



Workshop Highlights

IPAC-RS Workshop on OINDP Extractables and Supplier GMP

Basel, Switzerland 24-25 September 2007

The International Pharmaceutical Aerosol Consortium on Regulation and Science's (IPAC-RS) OINDP Materials and Supplier QC Working Groups hosted and extractables and GMP workshop on 24-25 September in Basel, Switzerland. A total of 54 people attended the workshop, representing 9 suppliers, 14 pharma companies, 4 CROs/consultants, and 2 regulatory agencies.

The workshop's primary goal was to continue the dialogue between suppliers and OINDP manufacturers on critical issues for OINDP materials and components, including extractables, change control, and GMP. Additionally, the workshop sought to introduce the IPAC-RS GMP Guideline to suppliers and OINDP manufacturers in Europe and to explain its application and use.

All workshop slide presentations are available at: www.ipacrs.com/supplier.html. For ease of reference, the workshop program is attached to this report. Day 1 included discussions on Extractables – the Challenges for OINDP, Application of Supplier GMP Guideline and a Regulatory Perspectives panel. Day 2 included presentations and panels on Audits, Quality Agreements, Supplier-Pharma Relationships, Regulatory Perspectives, Change Control, and QbD and the Supply Chain.

This report summarizes by topic the questions, comments and discussions that occurred at the workshop. The comment source is identified generally after each comment.

Implementation of GMP Guideline

- § The Guideline is an excellent document, not just for OINDP, but possibly for other dosage forms – more safety and quality is good for regulators and the industry. (Health Canada)
- § Who is in charge of encouraging n-2 suppliers to apply concepts in the GMP guideline? N-1 suppliers? The guideline should be available electronically to increase accessibility. (N-2 Supplier)
- § Much of the burden of training n-2 suppliers regarding the GMP guideline will fall to n-1 suppliers. As a pharma company, we are communicating to our n-1 suppliers that this needs to be done, and are including this in our GMP guideline training of n-1 suppliers. (Pharma)
- § If the guideline is used by suppliers, would reduced testing be acceptable? (N-1 supplier)
- § Right testing at the right time is key. The appropriate tests and amount of testing needs to be worked out between supplier and customer through communication and a relationship built on trust. (Pharma)

Information Sharing and the Supplier/Pharma Relationship

- § Sharing technical knowledge and understanding between pharma and suppliers is important. For example, details such as whether a mould release agent was used, why it was used, and why in some cases the agent is changed, should be discussed with customers to achieve improved understanding. (N-1 Supplier)
- § Emphasis on knowledge of materials up front, communication with suppliers and toxicologists early in the development and design processes, and emphasis on importance of risk assessment in identifying critical changes, are all areas with an important relationship to quality of OINDP components.
- § Routine extractables testing on every batch of material is expensive. Costs will invariably be shared with patients. (N-1 Supplier)
- § However, perhaps if at the supplier level, QbD concepts are applied, such as improved understanding of products and manufacturing

processes, then testing on every batch may not be necessary. (Health Canada)

- § Pharma companies need to be more engaged with their n-2 and n-3 suppliers – they need to know and understand better what such suppliers are doing in relation to the relevant materials. (Pharma)
- § There are generally two different types of n-2 suppliers: (i) medical grade materials suppliers, and (ii) commodity suppliers that supply large amounts of materials through distributors. N-1 suppliers are a very small percentage of commodity suppliers' business. There are also international pressures on some n-2/n-3 suppliers. For example, demand for lower-grade materials in China and India is very high, so n-2 suppliers are increasing production of these materials at the expense of high-grade materials. Also, the European REACH legislation requires an official filing for all chemicals imported into the EU, which can discourage importation of relatively small amounts of material. (N-1 suppliers)
- § It is beneficial to share extractables information with customers early in the process. Having clear goals and ideas regarding what information will be shared will facilitate effective and timely information sharing. (N-1 Supplier)
- § It is difficult for n-2 suppliers (e.g., raw materials suppliers, converters) to understand what N-1 and pharma require regarding implementation of changes, and other quality issues. We would like to have more discussions with pharma, n-1 and other n-2 suppliers to improve understanding. Further, n-2 suppliers may have information on degradation products that they may be willing to share. (N-2 Suppliers)
- § Ultimately it is pharma that makes the final decisions on the type and quality of materials that will be produced by suppliers, and pharma must be willing to consider using/ordering more expensive materials. (N-2 Supplier)
- § Conversations with and about the supply chain should include materials purchasing as well as development departments at pharmaceutical companies. The relationship between purchasing and development needs to be strengthened. (Pharma)

