

Lifecycle Approach to Specification Setting

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Challenge:

Integrate { **Process Understanding**
Product Knowledge { **Product Attributes**
Clinical Experience
Measurement System Capability

To benefit patient, regulator and producer

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HOW?

Demonstrate that the process and QA/QC systems will:

- (1) consistently deliver good product**
- (2) ensure high probability that good product is declared acceptable**
- (3) ensure high probability that unacceptable product is rejected**

There is a loss to the patient as well as to the producer if good product is unnecessarily rejected

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3

How to characterize acceptable versus unacceptable product?

- **Relevant product characteristics (i.e., CQAs)**
 - which predict in vitro CMC product performance
 - which in turn predicts suitability for intended purpose (i.e., clinical performance)
- **Specification setting**
 - defined test for each CQA (keep as simple as possible without jeopardizing effectiveness)
 - limits to which test results are compared

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4

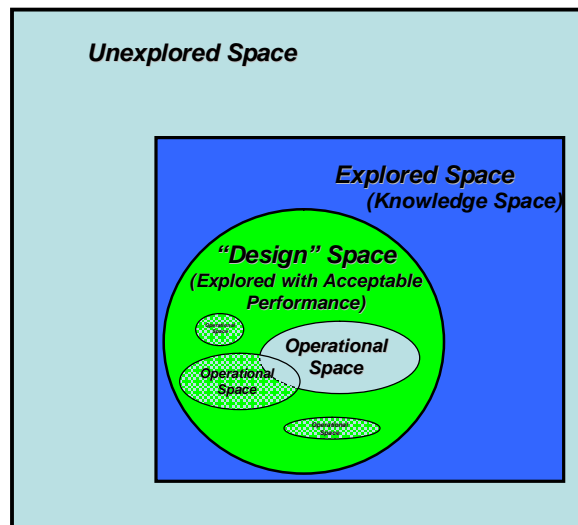
Design Space

- **Design space depends on, and is defined in terms of, specification limits**
 - region of process parameter settings and a model which, with high confidence, ensures production of acceptable product
 - i.e., high confidence that CQAs will consistently be within specification limits
- **Specification limits must be established before design space can be defined**
 - key driver is clinical relevance
 - in its absence, process capability can be considered

