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WORK PLAN PROPOSAL

PROJECT NAME Excipient Control Strategy

Name of Working Group Excipient Working Group

Technical Committee Drug Product Technical Committee Date: 5 October 2004

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I. INTRODUCTION / PURPOSE

- A proposal is made to determine the range of excipient control strategies used by the pharmaceutical industry. A survey will document reasonable practices from which the group can make proposals.
- Survey results will lead to proposals for test reduction and decreased regulatory burden. For example, listing excipient specifications relevant to drug product quality and manufacturing processes in submissions, and documenting the related excipient control strategies at the drug product manufacturing site will be evaluated. The goal is a risk-based tool that will reduce paperwork and at the same time increase compliance with global specifications.
- The survey will collect baseline information about and raise awareness of excipient “processability”. Recent FDA proposals for Process Analytical Technology (PAT) have described the need for excipient processability control strategies. For the purposes of this document, processability is defined as attributes of an excipient that enable the predictable and consistent processing of a drug product batch in which the excipient is present. If the processability of an excipient is similar (e.g., within a range) when procured from multiple sources, as indicated by suitable tests, analytical procedures and acceptance criteria, such sources of the excipient can be deemed equivalent for the intended purpose.
- Lastly, the outcome of the survey may underscore industry’s desire for global harmonization of excipient specifications. Although beyond the charter of PQRI, this may be an opportunity for PQRI to establish a dialog with the Pharmacopoeial Discussion Group (PDG) which can strive for that objective. Both USP-NF and IPEC-Americas are members of PDG, and can begin this dialog.

II. DESCRIPTION OF OBJECTIVE

The pharmaceutical industry will be surveyed to gather information that will:

- Assess the range of current industry practice for excipient control to comply with applicable 21 CFR Regulations, USP-NF and Harmonization monograph requirements. These control strategies include excipient user monograph testing, excipient manufacturer monograph testing, manufacturing controls, manufacturer audits and alternate analytical methods.
- Assess the use of reduced testing.
- Assess availability and use of simple, reliable, extra-monograph excipient tests to determine excipient processability.
- Assess need to meet global requirements, use of alternate methods in meeting those requirements, and the impact of PDG harmonization.

The information will document reasonable excipient control practices, and current excipient processability measurements.

III. GUIDANCE OR REGULATION TO BE ADDRESSED

- Docket No. 02D-0526 – Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing, and Controls Information
- CPMP Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier CPMP/QWP/419/003/

IV. BACKGROUND

- Recent Draft Guidelines^{1,2,3} from the United States and Europe have the potential of causing excess paperwork and testing for excipient control strategies without adding benefits. In addition, both the US Drug Product CMC and the European excipient guidelines result in the elimination of generally accepted and common excipient control strategies by creating paperwork barriers for these strategies. For example, a Certificate of Analysis based on PhEur cannot easily be used in the US without duplicate testing. In addition, use of PhEur or JP testing alternatives to meet USP requirements is greatly restricted. The worst case is a global excipient tested by performing all methods of at least three compendia.
- The guides require the explicit registration of alternative procedures used for testing excipients that have pharmacopeial monographs. On the other hand, the US draft guidance¹ allows a simple submission reference to the USP-NF monograph. It is agreed that specifications of excipients must be consistent with those of the pharmacopeias, and that the tests and procedures used must be appropriate to demonstrate compliance. The question to be carefully considered is the amount of paperwork necessary to ensure appropriate control of those excipients when alternative control strategies are used.
- Regulatory/Compendial History: The United States Pharmacopeia has been clear that alternate methods are acceptable to demonstrate compliance with USP-NF requirements.

¹ "DRAFT GUIDANCE FOR INDUSTRY, DRUG PRODUCT: CHEMISTRY, MANUFACTURING, AND CONTROLS INFORMATION", Federal Register Vol. 68, No. 18 (January 28, 2003), Docket No. 02D-0526, CDER 1997127.

² "NOTE FOR GUIDANCE ON EXCIPIENTS, ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT", EMEA document CPMP/QWP/419/03, 20 February 2003.

³ 314.70(c)(2)(iii) now require a CBE-30 Supplement for "Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements." The corresponding Final Rule/Preamble, Guidance and Federal Register announcement links are included below.

- Supplements and Other Changes to an Approved Application. Pages 18727-18767 [FR Doc. 04-07532] [PDF] Effective date June 22, 2004 <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-7532.pdf>
- Guidance (<http://www.fda.gov/OHRMS/DOCKETS/98fr/1999d-0529-gdl0003.pdf>) and
- Availability of Guidance. Pages 18767-18768 [FR Doc. 04-07533] <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-7533.pdf>

- “Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.” USP General Notices section Tests and Assays.