Change Control

- § In general, N, N-1, and N-2 suppliers have similar perspectives regarding what constitutes a “change.”
- § Pharma companies would benefit greatly if suppliers communicated clearly important changes to a

product, and how that change might affect the product. (Pharma)

- § Risks should be prioritized and high risks with impact on patients identified through risk assessment. This process should assist suppliers and pharma in identifying changes for which change notification is important. (FDA)
- § Risk assessment is key in working with suppliers on change control. Our company shares its risk assessment with our n-1 supplier. We specifically describe to our suppliers certain types or levels of change, and what affect such changes will have in the drug product. We define the level of change, a level of notification, and a schedule for notification and share this with supplier. (Pharma)
- § Managing change with multiple customers simultaneously is a big challenge for suppliers. Some suppliers will not improve or add innovations to products or processes because of this challenge. (N-1 Supplier)
- § Suppliers should provide change information to Pharma. However, there are many different types of changes, and reasons why changes might occur – for example, an n-1 supplier might lose its n-2 supplier. Multiple sources of supply for both Pharma and n-1 suppliers may be helpful in dealing with this particular issue. (N-1 supplier)
- § Multiple sourcing is a good idea, but must be managed properly. For example, all sources of supply must be kept in compliance and used regularly. If only one source is used and audited regularly then other sources may fall out of compliance. (FDA, Pharma)

Drug Master Files (DMFs)

- § The DMF system compromises both pharma and suppliers. In some instances suppliers and pharma use DMFs as a marketing tool, making assumptions regarding a level of quality that may not actually exist. FDA does not review DMFs unless an application specifically references the DMF, even regarding post-approval changes (unless the supplement refers to the DMF). Usually, on review, FDA will only review those specific pages or sections to which the application refers. If new information is added for an API DMF, then only the new information is reviewed; the entire DMF will not be reviewed due to lack of FDA resources. There are currently about 22,000 DMFs filed with the FDA. Half of these have never been reviewed, or have not been reviewed in the last 10-20 years. Companies can call FDA to ask about the review status of their DMFs. (FDA)
- § Quality agreements can play a significant role in sharing of critical/important information between pharma and suppliers. FDA understands that it has to drive and facilitate discussions on sharing of important information so that companies have access to the required information. (FDA)
- § FDA cannot completely remove the DMF system from its review processes. However, the process could be improved such that DMFs include only critical quality information, but FDA's question to DMF holders would still remain: What information does FDA need to receive that pharmaceutical companies don't need? (FDA)
- § Health Canada's DMF process is based on the FDA DMF system. Health Canada will accept the same DMFs as submitted to FDA. DMFs in Canada are not a legal requirement, and can contain "open" and "closed" portions. (Health Canada)
- § As a supplier company, we support the DMF process because it protects trade secrets and intellectual property. In some cases it is also considered dangerous to include pharmaceutical companies in discussions with N-2 suppliers because of intellectual property concerns. (N-1 Supplier)
- § Although the regulatory landscape is in transition, there is a trend to harmonization, and therefore many opportunities for working with regulatory agencies. (Pharma)

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General Regulatory Perspectives

- § FDA/CDER is moving more toward reliance on consensus standards. Going forward, the focus on guidances will be de-emphasized. (FDA)
- § Quality by Design concepts should be applied not just in development, but also post-market. (FDA)
- § On global harmonization, Health Canada overall has many ideas in common with FDA. Critical evaluations regarding regulations/standards in India and China should be done. (Health Canada)
- § Regulations (i.e., legislation) needs to evolve given the current push toward a QbD paradigm. For example, a company, operating under QbD, should be able to manage certain changes internally

without submitting a supplement (*i.e.*, regulatory flexibility) – this would promote innovation. However, the regulations need to be revised to accommodate regulatory flexibility. Q8-Q10 cannot be implemented without the regulations being revised. (FDA)

- § The Canadian food and drug regulations are very old, and there is recent discussion about modifying these regulations. Canada is working on a progressive licensing system, based on risk and product lifecycle management. (Health Canada)

Participants

OINDP Manufacturers

3M
Abbott
Aeropharm
AstraZeneca
Boehringer Ingelheim
GlaxoSmithKline
Nektar
Novartis
Novo Nordisk
PARI Pharma
Pfizer
sanofi-aventis
SkyePharma
Teva

