submitted, CAS #s missing on CSF, MSDSs provided for two suppliers but no alternate supplier identified on CSF, no information on active ingredients provided under "Description of the Starting Materials", incomplete discussion of reactant products in "Discussion of Formation of Impurities", difficulty in substitution of 2 inerts
B59	6/12/2006	Data not submitted - product chemistry	Amended CSF, new preliminary analysis data, and an amended label not submitted for a change in active ingredient name and concentration
B67	7/13/2006	Data Deficiencies - product chemistry, incorrect source, CSF	Source of the active ingredient does not match registration number given, enforcement analytical method, description of production process, and description of formulation process did not contain information on the product, ingredients in the certification of limits do not match the CSF, description of starting materials does not list purities of USP active ingredients and the MSDS for ingredient is not from the producer listed on the CSF, physical and chemical characteristics not provided
B67	3/10/2005	Allergen inert	Primarily efficacy, but also product name mismatch on certificate of analysis and in "Physical and Chemical Properties", lack of storage stability and corrosion characteristics
B75	11/30/2005	Data deficiencies	Full study reports for product characterization of Bt protein (analytical method, amino acid homology, in vitro digestibility) not provided
B73	3/16/2005	Data and label deficiencies - product chemistry, CSF	Discrepancy between nominal concentrations of active ingredients and impurities (and upper and lower certified limits) on CSF and that in product, discrepancy between relative amount of actives and that in the registered products used as sources, source of all actives not listed, description of the formation of impurities not relevant to end-use product, total weight of formulation omitted in box 17 of CSF, inappropriate identification as a "Me Too"

B67	3/9/2005	Data not submitted - acute tox	Primarily toxicity, also lack of storage stability and corrosion characteristics, lack of flammability, explodability, and miscibility, description of beginning materials lacking an MSDS for one component, inert ingredients listed before actives on CSF
B67	3/9/2005	Data not submitted - acute tox	Primarily toxicity, also lack of storage stability and corrosion characteristics, lack of flammability, explodability, and miscibility, description of beginning materials lacking an MSDS for one component, inert ingredients listed before actives on CSF
B67	6/20/2005	Data not submitted - acute tox	Primarily toxicity, also lack of storage stability and corrosion characteristics, questionable inert use
B67	3/9/2005	Data not submitted - acute tox	Primarily toxicity, also lack of storage stability and corrosion characteristics, lack of flammability, explodability, and miscibility, description of beginning materials lacking an MSDS for one component, inert ingredients listed before actives on CSF
B67	3/9/2005	Data not submitted - acute tox	Primarily toxicity, also lack of storage stability and corrosion characteristics, lack of flammability, explodability, and miscibility, description of beginning materials lacking an MSDS for one component, inert ingredients listed before actives on CSF
B67	2/28/2005	Data deficiencies - product chemistry	Nominal concentration of the active ingredient not reported on CSF, storage stability clarification not provided
B67	2/28/2005	Product chemistry, tox, etc.	Product chemistry data not provided for amended formulations (change of inerts)
B67	8/18/2005	Product chemistry, tox, etc.	Bridging information for product chemistry insufficient (not substantially similar), product chemistry data on product not provided
B67	10/13/2005	Product chemistry, tox, etc.	Bridging information for product chemistry insufficient (not substantially similar), product chemistry data on product not provided
B60	9/21/2005	Additional data - product chemistry, allergenic inerts	Information regarding morphological and biological properties of active ingredients to be used as quality controls for seed culture use and fermentation lot acceptance not provided, level of contaminants not described, certified limits do not reflect minimum guaranteed CFUs, rationale for storage stability sample times not provided, data for storage stability not provided, CSF address inconsistent with address of manufacturer, CSF pH differs from pH in product chemistry report
B67	12/30/2005	Data deficiencies	Storage stability and corrosion characteristics not submitted, CSF pH and bulk density reported as a range of values
B67	11/10/2005	Data submitted - delayed receipt	Inert not cleared for food use, storage stability and corrosion characteristics not reported, odor data not reported, CSF supplier and reg number incorrect and need updating