- “Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.” USP General Notices section Tests and Assays.

- The U.S. regulations “21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures” apply to components used in a drug product.
 - 21 CFR 211.84(a) states that each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit. 21 CFR 211.84(d)(2) states that each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.

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- In some cases, results from in-process tests (e.g., process tests, in-process material tests) during the manufacturing process can be used in lieu of testing the finished product (excipient, in our case) to satisfy a test listed in the finished product (excipient) specification (see Lines 937 to 941, Reference 1). Supporting data, analytical procedures, and validation information, should be provided in the submission (see Lines 944 to 951, Reference 1) Draft Guidance for Industry, Drug Product, CMC Information.
- Scientific Issues and Questions: Excipients are an important part of most formulations, and in many cases the quantity of excipients is much greater than the active substance. Clearly, excipients must be controlled to ensure the quality of the pharmaceutical product and patient safety. However, excipients differ from most active substances in that they are often used in multiple products.
 - Because of this fundamental characteristic, testing of a single excipient has a potential to impact many product registrations. Moreover, once initial product submissions are made, maintenance of excipient commitments in multiple registrations becomes a significant burden for both manufacturers and the regulatory authorities.
 - If a NDA/ANDA applicant seeks approval for performing the compendial tests by compendial procedures, (either through in-house testing, or by relying upon the COA of the supplier plus at least an in-house identity test on the excipient prior to its release; see Lines 1022 to 1026, Reference 1), then, only such a statement would suffice in the application, and no additional details need be provided (see Lines 981 to 984, Reference 1) in the application. In any other circumstance, information should be included in P.4 of the application (see Lines 984 to 987, Reference 1). Further, “when the specification for a compendial excipient differs from the compendial monograph, ... the in-house specification should be provided.” (see Lines 1035 to 1038, Reference 1)
 - The FDA interpretation of ICH CTD language used in Sections P.4 Control of Excipients (see Lines 1035 to 1038, Reference 1) would require that manufacturers specify each procedure used for routine testing of excipients, unless the procedure is exactly that of the pharmacopoeia and all monograph tests are performed. Two strategies for controlling excipients are negatively impacted by this requirement:
 - Suppliers generally perform tests to demonstrate compliance with pharmacopoeial requirements, and pharmaceutical manufacturers often accept the supplier results on the basis of Certificate Of Analysis (COA) after appropriate identification testing and adequate qualification of the supplier’s control systems. With proper auditing of supplier processes and laboratory capability, this practice ensures compliance.
 - Procedures are used which have been demonstrated to be equivalent or superior to those in the pharmacopoeia. Often an excipient manufacturer has procedures used internally that are shown to produce equivalent results to those in the pharmacopoeia. Also, many manufacturers must meet global requirements and seek to eliminate redundant testing of the same attribute (e.g., European

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Pharmacopoeia (Ph.Eur.), United States Pharmacopeia – National Formulary (USP-NF), and Japanese Pharmacopoeia (JP) Heavy Metals tests) by selecting a single method shown to be capable of ensuring compliance with all the requirements.

- In both strategies above, the pharmaceutical manufacturer must have systems in place to ensure compliance. However, in the sense of true global harmonization of excipient monographs, the regulatory hurdles in implementing and maintaining such systems under the guidance are significant.
- Because a particular excipient may be used in pharmaceutical, bio-pharmaceutical, and nutritional supplement products, submissions of the routine, but extra-compendial excipient-testing program would be required in many product registrations. If the testing program were to be changed, for example, to reflect acceptance on supplier COAs or adoption of tests shown to meet multiple compendia, each of these product registrations would have to be changed. Also note that compendia change frequently, so that testing regimes must also be amended to conform. Of course, this is not the case when compendial procedures are used for testing, and when such compendial tests are adequate for the intended use of the excipient (see Lines 981 to 984; and 1032 to 1035, Reference 1). No more than a statement in an annual report of an NDA or ANDA will be necessary for reporting a change in a specification made to comply with an official compendium (See VIII.D.1., Reference 3). The exception is when “relaxing an acceptance criteria or deleting a test to comply with an official compendia.”

