

IPAC-RS 2006 Conference
Inhalation and Nasal Drugs: The
Regulatory Landscape

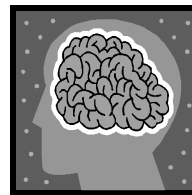
Considerations for Leachables
and Extractables in a Quality by
Design Environment

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Presentation Outline

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- Baseline definitions
 - Concept definition of Quality-by-Design
 - Concept definition of Design Space
 - Quality-by-Design and the Problem of Induction
 - Inductive Logic
 - Probability Logic
- Contributions of IPAC-RS and PQRI to the Quality-by-Design paradigm as it relates to L&E
- What is the real substance of Quality-by-Design?
 - Quantitative definition of Design Space
 - Engineering process example
- Concluding statements



Sources (concepts)



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- Nasr, M.M., "Risk-Based CMC Review and Quality Assessment: What is Quality by Design (QbD)?", 2006 FDA/Industry Conference, School of Pharmacy – Temple University, March 29, 2006.
- Hussain, A.S., "Quality by Design (QbD) – Integration of Prior Knowledge and Pharmaceutical Development into CMC Submission and Review", AAPS Workshop – Pharmaceutical Quality Assessment – A Science and Risk-Based CMC Approach in the 21st Century, North Bethesda, MD, October 5-7, 2005.
- Woodcock, J., "Pharmaceutical Quality in the 21st Century – An Integrated Systems Approach", AAPS Workshop – Pharmaceutical Quality Assessment – A Science and Risk-Based CMC Approach in the 21st Century, North Bethesda, MD, October 5-7, 2005.

Sources (concepts)



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- Yu, L.X., "Implementation of Quality-by-Design: Question-based Review", 42nd Annual Meeting Drug Information Association, Philadelphia, 2006.
- Poochikian, G., "Best Practices Recommendations: Regulatory Science Strategies", PQRI Workshop: Leachables and Extractables, Rockville, MD, December 5-6, 2005.
- ICH Harmonized Tripartite Guideline: Pharmaceutical Development Q8, dated 10 November 2005.
- ICH Harmonized Tripartite Guideline: Quality Risk Management Q9, dated 9 November 2005.
- Popper, K., *The Logic of Scientific Discovery*, Routledge, first published 1935.

Quality-by-Design (QbD) Concepts



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- “QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality.”

Yu (2006)

- “A systematic scientific approach to product and process design and development.”

Nasr (2006)

Quality-by-Design (QbD) Concepts



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In a QbD system:

- The product is designed to meet patient requirements.
- The process is designed to consistently meet product critical quality attributes.
- The impact of starting materials and process parameters on product quality is understood.
- Critical sources of process variation are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.

Nasr (2006)

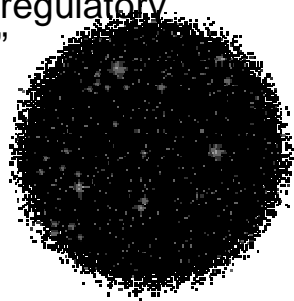
Design Space - Concept



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- “The multidimensional combination and interaction of design input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Design space is proposed by the applicant and is subject to regulatory assessment and approval.”

ICH Q8 (November 2005); Nasr (2006)



QbD and Inductive/Probability Logic



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- QbD can be considered in the context of “*The Problem of Induction*”
- “The question whether inductive inferences are justified, or under what conditions, is known as *the problem of induction*.” (Popper)
- Inductive Logic does not exist.
- “The attempt has often been made to describe theories as being neither true nor false, but instead more or less probable.According to those who believe in *probability logic*, induction should determine the degree of probability of a statement.” (Popper)

QbD and Inductive/Probability Logic



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- “Every test of a theory, whether resulting in its corroboration or falsification, must stop at some basic statement or other which we *decide to accept*.Thus if the test is to lead us anywhere, nothing remains but to stop at some point or other and say that we are satisfied, for the time being.” (Popper)