B67	11/10/2005	Data submitted - delayed receipt	Inert not cleared for food use, storage stability and corrosion characteristics not reported, odor data not reported, CSF supplier and reg number incorrect and need updating
B67	7/20/2005	Data deficiencies	Preliminary analysis quantifying each active component not provided, analytical methods for analysis of active ingredients not provided, storage stability and corrosion characteristics not reported, manufacturing process incompletely described
B67	7/20/2005	Data deficiencies	Storage stability and corrosion characteristics not reported, manufacturing process was incompletely described, CSF certified limits of inerts do not match provided studies
B81	2/1/2006	Data deficiencies - benefits and insect resistance	Deficiencies in analytical method, more time needed to review independent laboratory method validation

		management plan	
B67	12/30/2004	Data deficiencies	Storage stability and corrosion characteristics not submitted, CSF pH and bulk density reported as a range of values
B60	2/28/2005	Data Deficiencies	Mode of action data not submitted, exact formulations including CAS numbers of starting and intermediate materials, sources, and purities for all alternate media and active ingredient formulations not provided, quantification and limits for contaminating microorganisms not provided, certified limits on CSF not listed as %w/w with an upper and lower range in CFU/g, complete list and limits for all ingredients not provided, justification for exceeding 40 CFR cert limits not provided, storage stability and corrosion characteristics not provided, methods for "Physical and Chemical Characteristics" not provided
B67	1/24/2005	Data not submitted - efficacy	Primarily toxicity and label issues; secondarily, inert ingredients, CAS #s, and limits not provided on CSF,
B67	3/14/2005	Data not submitted - product chemistry, eco tox, human health	Concentration of active ingredient in plant extract not provided on CSF, inert ingredient information not provided on CSF, Product Identity and Composition, Description of Starting Materials, Production and Formulation Process, Discussion of Formation of Impurites, Certified Limits, and Enforcement Analytical Method not provided
B67	5/9/2006	Data deficiencies - product chemistry, acute tox, ecological effects	No statement of TGAI purity and cfu/ml of TGAI or formulation on CSF, CSF-label discrepancy in regards to cfu/ml, purity and cfu/ml in Manufacturing Process not provided, microbial contaminants identified in preliminary analysis but not discussed, methods used to determine Physical/Chemical Properties not provided
B59	5/9/2006	Data deficiencies - product chemistry, acute tox, ecological effects	No statement of TGAI purity and cfu/ml of TGAI or formulation on CSF, CSF-label discrepancy in regards to cfu/ml, purity and cfu/ml in Manufacturing Process not provided, microbial contaminants identified in preliminary analysis but not discussed, methods used to determine Physical/Chemical Properties not provided
B67	10/21/2005	Label, data matrix, Data deficiencies - product chemistry	Discrepancy between source material (and purity) used in product chemistry studies and that reported on CSF, storage stability and corrosion characteristics not reported
B59	10/18/2005	Data not submitted - tox, eco, data deficiency - efficacy	CSF and product chemistry inconsistencies were not addressed, analytical methods not sufficiently reported
B59	7/20/2006	Data deficiencies	CSF and product chemistry inconsistencies were not addressed, analytical methods not sufficiently reported
B68	7/7/2006	Data deficiencies - product chemistry	Starting materials and impurities insufficiently described, incomplete description of alternate manufacturing process
B67	2/8/2005	Data deficiencies	CSF-label inconsistencies, inadequate inert ingredient description, upper and lower cert limits outside 40 CFR recommendations, storage stability pending
B67	6/2/2005	Label, data deficiencies - product chemistry	Active ingredients were listed last on the CSF, CSF CAS numbers for two ingredients were incorrect, certified limits for 2 ingredients outside range presented in 40CFR, product name inconsistent between CSF and label, oxidation/reduction, explodability, miscibility, and viscosity not provided, manufacturing process incomplete
B67	9/7/2005	Label, deficient waiver rationale	Primarily toxicology and label issues; secondarily, product name inconsistent between CSF and label
B59	10/13/2005	Uncleared inert	Inert ingredient not cleared for food use, inert ingredient considered active ingredient because of concentration, additional new active ingredient added to formulation

B67	1/13/2005	CSF, Data deficiency - efficacy	Primarily efficacy; secondarily, CSF with inaccurate active ingredient and impurity names (and percent), lack of unit amounts in block 13a, incorrect percent by weights and upper and lower certified limits, percent active ingredient on CSF different than label, incorrect nominal concentrations and upper and lower certified limits (on a percentage by weight basis) for actives and inerts, total weight of product inaccurate