V. POTENTIAL IMPACT

- With the adoption of alternate control strategies, reduced testing, and receipt on COA the submitter increases efficiency and complies with global requirements. Avoiding triple compendial testing for the same attribute of each excipient increases efficiency and compliance without compromising the quality and control. (Note: FDA would accept alternate procedures “if they are in the current compendium (USP) or another FDA-recognized standard reference (e.g. AOAC International Book of Methods) and the referenced analytical procedure is not modified, a statement indicating the analytical procedure and reference can be provided rather than the analytical procedure itself.” (see Lines 1053 to 1057, Reference 1). The regulatory agency increases efficiency and effectiveness through a risk-based focus. A significant paperwork reduction is predicted because of a substantial reduction in multiple submissions and updates required for each excipient. This risk-based proposal ensures compliance without redundant lab testing or burdensome paperwork.
- With suitable processability evaluation of raw materials, drug product manufacturers will better control manufacturing processes, and reduce product

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variability. Processability evaluation can also identify equivalent, multiple-sourced excipients.

- With identification of more resources and data in support of international monograph harmonization the PDG effort can be accelerated.

VI. WORK PLAN OUTLINE

- 1) Survey excipient suppliers, distributors, and drug manufacturers to determine current excipient control strategies. Assessment will cover use of:
 - a) 21 CFR 211.84 required control strategy based on excipient manufacturer's COA receipt plus identification tests, and/or additional tests as appropriate to maintain quality of product.
 - b) Testing according to USP-NF requirements.
 - c) Excipient manufacturer's process controls.
 - d) Drug product manufacturer's audits.
 - e) Alternate methods that have advantages over USP-NF compendia methods such as ACS reagent, AOAC, or other compendia.
- 2) Survey the use of reduced testing. Assessment will cover use of:
 - a) Skip lot testing.
 - b) Elimination of redundant testing.
- 3) Survey the availability and use of simple, reliable, extra-monograph excipient tests to determine excipient processability. Assessment will cover:
 - a) Use of extra-monograph excipient tests found by the Drug Product Manufacturer to show excipient processability.
 - b) Identification of suitable tests capable of showing processability. Such tests may include specific or general methods, physical or chemical tests, and product specific test(s), that have relevance to a drug product manufacturing process.
- 4) Survey the impact of meeting Global requirements. Assessment will cover:
 - a) The impact of redundant testing.
 - b) Use of alternate methods in meeting global requirements.
 - c) Impact of PDG harmonization.
 - d) Requests for data to support equivalence of global testing for selected excipients. For example, evaluations of multiple compendia specifications for equivalence or identification of the most stringent specification.
- Decision Tree: Method evaluation tree to be created by the Working Group.

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- Milestone - Time Frame:
 - a) Steering Committee Approves Work Plan.
 - b) Design questionnaire (See Survey Timeline for details.)
 - c) Submit questionnaire for PQRI approval to distribute.
 - d) Prepare questionnaire mailing list.
 - e) Mail questionnaire.
 - f) Compile completed questionnaires.
 - g) Data entry and data analyses.
 - h) Prepare survey report.
 - i) Prepare recommendations.
 - j) Prepare publications.
 - k) Review report, publications and recommendations within working group.
 - l) Submit survey report, publications and recommendations for PQRI approval.

VII. WHAT WILL BE IN FINAL REPORT?

- The final report will summarize the survey of current use of excipient control strategies, use of any extra-monograph processability tests, alternate methods, and global testing by excipient users. The report will form the foundation for a work plan to remedy identified situations. Excipient Control Strategies will be defined and listed in an evaluation tree. It is anticipated that these results will be published in the public domain. Guidance will be proposed to FDA that the product submission contains the excipient specifications, and asserts that the excipient meets current compendial requirements if tested. The guidance further states that additional excipient documentation is available on site, if requested. Consideration may be given to form a liaison with the PDG should some of the remedies go beyond the charter of PQRI.

VIII. DETAILED WORK PLAN

- What specific work will be needed to address the research question? *The research question will require creation and distribution of a survey tool. In addition, the returned surveys will be summarized and evaluated. The work plan will be modified based on the data. Suitable excipient control strategies and an evaluation tree will be described.*
- What are the required resources?
 - Human Resources: *volunteers for survey creation, distribution, and data evaluation. A statistician is needed for survey design and analysis. Working Group will assemble and evaluate suitable control strategies. Finally, an evaluation tree will be assembled.*
 - Laboratory Resources: *Not required.*
 - Financial Resources (Budget) *The expense involves surveys of current excipient suppliers, distributors, and drug product manufacturers. The surveys will be provided by interested company volunteers as “sweat equity”. Mailing and copy costs will have a budget of \$600, and other costs will be provided as part of PQRI office support. Additional expense would be evaluated after survey completion and result evaluation.*
- Will the study utilize Data Mining or Prospective Research? *Prospective survey results will lead to study conclusions.*
 - What data /information will be needed to complete the objective of this work? *Survey results will provide the information to complete the objective of this work.*
 - Will the study utilize existing data (Data Mining)? *If data mining is to be used, please review the established PQRI protocols for the submission of data. Data Mining will be used if related data for evaluation of Excipient Control Strategies or use of extra-monograph processability testing becomes available.*
 - Will the study require that new laboratory data be generated (Prospective Research)? *No new lab data will be needed.*
 - Please explain the data collection or generation process and protocol. *The process for the survey will be: Design survey, identify respondents, write survey content, send out survey, receive, input and analyze survey response data, and compile report.*
- Include the Timeline and key Milestones.
 - See Survey Timeline attached.

