Patient-Centric Drug Product Quality Specifications: A Convergence of Clinical and Nonclinical Considerations

Organizers

Stan Altan (Moderator)
Tim Schofield

Panelists

Katharina Reckermann
Trine Kvist
Sandra Suarez-Sharp
Hans Coppenolle

Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

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Abstract

The notion of "patient centric specifications" has received increasing attention over the past few years, following the passage of the Cures Act in 2016 by the US Congress. This act was intended to accelerate the development of modern medicines, with a patient focused view. Various guidances have been issued in connection with the act, mainly in the clinical space. The nonclinical quality implications have also been evolving in parallel with the clinical developments, where the term “patient-centric specifications” has become more widely used. This term has supplanted to some extent the earlier term, “clinically relevant specifications”. This panel session will review the emergence of these terms, and how it is currently impacting drug development. A major objective of the session is to explore the relevance of patient centricity to the development and implementation of CMC acceptance criteria and propose a framework for understanding of the concept from a more holistic perspective.

Specifications – What is it?

Quality Standards

Critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities

- Tests
- Analytical procedures
- Acceptance Criteria that are numerical limits, ranges, or other criteria for the tests described

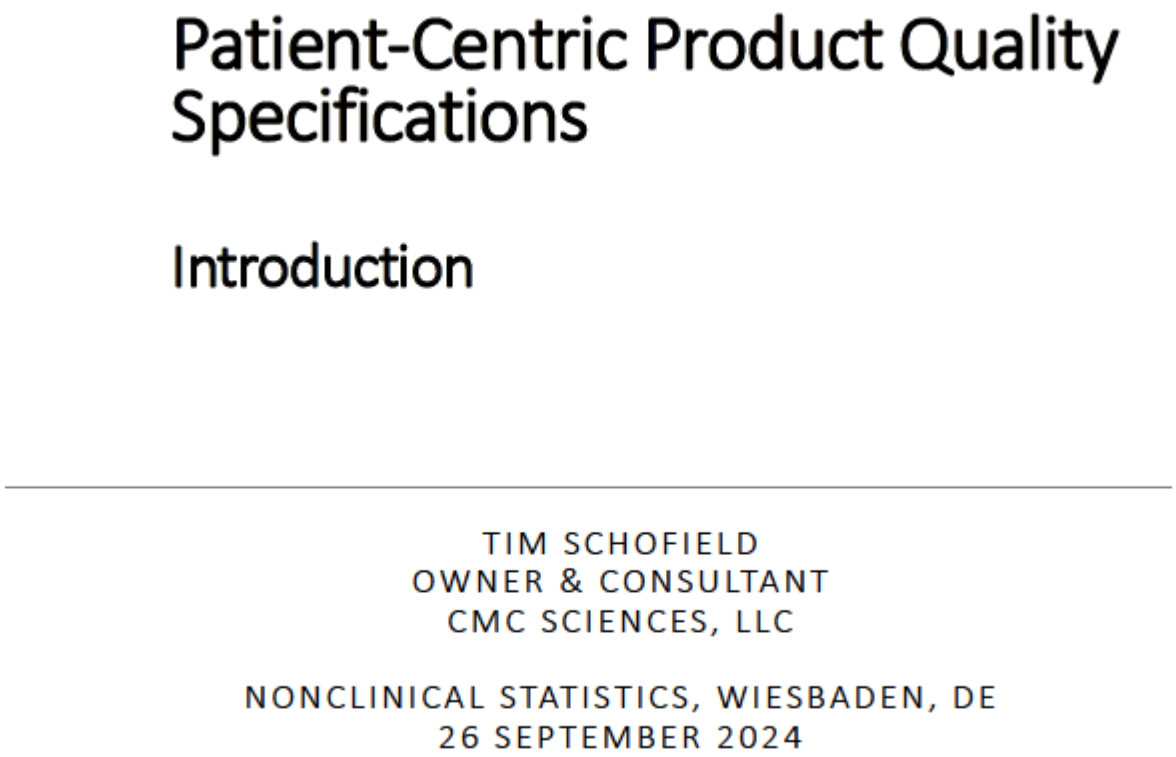
ICH Q6A (Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products) FR Vol 65(251) 1999