OINDP Suppliers

Aerocan
Alcan Packaging
BASF
Bespak
Ciba Specialty Chemicals
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Toxikon Europe
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Auditing and Quality Agreements

- § Companies should consider sharing audit reports. This would allow less auditing and would provide a direct way to use a guideline or standard to increase efficiency. (Health Canada)
- § Third party audits could aid in dealing with sensitivities regarding sharing of audit reports. (FDA)
- § Suppliers sometimes get audited by several auditors from the same company, throughout the year. It is helpful to develop a global audit schedule to prevent this or to require justification for second audits. (N-1 Supplier, Pharma)

Highlights from QbD Breakout Sessions

The breakout session topic was “collectively implementing the QbD paradigm and identifying challenges and opportunities.”

The goal of the sessions was to develop recommendations based on supplier and pharmaceutical company perspectives, that would help facilitate implementation of QbD into selection and control of OINDP container-closure system materials. Moderators used the following specific questions to encourage focused discussion:

- § Can OINDP container-closure L&E terminology be translated into QbD terms? For example, what are the Critical Quality Attributes and Critical Process Parameters to consider for materials control?
- § How can QbD concepts be applied throughout design and development of OINDP container-closure systems? How would use of a new material be handled? How would changes to a material be handled?
- § What are challenges that suppliers and pharmaceutical companies face in implementing QbD, specifically in the materials selection and control arena? How can these challenges be addressed?
- § How can suppliers and pharmaceutical companies strengthen their quality systems to encourage QbD implementation? What other areas can be strengthened to encourage QbD implementation?

Most session feedback consisted of identifying challenges to implementing QbD. For example:

- § Education/Communication: need better sharing of information among interested parties
- § Process validation – lack of understanding at supplier
- § N-2 suppliers lack cleaning validation knowledge

- § Pharma and suppliers do not understand each others' processes
- § Creating trust between manufacturer and supplier
- § Important to define what's critical (Who? How? When?)
- § "Real" recommendations for plastic components not readily available (as in food contact materials)
- § Can existing standards/requirements be used in selecting new polymers/additives?
- § Changing company mindset and cultures:
 - Companies recognize QbD benefits but do not want to be "first."
 - How to get buy-in and change 'Back Home'
- § Mindset of regulators and standards bodies, especially in Rest of World
- § Time/resource investment is high for implementing a QbD approach
- § Continuity of supply

Some areas to strengthen to encourage QbD implementation:

- § Partnerships between pharma and suppliers
- § Pharma and suppliers should consult on processes not just materials
- § Develop standard methods for extractables testing that can be shared with suppliers (e.g. currently one supplier applies 8 different methods from 8 different customers to 1 polymer)
- § Move from a testing mindset (QC) " to an auditing mindset (QA)
- § Pharma could establish development teams that include N-1, 2, 3, 4 suppliers
- § Manufacturers pre-screen materials as part of risk mitigation
- § Suppliers consult with primary customers to do preliminary testing

Next Steps

The Supplier QC Working Group and the OINDP Materials Working Group will convene to discuss suggestions made at the Workshop for continued improvement of supply chain education and interaction.

Please contact the IPAC-RS Secretariat (lee.nagao@dbr.com or mary.devlincauzzi@dbr.com) with any questions.

General Comments From Evaluations

- § *"Continue the great job of bringing all the right people to the table to discuss the important matters; the message will get through!"*
- § *More case studies regarding extractables control and including protocol examples would be helpful.*
- § *"Good networking and multilateral exchanges, especially with FDA and Health Canada."*

Suggestions for Future IPAC-RS Workshops, Collaborations, or Working Group Activities

- § *Continued discussions with regulators – ideally including EU regulators; more interaction with n-2 suppliers – polymer, elastomer, metals suppliers.*
- § *How can IPAC-RS bring more N-2/N-3 suppliers to conferences.*
- § *How can IPAC-RS bring "development and design" folks to the conferences, many folks are "quality" folks but the information needs to get to design & development folks most importantly as they are the 1st to design the component.*
- § *Joint audit sharing and approaches.*
- § *More discussions on control of materials (i.e., how can a partnership be formed to achieve the sharing of information and details on potential changes to material composition).*
- § *Presentation of an n-1 supplier on the topic "how to involve the n-2 suppliers and promote the IPAC-RS Guidelines".*
- § *Foreign particulate matter may become a challenging subject in the future, collaboration is needed.*