Proposed QbD statistical design to facilitate patient centricity

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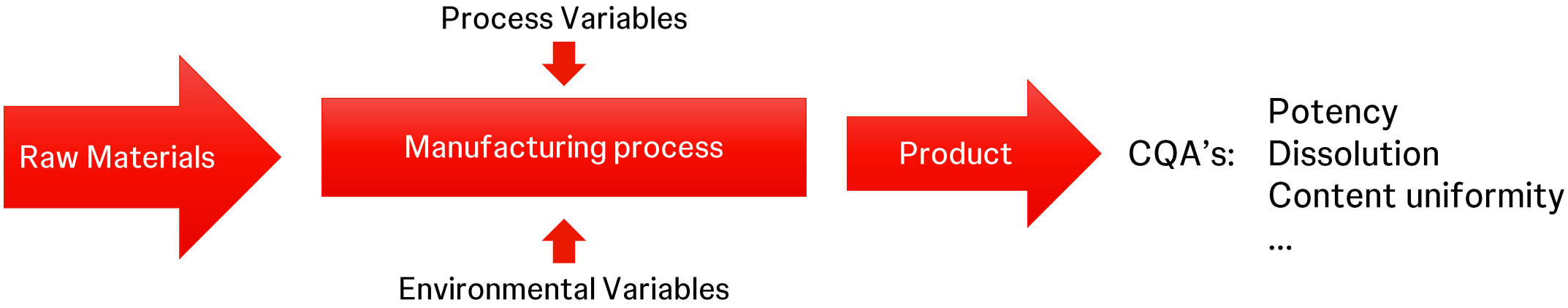
Connection between clinical AND nonclinical



CQA's have acceptance criteria which define **quality based on specifications**

CQA's are believed to be linked to **in vivo performance (safety, efficacy)**

Regulatory expectations for **process and product understanding**

- Call for science- and risk-based approaches
- Patient-centric drug product development

Linking manufacture to clinical outcomes

- Causal linkages from manufacture to surrogate/clinical outcomes by the use of statistical designs

  - In terms of the controllable process variables/material attributes
  - Important to
    - Separate process and analytical variability
    - Consider patient variability

Example of linking manufacturing DoE to a human PK study

- Objective – Characterize formulation/process parameter effects on PK performance (AUC, Cmax, Tmax)

Example QbD study

CMC formulation/process study with following factors:

- ✓ Factor 1 – Disintegrant level (Low, High)
- ✓ Factor 2 – Particle Size level (Low, High)
- ✓ Tablet Hardness (Low, High) as a split plot factor

2^2 factorial + 1 split plot factor + Center Pts
Responses: dissolution, tablet properties are studied

QbD manufacturing design

Design Point	Factor 1	Factor 2	Factor 3	
			Low	High
1-2	Low	Low	A	B
3-4	Low	High	D	E
5-6	High	Low	F	G
7-8	High	High	H	I
9	Mid	Mid	C1	
10	Mid	Mid	C2	

Example of linking manufacturing DoE to a human PK study

BIB Design for 10 Formulations 15 Subjects in 4 Periods				
Subject	**Period 1**	**Period 2**	**Period 3**	**Period 4**
1	E	I	A	G
2	C1	E	A	D
3	I	G	D	B
4	D	C2	F	G
5	F	H	I	C1
6	C2	C1	D	I
7	G	B	C1	H
8	E	G	C1	F
9	A	H	G	C2
10	F	I	B	A
11	B	F	E	C2
12	D	E	B	H
13	C1	A	C2	B
14	H	D	F	A
15	I	C2	H	E

BIBD design of the 10 factor combinations in as few human subjects as possible (15 subjects, 4 periods)