B67	11/10/2005	Resubmission of data/information	Primarily efficacy; secondarily, CSF producer not identified in block 2, identification of the active ingredient inaccurately identified on label and CSF, pH block 8 inaccurate, flash point required in block 9, analytical method insufficient
B67	12/21/2004	Data deficiencies - product chemistry, eco other studies	Primarily toxicology; secondarily, lack of storage stability, CSF spelling error, CSF listed proprietary compound names (not chemical names and CAS numbers)
B67	3/17/2005	Data deficiencies - acute tox, eco	Primarily efficacy; secondarily CSF with unreported ingredient (and percent composition and CAS), unsubmitted storage stability
B67	12/21/2004	Data deficiencies - product chemistry, other studies	Primarily toxicity and efficacy; secondarily, CSF listed proprietary compound names, not chemical names and CAS numbers, CSF has incorrect CAS number for an ingredient, incomplete description of manufacturing process
B67	12/21/2004	Data deficiencies - product chemistry, other studies	Primarily toxicity and efficacy; secondarily, CSF listed proprietary compound names, not chemical names and CAS numbers, CSF has incorrect CAS number for an ingredient, incomplete description of manufacturing process
B67	9/15/2005	Data deficiencies	Primarily toxicity and efficacy; secondarily, CSF-label name inconsistency, and CSF ingredient spelling, and percentage of active ingredient on CSF
B67	12/21/2004	Data deficiencies - product chemistry, other studies	Primarily toxicology and efficacy; secondarily lack of storage stability
B67	12/21/2004	Data deficiencies - product chemistry, other studies	Primarily toxicity and efficacy; secondarily, incorrect CSF CAS number, incomplete description of manufacturing process
B67	9/15/2005	Data deficiencies	Primarily efficacy; secondarily, percent of active on CSF and label inconsistent, CSF ingredient spelling, incorrect CAS number, manufacturing process incompletely described, discrepancy between ingredient amounts on CSF and amounts used in formulation
B67	12/21/2004	Data deficiencies - product chemistry, other studies	Primarily toxicity and efficacy; secondarily, CSF listed proprietary compound names (not chemical names and CAS numbers), CSF has incorrect CAS number for an ingredient, incomplete description of manufacturing process
B60	6/27/2005	Manufacturing process	Primarily toxicity and fate; secondarily, conflicting identification of active ingredient percentage in preliminary analysis, label, and CSF, problematic product composition, product characterization and analytical method
B60	9/27/2005	Data deficiencies	Submission of information later than agreed upon in the first renegotiation; Primarily toxicity and fate; secondarily, identification of active ingredient, problematic product composition, product characterization and analytical method
B60	12/14/2005	86-5	Renegotiation date allowed insufficient review time; Primarily toxicity and fate; secondarily, identification of active ingredient, problematic product composition, product characterization and analytical method
B67	12/14/2004	Data not submitted - product chemistry	CSF handwritten, inadequate active and inert descriptions and percentage on CSF, inadequate certified limits, source for TGAI different than in certificate of analysis, no preliminary analysis, inadequate description of the manufacturing process and analytical method, missing units for bulk density, dissociation constant, storage stability, corrosion characteristics, flammability, and explodability not submitted

B67	12/14/2004	Data not submitted - product chemistry	CSF handwritten, inadequate active and inert descriptions and percentage on CSF, inadequate certified limits, source for TGAI different than in certificate of analysis, no preliminary analysis, inadequate description of the manufacturing process and analytical method, missing units for bulk density, dissociation constant, storage stability, corrosion characteristics, flammability, and explodability not submitted
B63	4/6/2005	Data not submitted - product chemistry	Proprietary inert on CSF (with no CAS number), inadequate manufacturing process, physical-chemical data not submitted
B63	12/7/2005	Data not submitted - product chemistry	Inadequate manufacturing process and discussion of formation of unintentional ingredients, physical-chemical data not submitted
B67	12/7/2005	Data deficiencies acute tox, product chemistry, label, CSF	Primarily toxicity; secondarily, CSF certified limits of alternate and basic formulation, active ingredients on CSF and label inconsistent, source composition discrepancies
B67	6/23/2005	Data deficiency - efficacy	Primarily efficacy; secondarily, CAS numbers on CSF, submission of storage stability
B67	6/23/2005	Data deficiency - efficacy	Primarily efficacy; secondarily CAS numbers on CSF, submission of storage stability
