



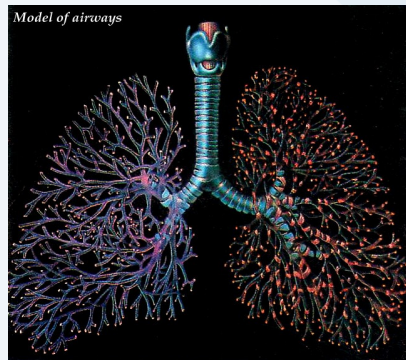
Experiences with the adoption of the PQRI best practice guidelines when applied to development of an E&L development package for a DPI

March 2011

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Anatomy of this presentation

- A personal list of highlights of the PQRI best practice guidelines
- Limitations
- Examples of “bear-traps” for the careless
- How a risk based approach can build upon the PQRI guidelines



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A personal list of key parts of PQRI recommendations – THE PROS

1. Definition of a threshold for leachable safety assessment
 - Has allowed development of methods for leachables which are targeting leachables at a level directly linked to a clearly defined justification
 - Clearly sets a universal standard, which mitigates the risk of developing methodology which is ultimately unsuitable for regulatory use.
 - Provides clear benchmark and expectations of analytical methods
2. Underlines the importance of a scientific approach to study of extractables and their link to leachables
 - Emphasises that studies should begin with considered material selection or “Quality by design”
 - Need to plan studies based on consideration of product type and how drug product is delivered to a patient
 - Studies of extractables should be analytically comprehensive pulling together a wide range of analytical techniques and approaches



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A personal list of key parts of PQRI recommendations (2)

3. Places a lot of importance on identification of unknowns
 - Definitions of SCT and AET (and ½ AET) are specifically aimed at assessing risks associated with unknown compounds
 - Identification of unknowns are paramount in safety assessment of leachables
 - Material selection decisions may depend on number and quantity of unknown compounds
4. Introduces some concepts around risk assessment
 - A process is described for “risk assessment” of discovered leachables
 - Safety Concern Threshold (SCT) is based upon a probability severity argument
5. States that methodologies employed should be validated
 - Analytical methods should be formally validated if used for critical decisions around safety assessment or formal specifications



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Definition of a threshold for leachable safety assessment – THE CONS?



- A definition for leachable safety is most welcome. However:
 - The threshold when converted to an AET works best with identified compounds of known toxicity
 - The AET is not easily to apply when identity cannot be established
 - The AET modification to account for variation in response factors in detectors only really works for GC detectors such as Flame Ionisation Detector where there are small and predictable variations in response.
 - Model systems in extractable studies have to be carefully chosen
 - Identification of potential leachable missed due to co-eluting non-relevant components
 - Some toxic and genotoxic leachables being defined as “special cases” without a clear definition of what constitutes a special case. This is ambiguous.

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Underlines the importance of a scientific approach to study of extractables and their link to leachables



- The scientific approach it outlines is sound. However:
 - There have been examples where people have simply adopted the best practice recommendations as doctrine
 - Eg. The recommendations for controlled extraction studies
 - Selection of analytical approaches and sample preparation techniques
 - Recommendations suggest that extractable studies are conducted prior to leachable studies and that extractables studies inform leachable studies
 - Leachable and extractable studies can be performed in parallel
 - Leachable studies might inform extractable studies to further understand materials, processes and manufacturing steps

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Places a lot of importance on identification of unknowns



- Without the identification of unknowns much of the safety assessment process outlined cannot proceed or is hamstrung
 - SAR needs a description of functional groups
 - Application of SCT and QT thresholds, requires identification prior to application for truly accurate quantification
- Alternative approaches to safety assessment are not discussed in any detail
 - What place do in-vitro measurements of leachables toxicity have?
 - If leachables are of no safety concern (as measured by in-vivo measurements on material extracts) but not identified, would this be acceptable?

