

Implementing Quality by Design Principles in the Analytical Laboratory

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Outline

- What is QbD and how is it relevant to analytical development?
- QbD approach to methods development and validation.
- The role of PAT in understanding products and processes.
- Merging a deeper scientific understanding with efficiency and cost savings

The Desired State:

- The application of manufacturing science to facilitate the manufacture of pharmaceutical active ingredients and drug products in a reproducible manner, and to mitigate the risk of an event impacting fitness for use.
- The sharing of knowledge between pharmaceutical firms and FDA to define risk in a culture of trust.
- The application of regulatory processes proportional to the level of risk and applied manufacturing science demonstrated by the firm.
- Consistent application and predictability of the regulatory processes .

PQRI/FDA Report on the Workshop
"A Drug Quality System for the 21st
Century," April 22-24, 2003 Washington, D.C.

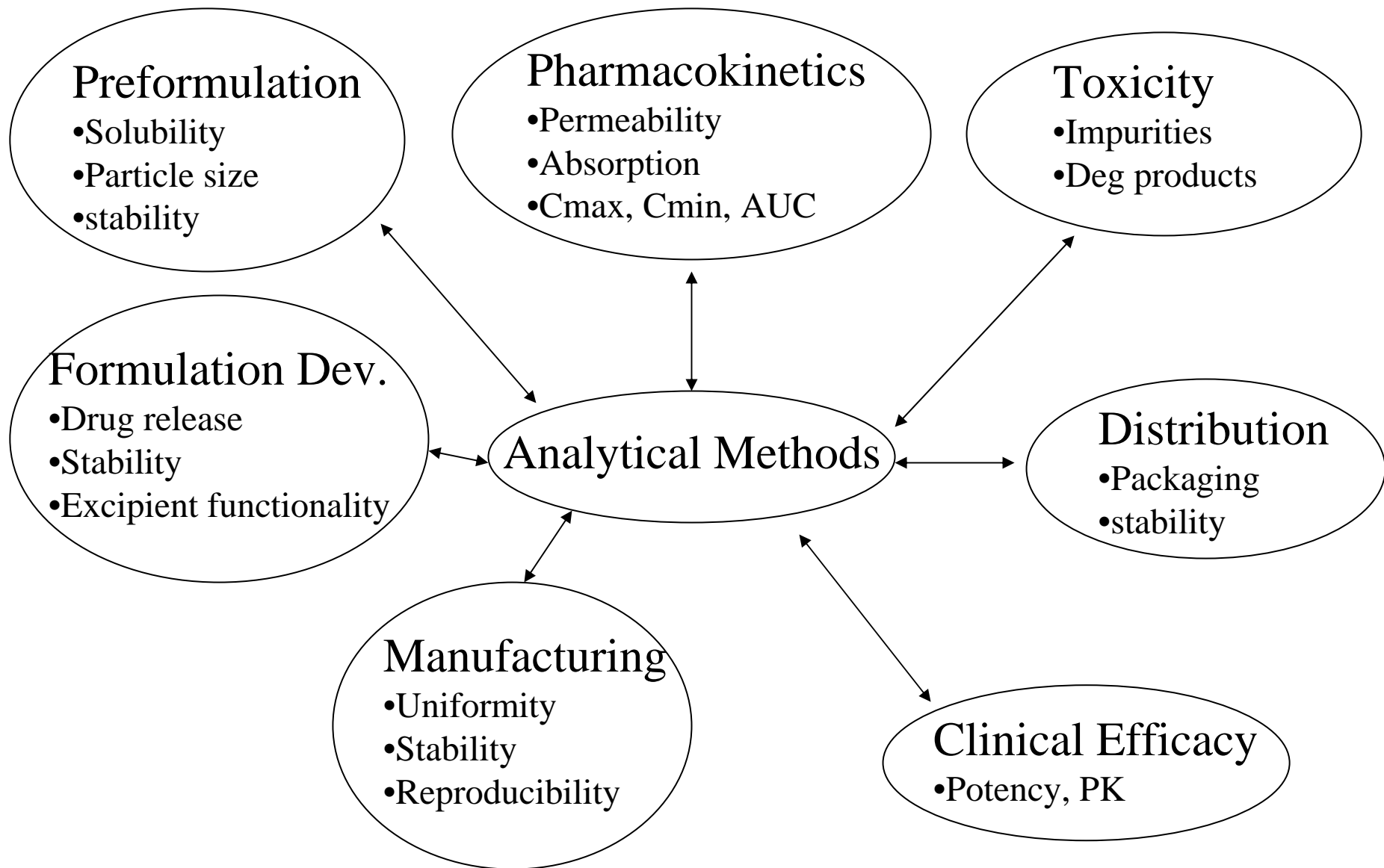
What is QbD in Relation to Analytical Development