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Approval: Working Group Chairman _____ Date: _____

Technical Committee Chairman _____ Date: _____

Steering Committee Chairman _____ Date: _____

VIII. FREQUENTLY ASKED QUESTIONS

1. What is the value and benefit of the excipient proposal?
2. What is the cause of "excess paperwork"?
3. What is processability, and why is it important?
4. What is meant by "Reduced Testing"?
5. How does this parallel the official compendia harmonization effort?
6. Will the objective be expanded to include "global regulatory and compendia expectations"?

1. What is the value and benefit of the excipient proposal?

The benefit of the excipient proposal is first to identify current trends in the industry when faced with changing global compendia requirements. Following these results, the WG can determine future activities or suggest recommendations for changes in the CMC guidance. The strategies for control of excipients that must meet US plus global requirements must be first identified. The 21 CFR 211.84 requirements are the starting place, and the WG will determine additional steps taken by industry. These additional steps include non-USP compendia testing, and extra-monograph testing using alternative procedures and "processability" procedures.

2. What is the cause of "excess paperwork"?

The draft guidance requires detailed specifications when the specification differs from the compendial monograph. Alternate methods must be listed and maintained in a US registered drug product submission (Reference 1). For global products, a common issue is confirming the excipients meet USP, PhEur, and JP requirements. Monograph changes are common due to recent success with PDG harmonization. This translates to maintenance of the submission (Reference 3) for each product containing the modified excipient. The number of product submissions multiplied by the excipient changes creates a cost prohibitive submission nightmare that is resolved by simply testing according to USP and thereby losing the benefits of globalization. The regulators and the submitters both must deal with this excess paperwork.

3. What is "processability", and why is it important?

For the purposes of this document, "Processability" is defined as the attributes of an excipient that enable the predictable and consistent processing of a drug product batch in which the excipient is present. Recent FDA proposals for process analytical technology (PAT) have described the need for excipient processability control strategies. If the processability of an excipient is similar (e.g., within a range) when procured from multiple sources, as indicated by suitable tests, analytical procedures and acceptance criteria, such sources of the excipient can be deemed equivalent for the intended purpose.

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4. What is meant by "Reduced Testing"?

"Reduced testing" refers to reduction of testing by skip lot testing⁴, use of excipient manufacturer's Certificate of Analysis (COA), or reliance on alternate methods. Note that this option is already available for NDA/ANDA applicants.

5. How does this parallel the official compendia harmonization effort?

The official compendia harmonization efforts are led by the Pharmacopoeial Discussion Group (PDG). PDG was co-founded by Ph.Eur., USP-NF, and JP. This international organization is designed to increase convergence and harmonization among the three pharmacopoeias. Indeed, since PDG was created in 1989, work has proceeded on 61 excipients of which 31 have been published and implemented in each region (Harmonization Stage 6). In addition, International Conference on Harmonization (ICH) recently adopted the concept of "Interchangeability". That means different compendia test chapters or procedures for the same attribute and specification may be shown equivalent or interchangeable. PDG also provides regular reports to ICH. ICH guidance for compendia harmonization is in ICH Q4. ICH has an interest in compendia harmonization, because it has been determined that harmonization of 10 compendia test chapters is critical to successful global registrations.

The PQRI Excipient Working Group proposal will be parallel and complementary to PDG work. PQRI scope is US-based, but it is conceivable that resolutions could be blended to a global proposal.

6. Will the objective be expanded to include "global regulatory and compendia expectations"?

PQRI is a unique US organization designed to resolve pharmaceutical issues with academia, regulators, and industry at the same table. There is no other organization like it in the world. Building on the strengths of PQRI diversity, the Excipient Working Group will work locally and think globally. Working together to do it right in the US means there is an excellent chance it will be good for global use.

⁴ Federal Register Notice, 65 FR 251, page 83043, Friday, 12/29/2000