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Introduces some concepts around risk assessment



- Risk Assessment approaches are limited, all potential sources given equal weighting
 - Some discussion of Quality by Design in material selection.
 - Use of risk assessment term describing safety assessment process
- Risk Assessment can be used throughout the process of extractable and leachable assessment.
 - A FMEA process can be used to define the scientific approach to study of extractables and leachables
 - Extractable studies and leachable studies can act as mitigators of risk
 - Control Strategies for leachables can be linked to risk assessments
 - No Leachables of Safety Concern, might mean no requirement for extractable controls. Control via a well defined change control process (As supported by ICH Q9 and Q10)

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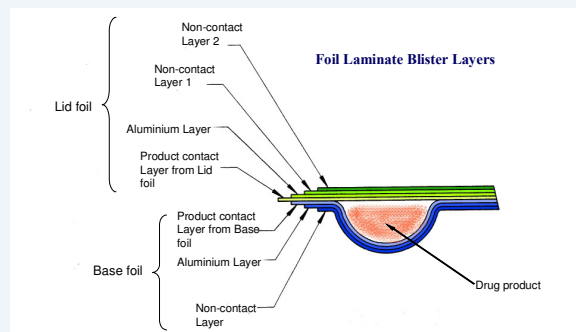
Illustrations of PQRI best practice guideline limitations



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Illustration of risk based approach for typical DPI

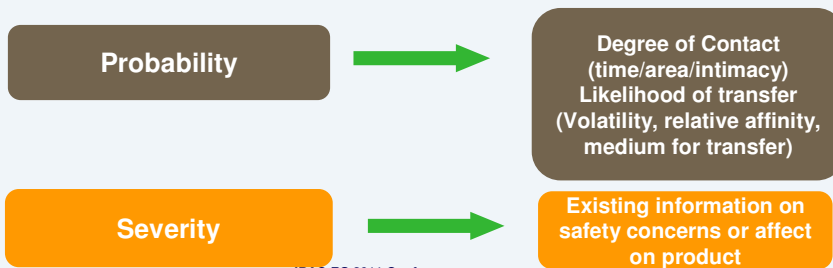
- Many DPIs contain foil laminate blisters which are in direct contact with dry powder drug product
 - It is clear that risks from leachables are different depending on which material layer in the laminate is considered
 - Examination of system must recognise this



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How risk assessment can be applied to study of extractables & leachables in Dry Powder Inhalers (DPIs)?

- A **Failure Mode Effects Analysis (FMEA)** can be conducted to identify formally areas which are “High”, “Medium” or “Low” risk
- What does this mean for DPI leachables
 - Need to define what “failure mode” means in this context
 - Exposure of leachables to patient using DPI
 - Need to define factors which will be used to calculate risk number
 - Traditionally this is: probability and severity
 - Needs to be adapted to be relevant to leachables and DPIs



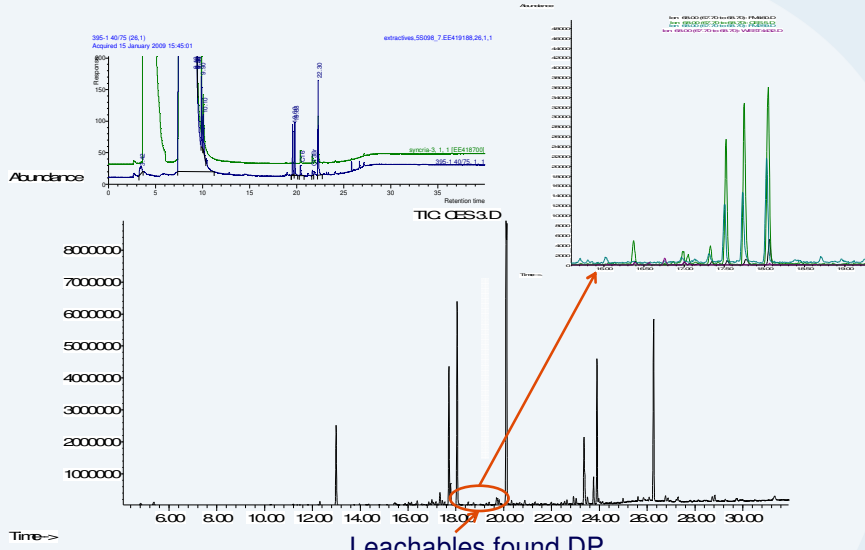
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Example of Part Output from FMEA