- “Quality can not be **tested** into products; it has to be built in by design” (ICH Q8)
- Implications:
 - Tests should be developed to assess meaningful quality attributes
 - Those meaningful attributes can and do change during development and are not the same for every product or dosage form
 - Tests without a clear link to a quality attribute should be eliminated (arguably)

Meaningful Quality Attributes

- Ultimately analytical tests are in place to assure the safety and efficacy of products
 - Potency, Uniformity, Impurities, Degradation Products
 - Drug Absorption: disintegration, dissolution, absorption
 - Physical, particle size, others
- Varies by Phase
 - Phase I: safety, PK, maybe early efficacy
 - Phase II: safety, dose ranging, efficacy
 - Phase III: safety, efficacy

Using QbD in Methods Development



The Challenge for the Analytical Scientist

1. How do you know which attributes are truly important?
2. How do you determine how to best assess those attributes (methods & acceptance criteria)?
3. How do you get everyone in your company to agree with your assessment?
4. How do you get xx number of regulatory agencies around the world to agree?

General Approach

- What properties of the product are truly impacting the quality attribute.
 - Eg. Particle size for absorption, moisture for degradation products, etc.
- Where are those properties best assessed?
 - Manufacturing, release, stability, packaging, distribution
- How are those properties best assessed?
 - What tool to use: chromatography, spectroscopy, physical testing, in-lab or PAT, cost vs return on investment
- What are meaningful limits?

How QbD Impacts Our Typical Quality Assessments

- More straightforward:
 - Potency
 - Physical parameters
- Warrants a closer look:
 - Impurities/Degradation Products
 - Drug release

Impurities/Degradation Products

- Some references
 - Pharmaceutical Stress Testing Predicting Drug Degradation, edited by Steven Baertschi, 2005.
 - Harmon, et al., A Novel Peroxy Radical Based Oxidative System for Ranking the Oxidizability of Drug Substances, J. Pharm. Sci., 2006.
 - Many others

What properties of the product are Impacting Degradation

- Using a QbD approach to understanding and controlling product degradation requires a fundamental chemical understanding of the compound and its environment.
- Begins early in development and is enhanced throughout the development life cycle.

Degradation Information

Preclinical info

- Structural alerts
- Synthetic route
- Polymorph info
- Environmental sensitivity



Method Development

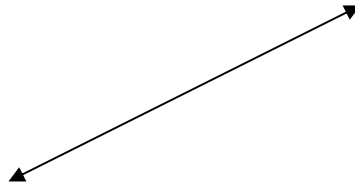
- Possible and LIKELY degradation routes
- Early phase favors more selectivity
- Excipient compatibility
- Process effects



Very streamlined
product methods

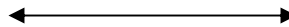
Early Phase Stability

- Favor open dish studies
- Early phase favors more selectivity
- Excipient compatibility
- Process effects

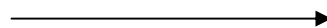


Late Phase Stability

- Package studies
- Focus on specific degradation issues
- “minor” sensitivities
- Process effects