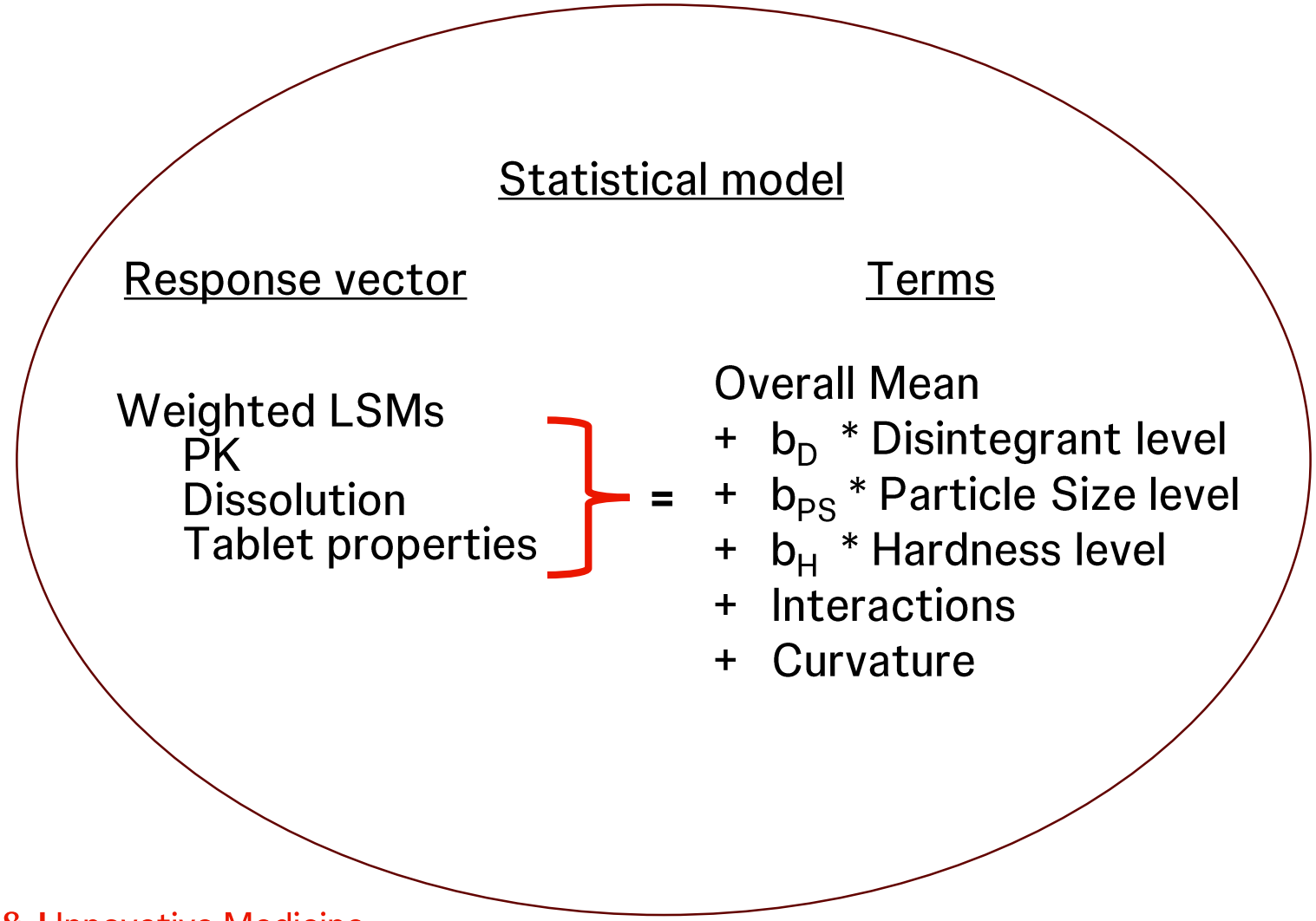
Parameters of the BIBD

v = 10 treatments (formulations)
r = 6 replications
b = 15 blocks (subjects)
k = 4 treatments/block
λ = 2 number of times each pair occurs together

PK responses are measured for each subject across 4 periods

More than 4 periods is not practical: wash out at least $5xt_{1/2}$

Example of linking manufacturing DoE to a human PK study



- Therapeutic effect and product quality attributes (dissolution, tablet properties) as a multivariate response are linked to the CMC formulation /process parameters

- Final deliverable is a mathematical relationship describing effects on subject exposure
  - Risk control strategies and common model to describe risk

Linking manufacture to clinical outcomes

- Proposed statistical design to facilitate patient centricity and inform scientists to define patient-centric specifications
- Holistic approach to quality serving patients' needs
- Strategy for patient-centric drug development builds on
  - Collaborative culture between different stakeholders
  - Prior and platform knowledge about impact on safety/ efficacy and associated level of uncertainty
- Development databases capturing DOEs and results for future reference and guidance on new products and processes

Thank you

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BIO
Hans Coppenolle

Hans Coppenolle holds a master degree in Bioscience Engineering and completed a PhD in Agricultural and Applied Biological Sciences in 2002 from Catholic University of Leuven in Belgium. After his PhD, he joined Janssen Pharmaceutica in a postdoctoral position manufacturing statistics and currently holds a position as Distinguished Scientist Manufacturing Statistics in the Statistics & Decision Sciences organization of Johnson & Johnson Innovative Medicine. Hans Coppenolle is located in Beerse (Belgium).