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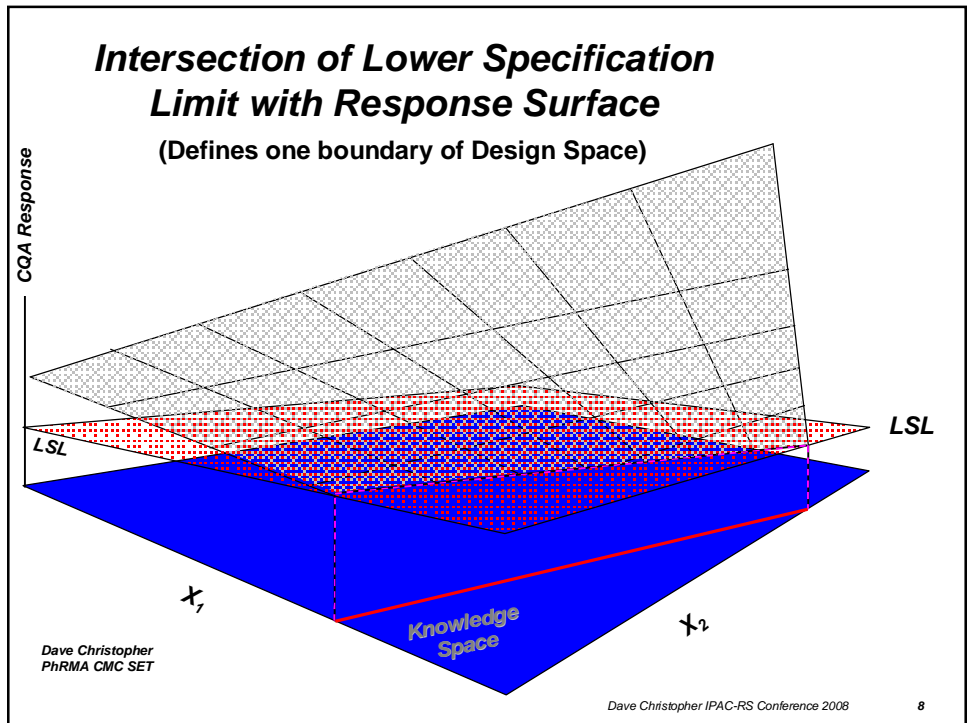
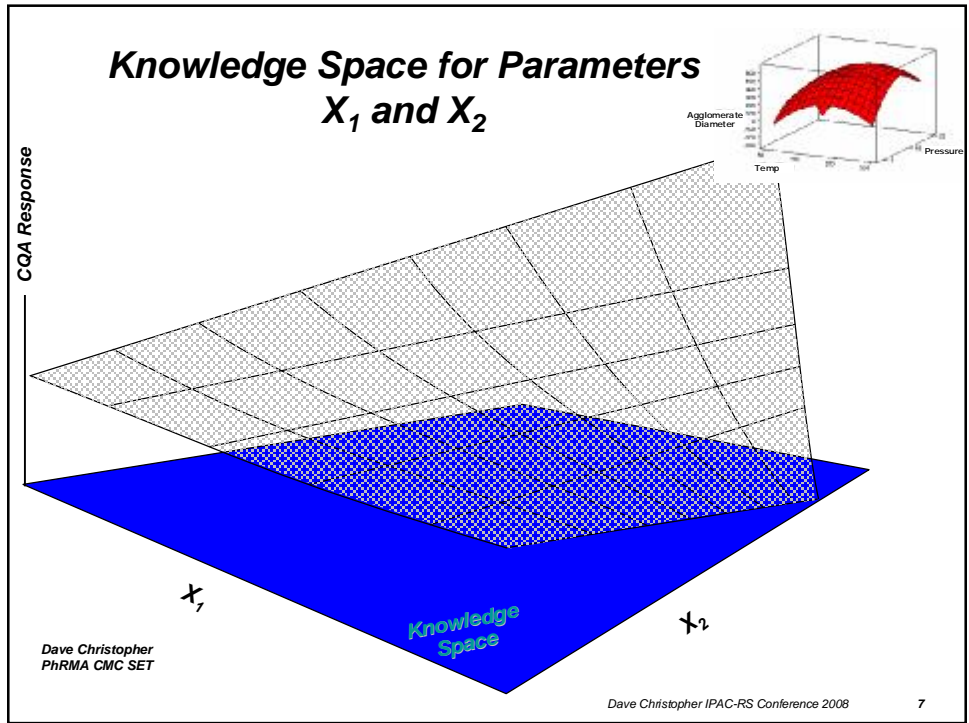
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Conceptual “Spaces” for a Process



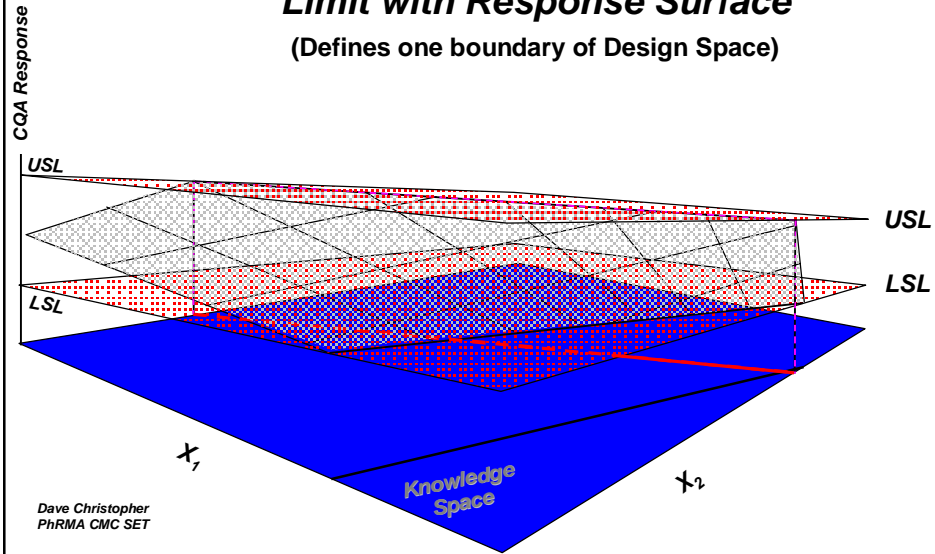
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6