Process Controls and/or
monitoring

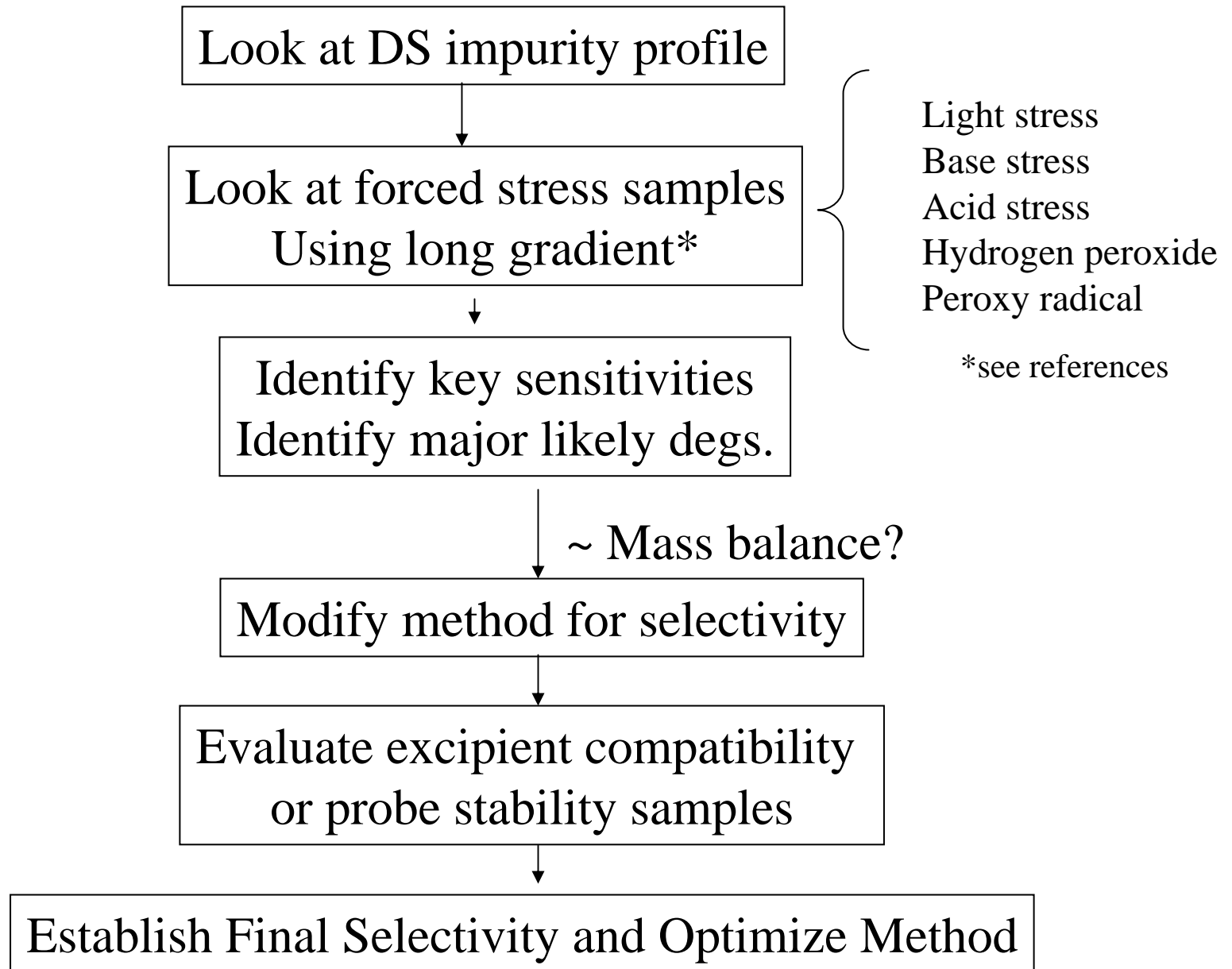


Reduce or eliminate

Focus on Method Development Piece

- Forced stress testing should be used as an early phase development tool; not a late phase validation exercise
- Used to assess what are likely degradation products and assure selectivity for early detection and tracking
 - Hydrolysis
 - Oxidation
 - Acid/base sensitivity
 - Photo-sensitivity
 - Heat
 - Excipient interaction