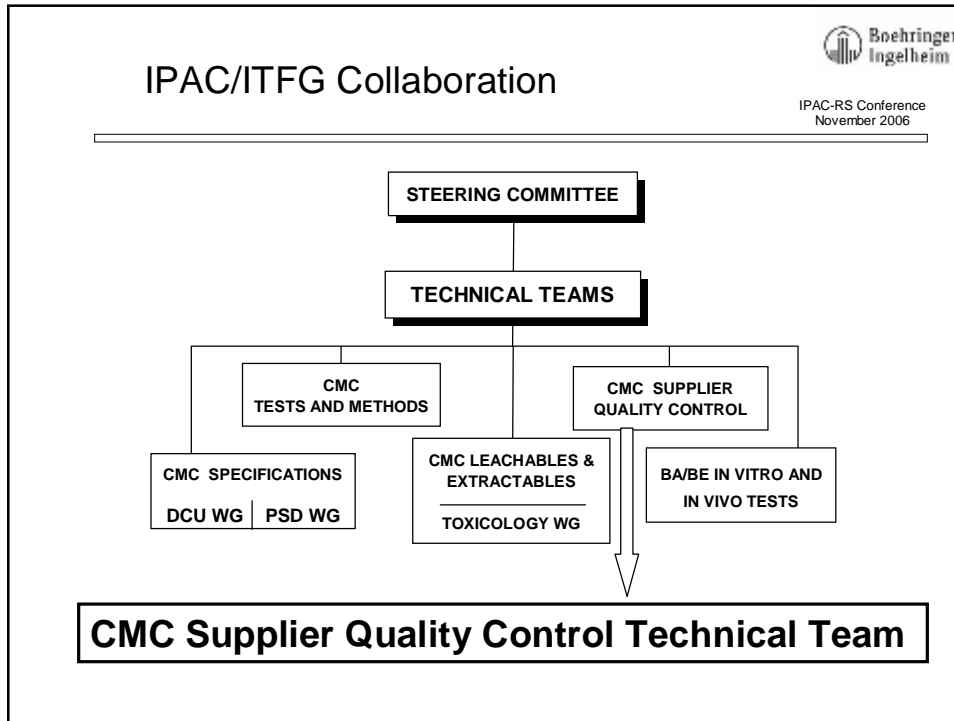
Design space is proposed by the applicant and is subject to regulatory assessment and approval.”

Summary Points from Concepts



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- Define the “Design Space”
- Control the “Design Space”
- Come to an agreement (i.e. get regulatory approval)




Boehringer
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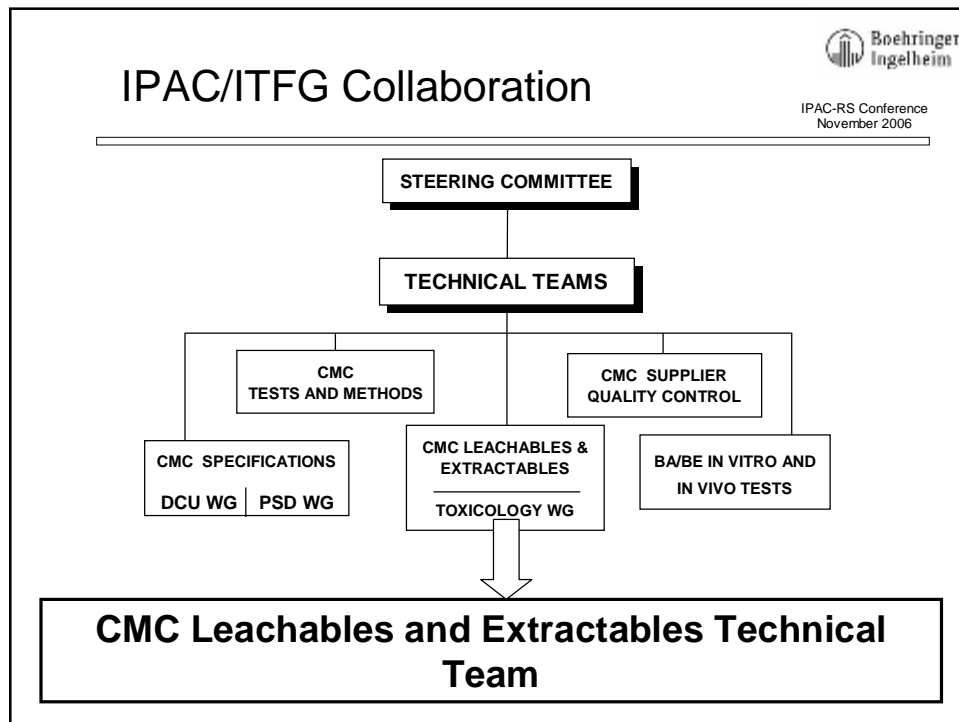
CMC Supplier Quality Control Technical Team


- *Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products (2006)*
 - Quality Management System
 - Management Responsibility
 - Resource Management
 - Product Realisation
 - Measurement Analysis and Improvement
 - Contamination Control



Good Manufacturing Practices
Guideline for Suppliers of
Components for Orally Inhaled
And Nasal Drug Products

Definition and control of “Design Space”




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CMC Leachables and Extractables Technical Team

- Submitted *Points to Consider* (March 2001) technical paper which proposes:
 - Alternate language for the draft Guidances, which clarifies the requirements for leachables and extractables studies
 - Reporting and qualification thresholds for leachables
 - A leachables qualification process
 - Some “Best Practices” recommendations
 - Led to formation of PQRI Working Group