Sample Mock-up Specification

Active Formulation		
Test	Acceptance Criterion	Analytical Procedure
1. Assay	90.0 – 110.0 % of label claim	AD-01
2. Chromatographic Purity (Organic impurities)		
a. RT-10.5	Not more than 0.5% (w/w)	AD-02
b. Any other single impurity	Not more than 0.5% (w/w)	AD-03
c. Total Impurities	Not more than 0.8% (w/w)	AD-04
3. Chromatographic Purity (Inorganic impurities)		
a. Sulfate	Not more than 0.5% mole%	AD-05
b. Sulfamate	Not more than 0.5% mole%	AD-06
4. Uniformity of Dosage Units	Conforms to USP requirements for Content Uniformity	AD-07
5. Dissolution	Not less than 80% (Q) of the labeled amount of API is dissolved in 20 minutes	AD-08
6. Water Content	Not more than 2.5% at 100°C	AD-09

General Principles (video)

- Tim Schofield (owner and consultant, CMC Sciences) - virtual presentation



Setting Specifications

Company strategy

- Quality by Design
- Process capability leading to control limits
- Scientific/Clinical judgment

FDA strategy

- Assess empirical ranges of product used in phase 3 clinical trials
  - Example – Dissolution Guidance (1997) - … the specifications should be based on the dissolution characteristics of batches used in pivotal clinical trials ...

Some Issues

- Clinical outcomes are related to batch parameters, not to individual dosage units but many quality acceptance criteria apply to individual dosage units.
  - Conflation of product with analytical determinations (Parameter space vs Data Space) – Patients get dosage units, not analytical determinations.

- *Specifications are intended to address customer requirements but a formal empirical nonclinical (CMC) - clinical causal linkage is generally not established.*

Regulatory Impetus

Early initiatives (<2017)

- FDA Dissolution guidance (1997)
  …determining the relationship between critical manufacturing variables (CMV) and a response surface derived from an in vitro dissolution profile and an in vivo bioavailability data set..
- Janet Woodcock (2004, 2007)
  - Critical Path Initiative (Jan 2007)
  - *"Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes".*
- Sandra Suarez (2012) FDA perspective
  - Establishing *Clinically Relevant* Drug Product Specifications: FDA Perspective
  - CRS implies a link

Later initiatives (>2017)

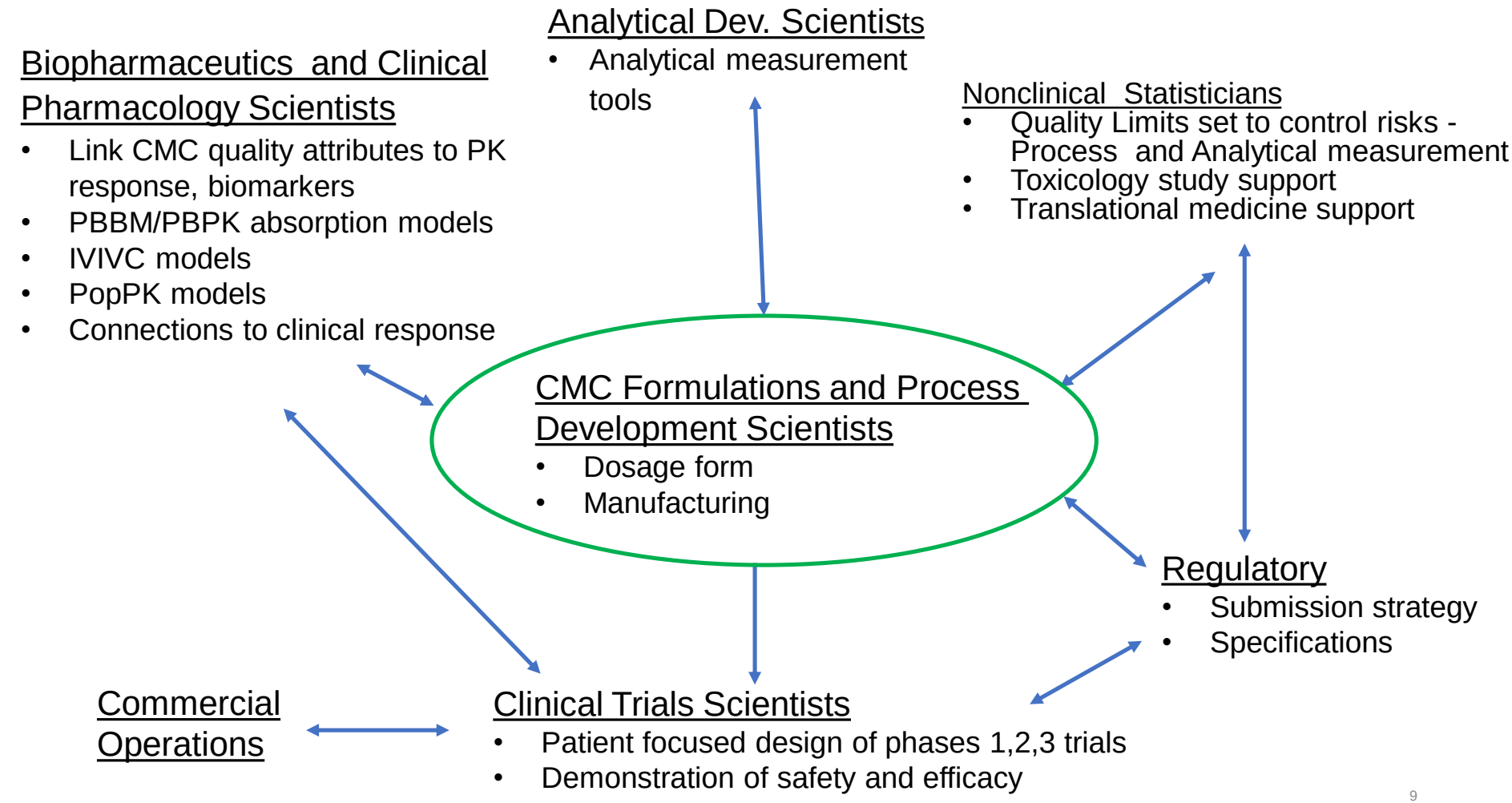
- Cures Act 2016 mandating "Patient Focused" drug development gave rise to "patient centricity"
- Michael Kopcha (FDA - OPQ) 2017
  - Sponsors should pursue development of a patient-focused, risk-based overall control strategy
- PRIME Toolbox guidance 2022
  - Section 4.4.3 : Setting of specifications
    The justification of specification limits for CQAs should be linked to clinical performance rather than solely derived from statistical methods such as tolerance intervals.