B60	8/9/2005	Data deficiencies	Product composition and size not described, quality control for manufacturing process not provided, manufacturing process inadequate, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate, impurities greater than or equal to 0.1% not listed on CSF, material packaging not described, viscosity, boiling point, specific gravity, and vapor pressure not provided, CSF active ingredient descriptions and units of measure inadequate, analytical method inadequate, storage stability issue
B60	12/1/2005	Data deficiencies not adequately address and information resubmitted	Percentage of ingredients not provided on CSF, storage stability and corrosion characteristics not provided, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate, material packaging description not provided
B60	6/23/2006	Data deficiencies not adequately address and information resubmitted	Storage stability and corrosion characteristics not provided, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate
B60	8/9/2005	Data deficiencies	Quality control for manufacturing process not provided, manufacturing process inadequate, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate, material packaging not described, viscosity, boiling point, specific gravity, and vapor pressure not provided, CSF active ingredient descriptions and units of measure inadequate, analytical method inadequate, storage stability issue
B60	12/1/2005	Data deficiencies not adequately address and information resubmitted	Quality control for manufacturing process not provided, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate, material packaging not described, CSF active ingredient descriptions and units of measure inadequate, storage stability issue
B60	8/9/2005	Data Deficiencies	Product composition and size not described, quality control for manufacturing process not provided, manufacturing process inadequate, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate, impurities greater than or equal to 0.1% not listed on CSF, material packaging not described, viscosity, boiling point, specific gravity, and vapor pressure not provided, CSF active ingredient descriptions and units of measure inadequate, analytical method inadequate, storage stability issue

B60	12/1/2005	Data deficiencies not adequately address and information resubmitted	Percentage of ingredients not provided on CSF, storage stability and corrosion characteristics not provided, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate
B60	6/23/2006	Data deficiencies not adequately address and information resubmitted	Storage stability and corrosion characteristics not provided, information on source and source quality control inadequate, microbial contaminant identification inadequate, method of manufacture inadequate
B60	10/11/2005	Data deficiency - analytical method	Preliminary analysis incomplete, discrepancy between CSF and impurities analysis, analytical method incompletely described, manufacturing process incompletely described
B59	4/5/2006	Data not submitted - infectivity, inhalation, manufacturing process	Primarily toxicity; secondarily, incomplete description of manufacturing process, inadequate identification of organism and classification, inadequate identification of inerts, viability not reported, storage stability not reported, CSF discrepancies regarding active ingredient amount and certified limits
B59	4/5/2006	Data not submitted - infectivity, inhalation, manufacturing process	Primarily toxicity; secondarily, incomplete description of manufacturing process, inadequate identification of organism and classification, inadequate identification of inerts, viability not reported, storage stability not reported, CSF discrepancies regarding active ingredient amount and certified limits
B60	11/4/2005	Data deficiencies	Quality control and assurance not provided for preliminary analysis, analytical methods deficient, manufacturing process incomplete and portions contradictory, data documenting microbial contaminants not submitted, storage stability issue, packaging material for product not identified, viscosity, boiling point, specific gravity, dissociation constant, vapor pressure not provided, analytical discrepancies not addressed, CSF name and purity of active ingredient insufficient, storage stability and corrosion characteristics not submitted
B60	3/16/2006	Data deficiencies - presence of pathogens	Quality control and assurance not provided for preliminary analysis, analytical methods deficient, manufacturing process incomplete, data documenting microbial contaminants not submitted, storage stability and corrosion characteristics not submitted
B60	9/7/2005	CSF and label	CSF active ingredient inadequately described, CSF and label inconsistent