History of PQRI Leachables and Extractables Working Group



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- Proposal to develop thresholds and examine best practices for L&E in OINDP drafted by IPAC-RS and submitted to PQRI
- Working Group formed in 2001, consisting of chemists and toxicologists from FDA, industry and academia
- Working Group developed a hypothesis and step-wise plan to investigate per established PQRI process
- Workplan approved by PQRI DPTC and Steering Committee in 2002
- Toxicologists and chemists formed sub-groups



History of PQRI Leachables and Extractables Working Group



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- Toxicologists: acquired data through extensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo leachables study
- Developed recommendations, "Safety Thresholds and Best Practices for Leachables and Extractables Testing in Orally Inhaled and Nasal Drug Products"
- Submitted final to PQRI and FDA in summer 2006
 - Science and data-based recommendations to PQRI and FDA. Not a policy/regulatory document

Leachables and Extractables Working Group Members



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Dan Norwood, Chair (IPAC-RS)	Roger McClellan (UNM)
Doug Ball (IPAC-RS)	Tim McGovern (FDA)
Jim Blanchard (IPAC-RS)	Diane Paskiet (PDA)
Lidiette Celado (AAPS)	David Porter (USP)
Fran DeGrazio (PDA)	Michael Ruberto (Lab - CIBA)
T.J. Deng (Lab - PPD)	Alan Schroeder (FDA)
Bill Doub (Lab - FDA)	Mark Vogel (PhRMA)
Tom Feinberg (AAPS)	Charles Wang (PhRMA)
Alan Hendricker (Lab - Cardinal)	Ron Wolff (IPAC-RS)
Jeff Hrkach (AAPS)	Michael Golden (DPTC, IPAC-RS)
	Guirag Poochikian (DPTC, FDA)
	Gordon Hansen (SC, IPAC-RS)

Recommendations Overview



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-
- Introduction and Summary of Recommendations
 - Derivation and justification of safety thresholds, and application of safety thresholds
 - Chemistry Best Practices
 - Appendices

Best Practices Overview



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- Application of safety thresholds
 - ∅ Safety Concern Threshold (SCT)
 - ∅ Qualification Threshold (QT)
- Integration of safety expertise into component selection, controlled extraction studies, leachables studies and routine extractables testing
- Analytical/chemistry
 - ∅ Selection of components
 - ∅ Controlled Extraction Studies
 - ∅ Leachables Studies and Routine Extractables Testing
 - ∅ The Analytical Evaluation Threshold (AET)

Definition and control of “Design Space”

Additional Sources

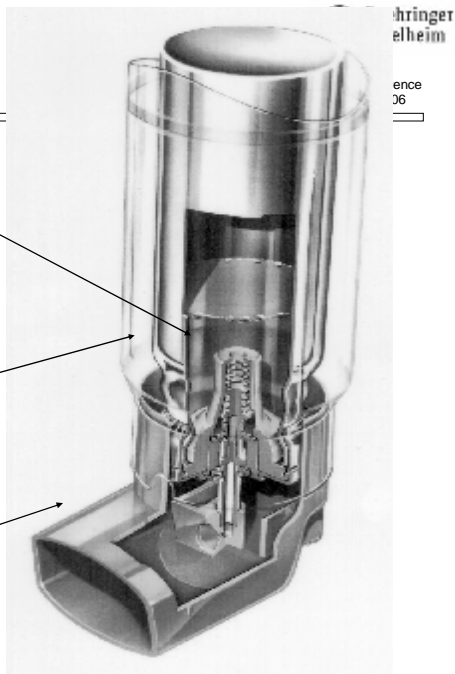


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- Juran, J.M., *Juran on Quality by Design*, The Free Press, New York, 1992.
- Barker, T.B., *Quality by Experimental Design*, Marcel Dekker, New York, 1994.
- Barker, T.B., *Engineering Quality by Design – Interpreting the Taguchi Approach*, Marcel Dekker, 1990.

MDI "Critical Components"

- Dose metering valve
 - Metering chamber
 - Stem(s)
 - Seals/gaskets
 - Sealing rings
- Canister
 - Coated?
- Mouthpiece/actuator