Moving to "CRS" and "PCS"

- Sharp SS. (2012) Establishing clinically relevant drug product specifications: FDA perspectives. AAPS Annual Meeting
  - "CRS are those specifications that take into consideration the clinical impact of variations in the critical quality attributes (CQA) and process parameters assuring a consistent safety and efficacy profile"
- Abend et al. The AAPS Journal (2018) 20: 60
  - …link between quality attributes, in vitro testing, and in vivo (clinical) drug product performance (e.g., systemic exposure). This link is essential and is a key component of patient-centric drug product development and the setting of specifications that are clinically relevant.
- Ruesch et al. Journal of Pharm. Sci. (2021) 110: 771-784
  - A set of tests and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled. Justifications for acceptance ranges focus on risk-based assessment of the impact to patients. Patient-Centric Specifications may also be referred to as clinically relevant specifications

Clinical relevance and patient centricity stakeholders

- Overarching objective - specification justification
  - Specifications are intended to define patient requirements, ensure it is fit for its intended purpose



Summary

- The terms CRS and PCS are both currently used, a convergence may be in progress
- The 2016 Cures Act led to the regulatory coining of the term "patient focused" mainly to capture the notion of "patient input" in clinical studies
- This term PCS may have been co-opted by CMC practitioners and modified to find alignment with the older and more prevalent "clinically relevant" term in parallel with the term "Patient-focused" on the clinical side
- Issues and challenges in finding a framework for pursuing patient centric specifications is the subject of this panel session.

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Stan Altan, Biography

Stan received his PhD from Temple University in Biometrics and Statistics in 1977. He joined J&J in 1986, where he has supported all phases of preclinical and nonclinical statistics. Stan is a fellow of the American Statistical Association, and was a founding member of the Nonclinical Statistics Leaders' Forum. He serves on various industry groups seeking to raise the visibility of nonclinical statistics more generally. Stan's current research interests are in experimental design, linear and nonlinear models, Bayesian methods and statistical applications in continuous manufacturing.