Quick route to a selective DP method

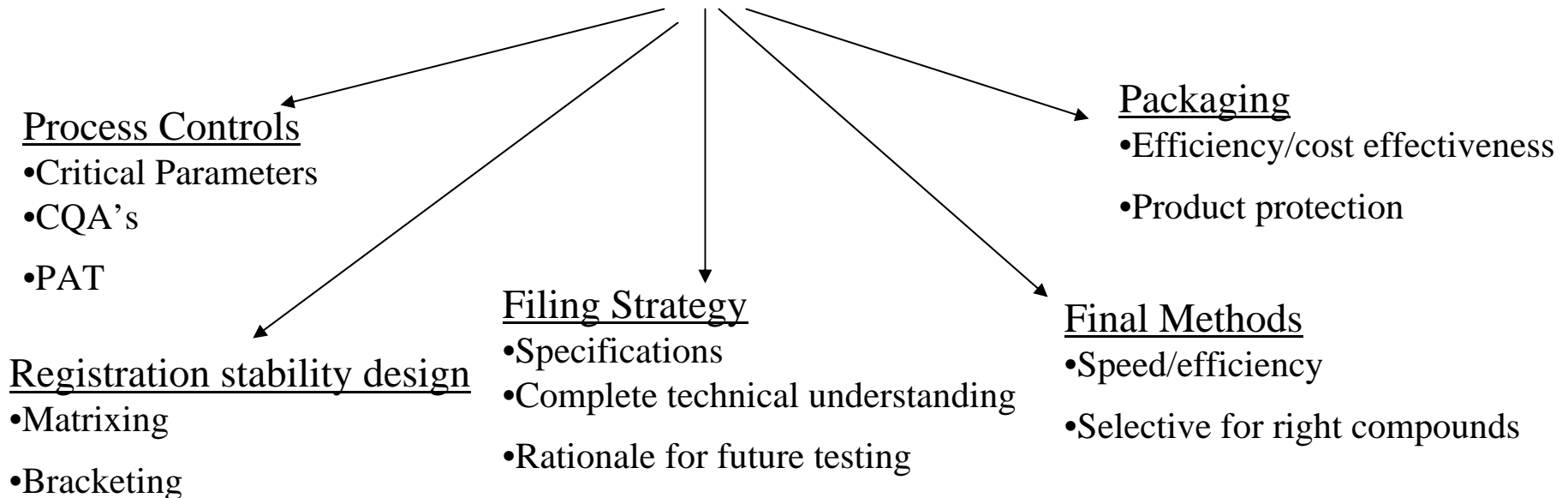


Stability

- Now have a good early phase method where likely degradation products are known
- Early Phase stability design depends on formulation strategy
 - Quick to clinic formulation: limited stability, in package, supports filing and storage
 - Developable formulation: expanded stability, open dish for scientific understanding, in package for filing support

Late Phase Stability (pre-registration)

- Build on prior learning, focus methods
- Continue open dish testing:
 - Understand critical moisture, oxygen, light thresholds in relation to chemical stability



Where are those properties best assessed? (integrating analytical knowledge)

- What are those sensitivities and where can you control and/or monitor them?
 - Production
 - Bulk Storage
 - Packaging
 - Distribution
 - In-use
- If you control/monitor during the product life-cycle do you need a “release” test?

How are those properties best assessed (tools)?

- Clearly the result of product sensitivity (degradation products) requires sensitivity to measure (i.e. HPLC)
- However, the cause of the degradation has broader potential for control/monitoring
 - Moisture: PAT potential (spectroscopy, water activity, in-package monitoring)
 - Oxygen: PAT potential (spectroscopy, in-package monitoring)
 - Light: PAT potential

Drug Release

- Some References:
 - Ajaz S. Hussain, Engineering a Proactive Decision System for Pharmaceutical Quality: Integrating Science of Design, Process Analytical Technology and Quality System, IFPAC 2005.
 - Robert Reed, A Quality by Design Approach to Dissolution Based on the Biopharmaceutical Classification System, DIA Meeting, June 28, 2005.
 - FDA Guidance for Industry.
 - others

What properties of the product are impacting PK

- Using a QbD approach to understanding how drug release impacts PK (safety & efficacy) requires cross-functional expertise and cooperation.
- Begins early in development and is enhanced throughout the development life cycle.

Assessing Drug Release

Preclinical info

- Polymorphs
- Particle size
- Solubility
- Permeability



Method Development

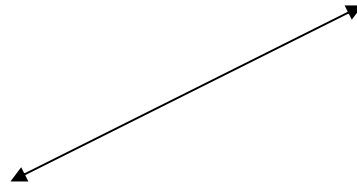
- BCS evaluation
- pH sensitivity
- Formulation design
- Physical effects



Very streamlined
product methods

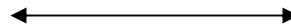
Early Phase Stability

- Gathering dissolution information
- Potential for IVIVC
- Process Sensitivity
- What's controlling dissolution?

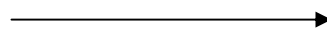


Late Phase Stability

- Package studies
- Develop IVIVC
- Robustness
- "discriminating ability"



Process Controls and/or
monitoring



Reduce or eliminate

Method Development

- Early phase method based on limited information and limited time:
 - Solubility and dosage form are key drivers – based on biopharmaceutical classification system (BCS)
 - Apparatus I or II for dissolution of most solid dosage forms

Biopharmaceutics Classification System (3 properties)

- Highly Soluble Drug Substance?
 - Highest dose unit is soluble in 250mL or less between pH 1.0 & 7.5
- Rapidly Dissolving Product?
 - 900mL media
 - UPS Apparatus I (100rpm) or II (50rpm)
 - pH 1, 4.5, 6.8
 - 85% in solution in 30min
- Highly Permeable API?
 - Absolute Bioavailability \geq 90%
 - In vitro methods (Caco-2 Cells) or in-vivo

Biopharmaceutics Classification System

	<u>Solubility</u>	<u>Permeability</u>
Class I	High*	High
Class II	Low	High
Class III	High*	Low
Class IV	Low	Low

* Highly-soluble substance target a rapidly-dissolving formulation. Like dosing an oral solution.

Method Development

- Early phase method based on limited information and limited time:
 - Little is known definitively about permeability so solubility and dosage form drive development:
- Class I & III (high solubility)
 - Get the drug in solution as fast as possible. Rapid dissolving formulation (UPS Apparatus I (100rpm) or II (50rpm))
- Class II & IV (low solubility)
 - Apparatus selected based on physical constraints. Media pH optimized for solubility. May involve surfactants.