B67	1/2/2006	Data deficiencies - product chemistry	CSF CAS number for active ingredient not submitted, purpose in formulation not provided for an ingredient, preliminary analysis and CSF limits conflict, oxidation/reduction not provided, CSF spelling not accurate, storage stability and corrosion characteristics not provided, CSF address not provided
B67	1/2/2006	Data deficiencies - product chemistry	CSF CAS number for active ingredient not submitted, purpose in formulation not provided for an ingredient, preliminary analysis and CSF limits conflict, oxidation/reduction not provided, CSF spelling not accurate, storage stability and corrosion characteristics not provided, CSF address not provided, conflicting physical descriptions provided for different studies
B60	1/2/2006	Data deficiencies - product chemistry	CSF CAS number for active ingredient not submitted, upper and lower certified limits for markers not provided, preliminary analysis and CSF limits conflict, physical and chemical properties not provided for the MP, additional impurities over 0.1% were not quantified, ingredient percentages on CSF do not total to 100%
B67	3/29/2006	Data not submitted - tox, non-target organism	Primarily toxicity; secondarily, inadequate claim for substantial similarity, ingredient percentages on CSF do not total to 100%, certified limits are not provided or are inaccurate, typographic mistakes in Box 2
B67	4/18/2006	Data deficiencies - product chemistry, labeling	Starting materials and formulation process inadequately described, quality control and packaging not described, preliminary analysis not provided, impurities greater than or equal to 0.1% not provided, storage stability and corrosion characteristics not submitted, inappropriate CSF for single ingredient, concentration of active ingredient inadequately described

Analysis of Product Chemistry Issues in RD Resulting in Renegotiated PRIA Due Date

PRIA Code	Div	Date	Reason	Detailed Description
R31	RD	7/7/2005	CSF errors	Major errors on the CSF, listed source was cancelled 8/25/04
R31	RD	8/4/2006	Inert information	Additional information on proprietary inerts and a revised CSF were required to support registration. Need for sufficient time to review the data.
New Registration	RD	10/14/2004	Data deficiency	Agency sent the deficient chemistry review to company. Company sent a new CSF and requested an extension
R30	RD	10/26/2005	Data deficiencies - product chemistry, CSF	TRB review found errors in resubmitted CSF and PC package. TRB needed more time to review the revised PC package
R31	RD	3/24/2005	Data not submitted - product chemistry	
R34	RD	12/22/2005	Data deficiencies - product chemistry	Agency requires the submission of chemical analysis of five production batches derived from new production site. Registrant submitted data from three.
R34	RD	2/10/2006	Data deficiencies - product chemistry	TRB concluded that data gaps remained. More time to submit and review the data needed.
R31	RD	12/1/2005	Data not submitted - product chemistry, acute tox, efficacy	No data submitted and still has incomplete chemistry data
R31	RD	12/1/2005	Data not submitted - product chemistry, acute tox, efficacy	No data submitted and still has incomplete chemistry data
R30	RD	10/25/2005	Data not submitted - product chemistry	PC data was needed in support of the application of the "me-too" fast track.
R31	RD		Data not submitted - product chemistry	
R31	RD		CSF	TRB review of CSF determined an inert to have possible mutagenic activity. TRB required a sample of the proposed product. Needed time to submit study and allow adequate time for review
R31	RD		Data not submitted - product chemistry	
R31	RD	7/12/2006	inert not cleared for food use - registrant to reformulate	An inert ingredient in the formula has not been cleared for wood use, need to replace inert.
R31	RD	7/12/2006	Data not submitted - product chemistry	More time to prepare and submit PC info. Physical/Chemical data gaps for TGAI application.

R30	RD	1/26/2005	Data deficiencies - product chemistry, efficacy	Cancelled and re-opened file did not contain PC data or acute toxicity data reviews. Company was not able to cite previous data, and was required to generate and submit data for Agency review.
R31	RD	4/20/2006	Data deficiencies - product chemistry	Product Specific data found unacceptable. Need for a 5-batch analysis for each production site.
R33	RD	6/6/2006	Data deficiencies - product chemistry	TRB determined that the PC data was not acceptable for products containing 66.85% ai and new PC must be resubmitted. Additional EFED data gaps. Extra time required for the resubmission and the review.
R33	RD	6/6/2006	Data deficiencies - product chemistry	
R34	RD	7/28/2005	Data not submitted - product chemistry	TRB needed time to look at data and re-write Memo because PC data submitted in March
R34	RD	11/16/2004	additional review - inerts	HED review was requested and was not completed by PRIA date
R34	RD	2/15/2005	Data not submitted - product chemistry	Registrant required to submit data to support a new impurity . Need for extra time to resolve problems with the CSF.