E to L process / Part of DPI system	Potential Failure Mode	Potential Effects of Failure	Severity / Safety Information: 1,4,7,10	Leachable pathway	Degree of contact (Time, area, intimacy) 1,4,7,10	Likelihood of transfer (Volatility, relative affinity, medium for transfer): 1,4,7,10	Prior experience of issues 1,4,7,10	RPN
Product contact: lidding/base foil	Leaching of extractables from lidding foil during manufacture	Exposure of patient to leachables	7	From product contact layer	4	10	4	1120
			7	From non contact layers 1&2 to product	4	7	4	784
	Leaching of extractables from base foil during manufacture	Exposure of patient to leachables	7	From product contact layer	4	10	4	1120
			7	From non contact layers 1&2 to product	4	7	4	784
	Leaching of extractables from lidding foil during long term storage	Exposure of patient to leachables	7	From product contact layer	10	7	1	490
			7	From non contact layers 1&2 to product	7	7	1	343
	Leaching of extractables from base foil during long term storage	Exposure of patient to leachables	7	From product contact layer	10	7	1	490
			7	From non contact layers 1&2 to product	7	7	1	343

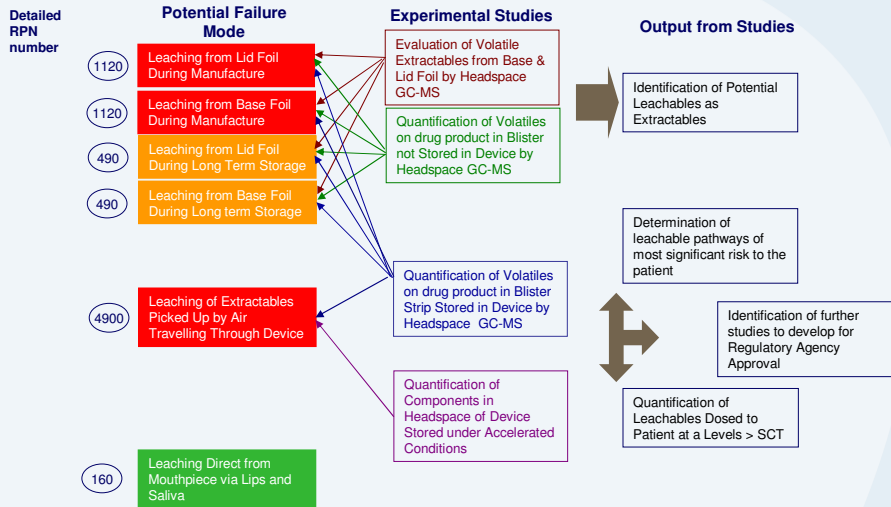
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Controlled extraction study – DCM extract



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FMEA Output & Interrelationships between Leachable Pathways, Experimental Studies and Outputs from Experimental Studies



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A Risk based approach in tune with ICH guidance

- Pharmaceutical Development
 - Q8 Pharmaceutical Development
 - This guideline is intended to provide guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development) of CTD
 - EU: Approved by CHMP: November 2005. Date for coming into operation: May 2006.
 - FDA: Published in the Federal Register, Vol. 71, No 98, Monday, May 22, 2006
- Quality Risk Management
 - Q9 Quality Risk Management
 - This guideline provides principles and examples of tools of quality risk management that can be applied to all aspects of pharmaceutical quality including development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances and drug (medicinal) products, biological and biotechnological products, including the use of raw materials, solvents, excipient, packaging and labelling materials.
 - EU: 2006 Published on the EMEA website, with an Explanatory Note
 - FDA: Published in the Federal Register, Vol. 71, No 106, pages 32105-32106, June 2, 2006

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What does Q8 say about risk based approaches?

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products;

i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

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What does Q9 have to say about risk based approaches?

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KEY POINTS

- PQRI best practice guidelines provide an excellent guide on strategies which can be adopted to study extractables and leachables
- Its threshold based assessment of safety of leachables provides a sound risk based approach to predicting risk from leachables – if the leachables can be identified
- The guidance given in the guideline needs to be thoughtfully adapted to fit a particular product under study
- A tailored risk-based approach seems to offer a viable alternative for study of E&L in a DPI

QUESTIONS?

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