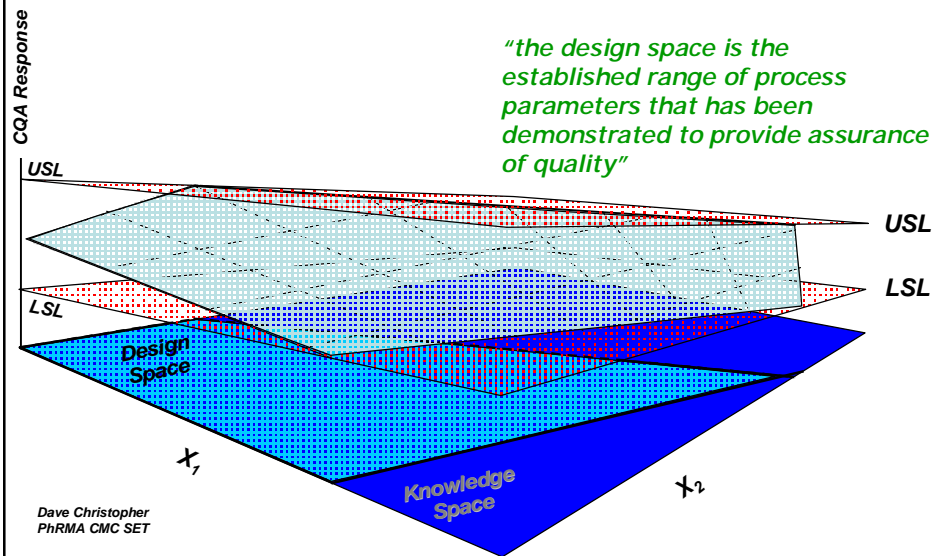


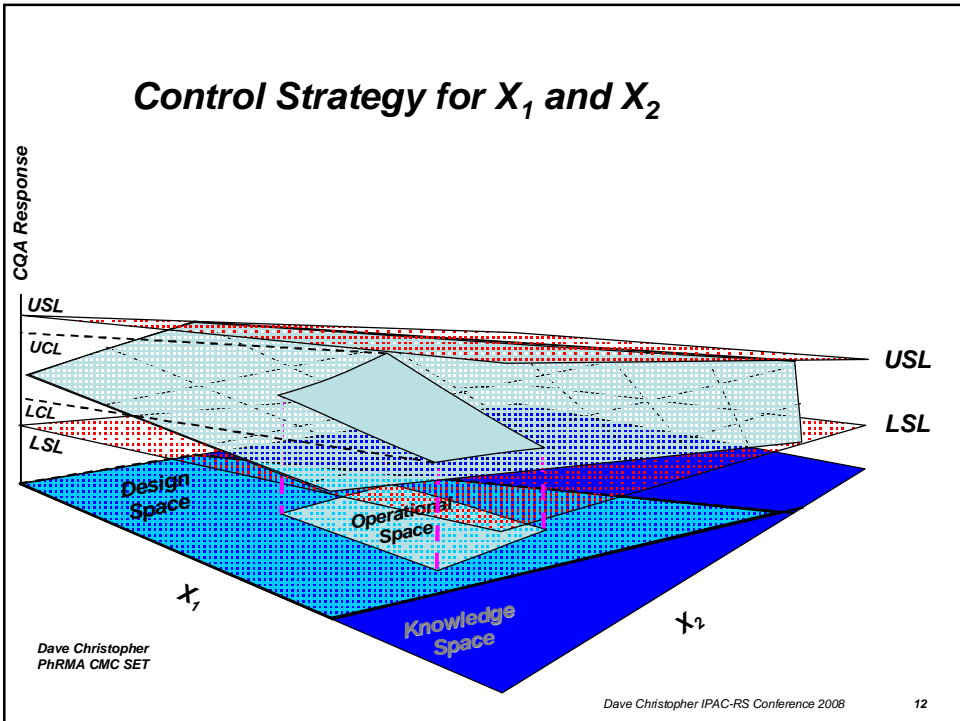
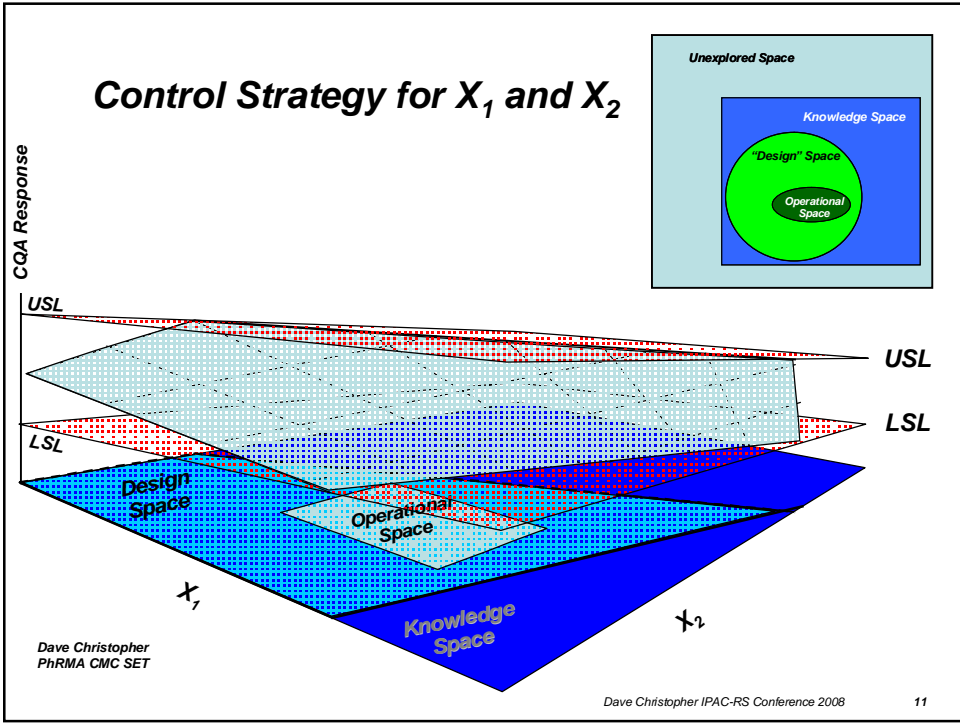
Intersection of Upper Specification Limit with Response Surface