Patient-Centric Product Quality Specifications

Introduction

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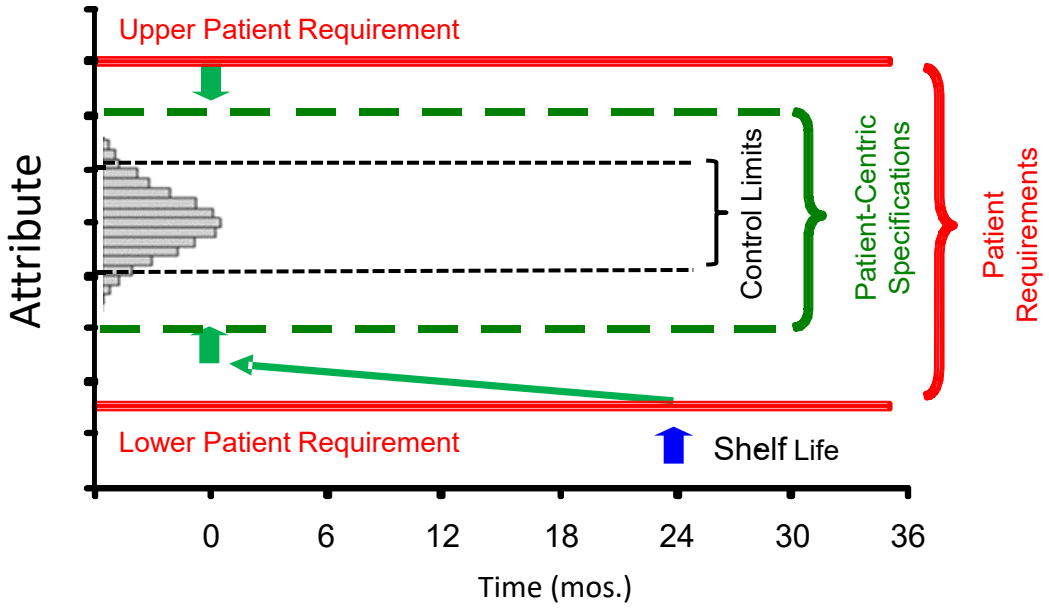
NONCLINICAL STATISTICS, WIESBADEN, DE
26 SEPTEMBER 2024

Problem statement
Why & when?

- In most industries specifications represent *customer requirements*
- Confounding manufacturing limits with specifications reduces opportunities to ***react to manufacturing deviations*** and to make ***product and analytical improvements***
- An early commitment to *patient centric specifications* drives clinical, preclinical, and nonclinical development
  - *Patient-centric drug development*

Building quality into the "specification"

- ***What*** are limits used for:
  - … to ***ensure quality*** throughout shelf life

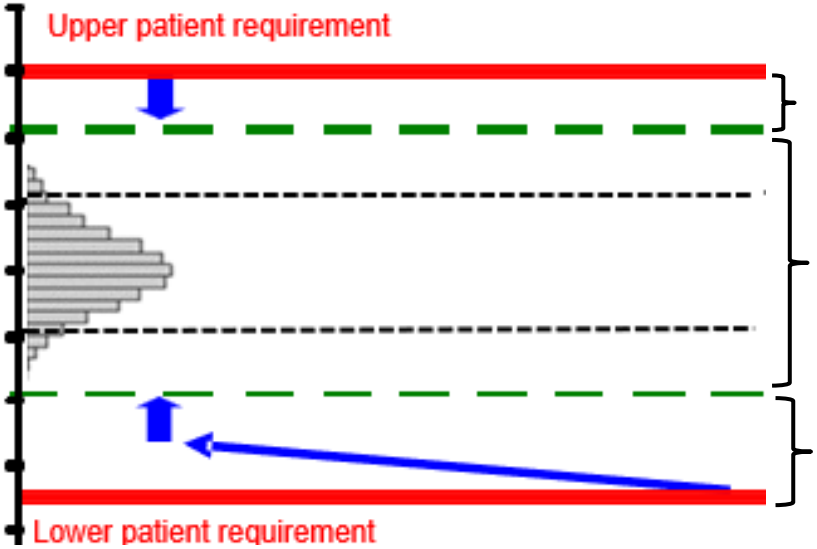


  - … and to ***control manufacturing***

- Scientifically/clinically justified ***patient requirements***
- ***Patient-centric specifications*** or ***release limits*** can be calculated to predict that patient requirements are met at release and throughout shelf-life
- ***Control limits*** formulated to manage process consistency and improvements

Translating this into quality of the "product"

- Limits which are built from ***patient requirements*** can be the basis of ***target development ranges*** and ***approaches to lifecycle management***
  - ***"Budget" allocation***