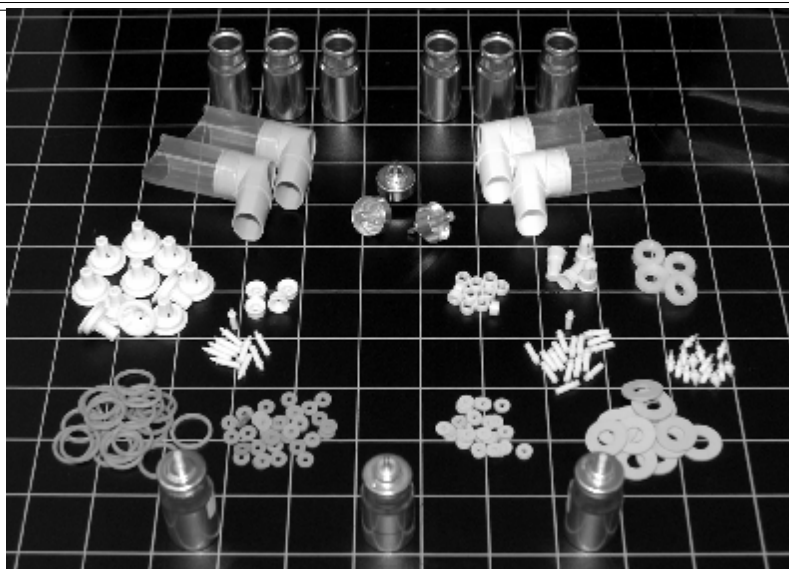


MDI Schematic Provided by Bespak Europe

OINDP Container Closure System Components



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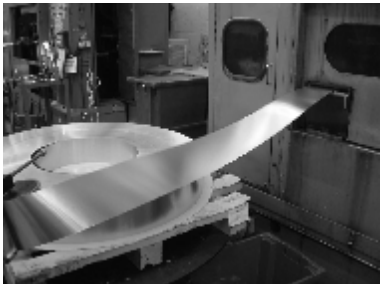


Raw Materials – Supply Chain

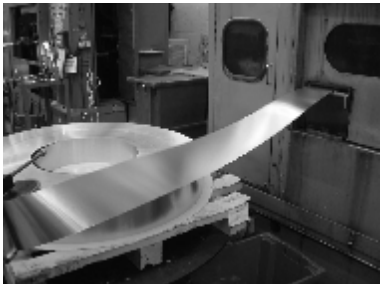

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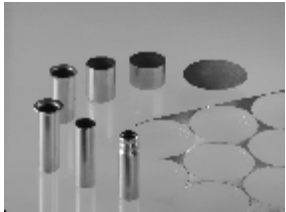
Deep Drawing Process



deep-drawing tool



metal rolls



Images provided by Presspart

Deep Drawing Process



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Images provided by Presspart
degreasing process

DPI



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Images provided by Bepak Europe

Raw Materials - Supply Chain



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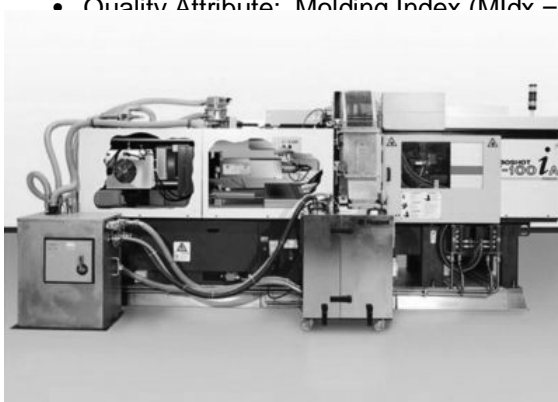
Design Space – Process Optimization Example (from Barker, 1990)



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- Plastic molding process
- Goal: "To find the system settings that will prevent short shots or flash despite molding machine variation and raw material fluctuations."
- Quality Attribute: Molding Index (MI_{dv} – 0)

Images provided by Bepak



First Noise Matrix
(from Barker, 1990)



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Run#	Temp	Press	Time	Gate	MI	Midx
1	475	950	.84	.23	20	-2.7
2	525	950	.84	.17	15	-2.4
3	475	1050	.84	.17	20	-1.7
4	525	1050	.84	.23	15	-1.4
5	475	950	.86	.23	15	-4.1
6	525	950	.86	.17	20	-1.8
7	475	1050	.86	.17	15	-3.1
8	525	1050	.86	.23	20	-0.8

Midx Average = -2.25
S/N (T) = 11.6

Final Experimental Data
(from Barker, 1990)



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tc	Temp	Press	Time	Gate	Midx	S/N(T)
(1)	500	1000	0.85	0.2	-2.25	11.6
a	550	1000	0.85	0.2	-0.75	18.4
b	500	1200	0.85	0.2	-0.25	18.6
ab	550	1200	0.85	0.2	1.25	15.5
c	500	1000	1.2	0.2	-0.50	18.6
ac	550	1000	1.2	0.2	1.00	17.1
bc	500	1200	1.2	0.2	1.50	14.1
abc	550	1200	1.2	0.2	3.00	9.5
d	500	1000	0.85	0.3	-2.25	11.8
ad	550	1000	0.85	0.3	-0.75	19.3
bd	500	1200	0.85	0.3	-1.75	13.4
abd	550	1200	0.85	0.3	-0.25	20.8
cd	500	1000	1.2	0.3	-0.50	19.6
acd	550	1000	1.2	0.3	1.00	17.8
bcd	500	1200	1.2	0.3	0.00	19.8
abcd	550	1200	1.2	0.3	1.50	14.8

Final Conclusion



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Thank You!