(Defines one boundary of Design Space)



Design Space for X_1 and X_2





Specifications and CQAs

- **Specification limits for some product attributes may be determined largely by precedent, regardless of clinical relevance**
 - e.g., may be unlikely to obtain approval for assay limits greater than $\pm 10\%$ LC
 - however, there may be opportunities for more regulatory flexibility where there is confidence of no patient risk
- **Some attributes for which there is less precedent may offer opportunities for a different approach**

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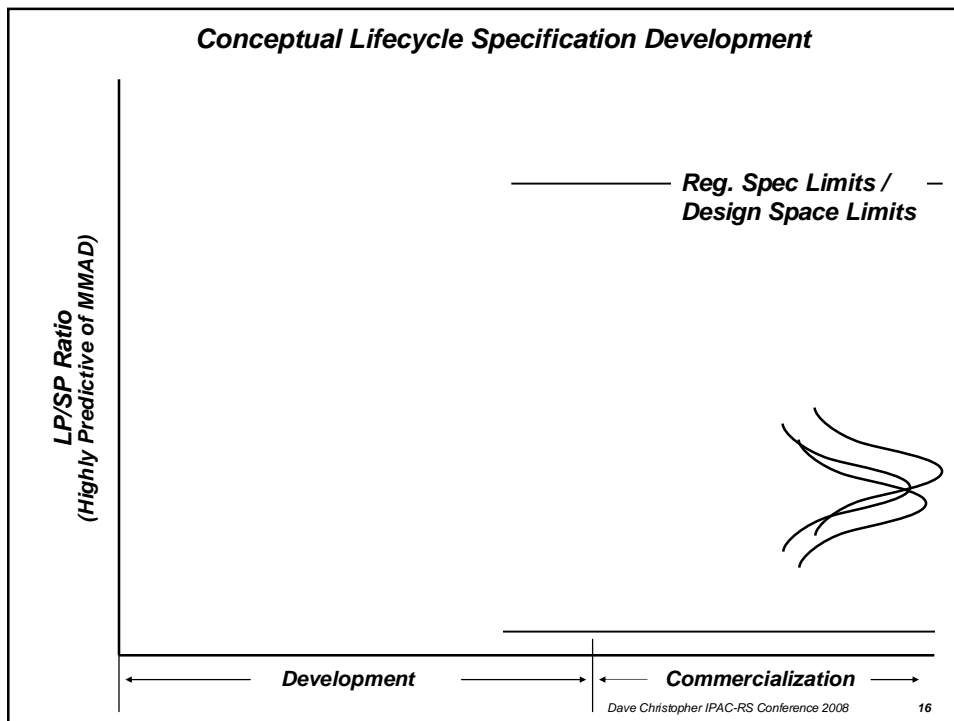
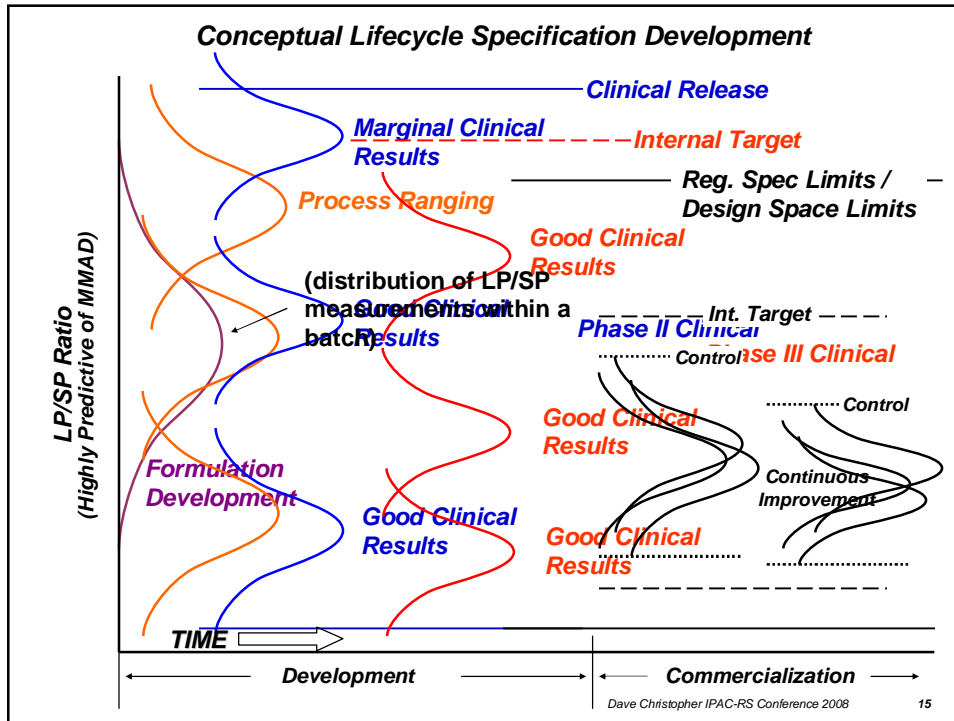
13

Consider APSD (to illustrate a concept)

- **MMAD may be an important product attribute predictive of clinical performance**
- **The ratio of carefully chosen Large Particle to Small Particle proportions of Impactor Sized Mass may facilitate the study of MMAD**
- **May provide improved precision compared to full-resolution impactors**
- **Specification limits for LP/SP might be established based on clinical experience over a range of particle size distributions**
- **References**
 - Usmani OS, Biddiscombe MF, Nightingale JA, Underwood SR, Barnes PJ. Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols. *J Appl Physiol.* 2003;95:2106-2112. DOI:10.1152/jappphysiol.00525.2003 8750-7587/03
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 - Zanen P, Go LT, Lammers JWT. Optimal particle size for beta-agonist and anticholinergic aerosols in patients with severe airflow limitation. *Thorax.* 1996;51:977-980.

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14



The “White Space” Dilemma

- **If regulators use process capability as the basis for setting specification limits, improved process capability can lead to over-tightened specification limits**
- **Can be a disincentive to process improvement**

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17

Or Comfort Zone?

- **With this approach white space is a positive characteristic**
- **Evidence that a capable process is delivering high quality product for the patient**

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18

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Abbreviations

- APSD Aerodynamic Particle Size Distribution
- CMC Chemistry, Manufacturing and Controls
- CQA Critical Quality Attribute
- ISM Impactor Sized Mass
- LC Label Claim
- LP Large Particles
- LSL Lower Specification Limit
- MMAD Mass Median Aerodynamic Diameter
- QA Quality Assurance
- QC Quality Control
- SET Statistics Expert Team
- SP Small Particles
- USL Upper Specification Limit