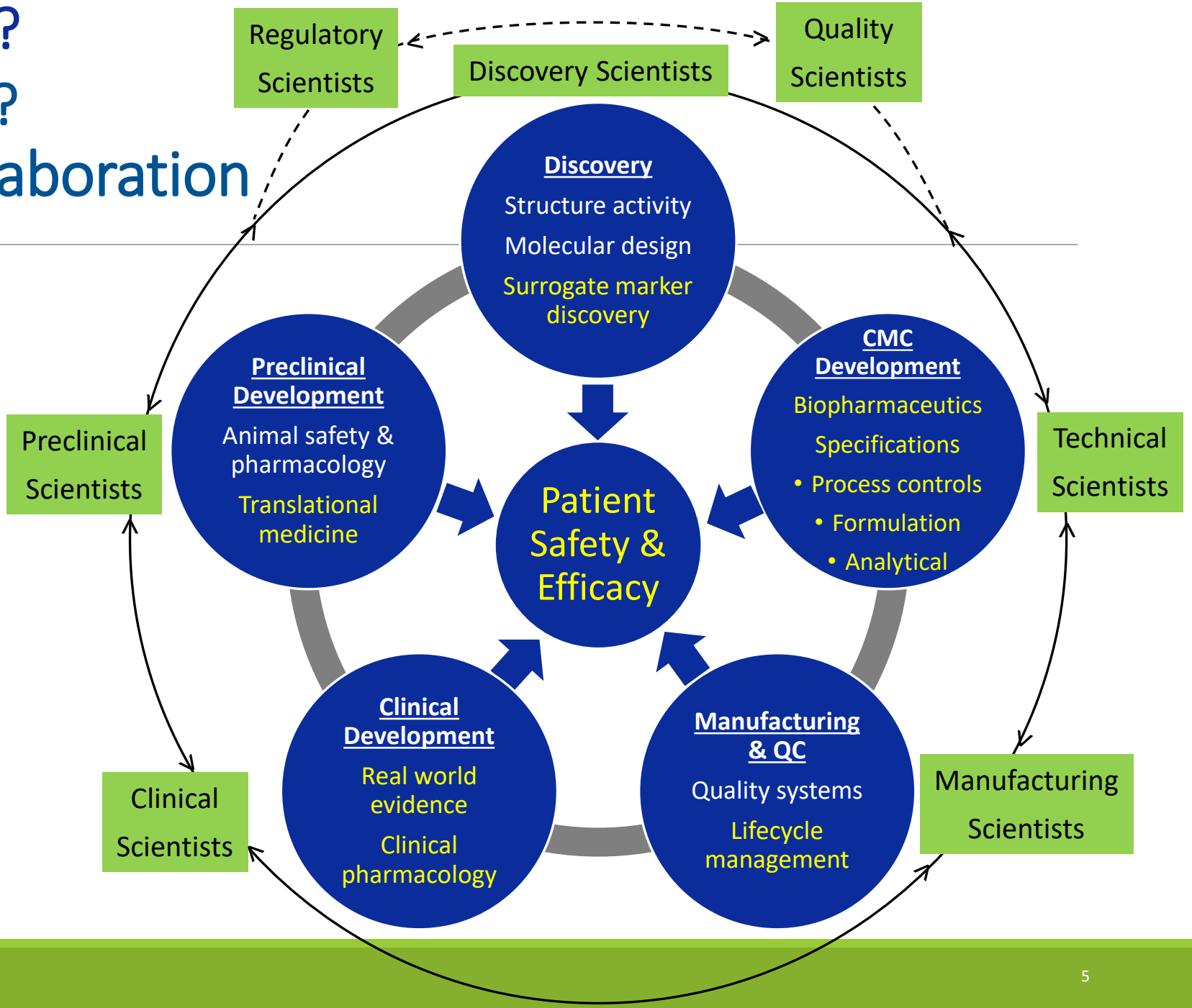


Analytical budget – driven by the ATP

Product & lifecycle management budget - the target range for product development, with room for lifecycle management (CPV & ChgMgmt)

Shelf life budget – target range for formulation development

Who?
How?
= Collaboration



Engaging in efforts to define and implement patient-centric specifications helps to ensure product quality, and provides nonclinical statisticians the opportunity to make meaningful contributions during product development and lifecycle management.

Thank you,

and enjoy the discussion!