R31	RD	27-Mar-06	Data deficiencies - product chemistry, CSF	Additional PC information and a revised CSF are needed to support registration
R31	RD	2/24/2006	Data deficiencies -product chemistry	TRB could not accept technical submission without additional info. Submitted in February on the chemical properties. Need time for front end processing and review of the revised submission
R31	RD	2/24/2006	Data deficiencies -product chemistry	TRB could not accept technical submission without additional info. Submitted in February on the chemical properties. Need time for front end processing and review of the revised submission
R31	RD	11/18/2005	review of worker exposure data and supplemental product chemistry data	~Pursuit of a registration for a product with a specific formulation which would use less protective engineering controls. A review of additional data required. HED review of worker exposure data will not be completed in time for PRIA date. ~Supplemental PC is being submitted to address registrant claims.

R31	RD	5/10/2005	Data deficiencies - product chemistry	Resubmission of PC data for new formulation
R31	RD	2/24/2006	Data deficiencies -product chemistry	TRB could not accept technical submission without additional info. Submitted in February on the chemical properties. Need time for front end processing and review of the revised submission
R34	RD	6/16/2006	Data not submitted - product chemistry	TRB stated that subgroup A data must be submitted
R31	RD	2/23/2005	Data deficiencies - product chemistry, efficacy	Data deficiencies and registration information needed before review could proceed.
R31	RD	1/6/2006	Data not submitted - product chemistry, acute tox	Company requested extension to generate and allow EPA review time of PC data
R31	RD	2/24/2006	Data deficiencies - product chemistry, CS	Additional PC and a revised CSF are required to support new source of ai. Extra time for review needed.
R31	RD	5/17/2006	Data deficiency - product chemistry	The PC review determined that one of the proprietary inerts in formulation was not cleared for application to growing crops. Company submitted new data
R31	RD	5/17/2006	Data deficiency - product chemistry	
R31	RD	10/25/2005	Data not submitted - product chemistry	Review indicated that one of the ai in the formulation was cancelled for outdoor use per the RED. Applicant needs to eliminate the ai or change to indoor use only. Deletion of the ai would require new PC data. Applicant deleted ai and renegotiated date.
R31	RD	2/15/2006	Data deficiencies - product chemistry	Resolving outstanding issues with inert ingredients in the formulation. Company requested new PRIA due date to allow EPA time to complete a review
R31	RD	11/7/2005	products not similar - additional data submitted	PC indicated insimilarities in impurity pro-life, therefore cited data cannot support the other product. Additional information was submitted and needed to be reviewed by TRB.
R30	RD	12/1/2005	Data not submitted - product chemistry may have been mailed to incorrect address	TRB stated that 2 necessary PC studies were mailed to wrong address. TRB requested an additional study with subgroup B data.

R31	RD	5/25/2005	Data deficiency - product chemistry	Registrant needed additional time to address Agency requirements for inert chemical clearance and TRB will require adequate time for PC review
R31	RD	12/10/2005	Data not submitted - product chemistry	Registrant did not submit required data in time. TRB and FB will require additional time for the review. Group B data was not received.
R31.1	RD	6/23/2005	CSF	
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R31	RD	6/23/2005	CSF	
R31	RD	6/23/2005	Data deficiencies - CSF and product chemistry	A revised CSF and PC was required and submitted on 6/2/05. EPA needed more time for review
R31	RD	10/24/2005	Data deficiency - CSF and Five batch analysis	TRB is requiring registrant a new 5 batch analysis to verify that the technical CSV's certified limits are supported.
R31	RD	10/24/2005	Data deficiency - CSF and Five batch analysis	~Reviews of PC determined that manufacturing process did not match with the stated limits on CSF. ~ CSF states that product may contain toxic inert. ~TRB required the submission of a new 5 batch analysis for "me-too" product. ~HB recommended extending the due date to give TRB adequate time to review submission.
R30	RD	5/10/2005	Data not submitted - product chemistry	Original application did not contain chem. studies and initial review determined that 830 series subgroup A data was needed. Trb requires extra time for review.
R30	RD	10/18/2005	Data not submitted - product chemistry	
R31	RD	8/10/2006	inert not cleared for food use - registrant to reformulate	One of inerts is not cleared for food use. Registrant wants extension to replace the inert.
R31	RD	10/4/2005	Data not submitted - product chemistry	PC data was required because the product CSF was not identical to the cited product CSF. Complete package arrived in October 2005 and agency needed more time for the review.