Phased Development

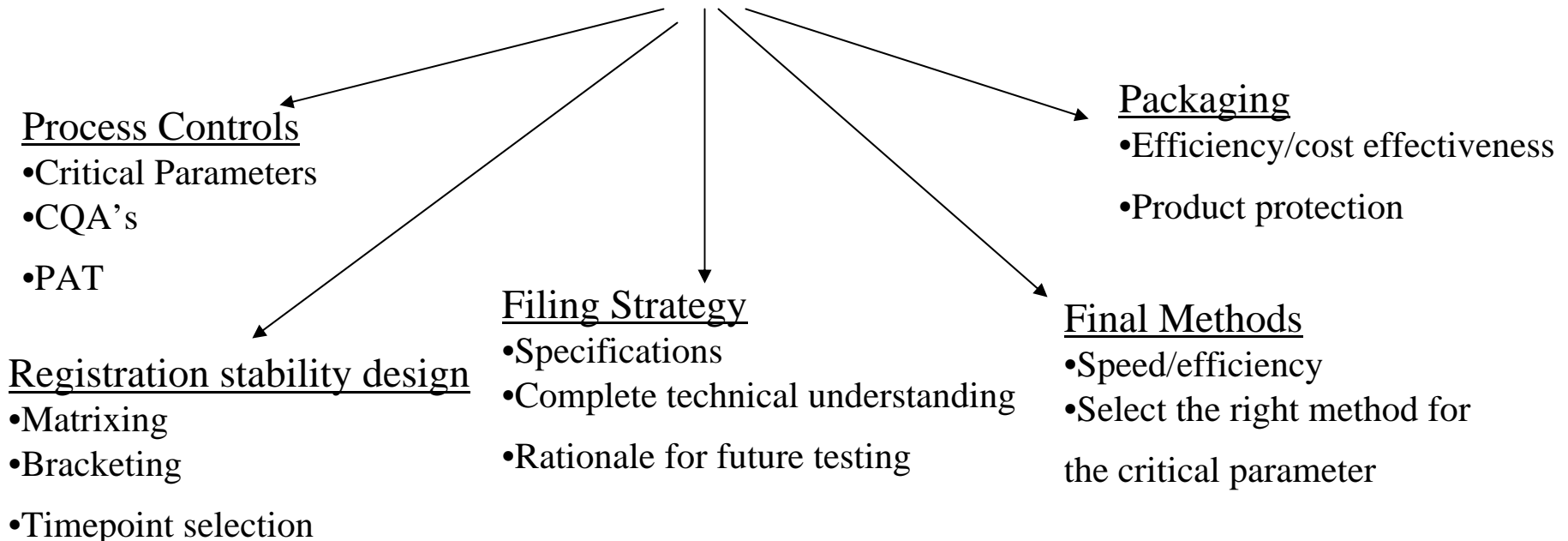
- Phase I: Do enough dissolution to get in the clinic and get PK data to provide guidance.
- Phase II: Develop the in-depth understanding of what formulation properties control drug release/in-vitro absorption
 - Particle size, erosion, disintegration, granule dumping, intrinsic solubility, capsule rupture (LFC's)
- Phase III: Develop the database to justify your method for assuring quality and specifications
 - Not necessarily only dissolution

Stability

- Now have an “adequate” early phase method
- Early Phase stability design for drug release also depends on formulation strategy
 - Quick to clinic formulation: profile at release, limited stability (single timepoint), in package, supports filing and storage
 - Developable formulation: expanded stability (profiles throughout), open dish for scientific understanding, in package for filing support

Late Phase Stability (pre-registration)

- Build on prior learning, focus methods
- Continue open dish testing:
 - Understand critical environmental sensitivities
 - Capitalizes on knowledge of what controls PK



Where are those properties best assessed?

- Is dissolution the best assessment of quality for a given formulation?
 - BCS class I & III, rapidly dissolving – probably disintegration
 - BCS class II & IV
 - Dissolution
 - LFC's – may be disintegration or capsule rupture
 - May be particle size control

How are those properties best assessed (tools)?

- Dissolution is clearly a straightforward lab activity
- However, opportunities to monitor/control the underlying properties determining absorption warrant exploration:
 - Particle size: PAT potential
 - Disintegration: In-process or lab
 - Texture analysis: orally disintegrating formulations

Role of PAT in the QbD Initiative

References

Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

<http://www.fda.gov/cder/guidance/6419fnl.ht>

A Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century

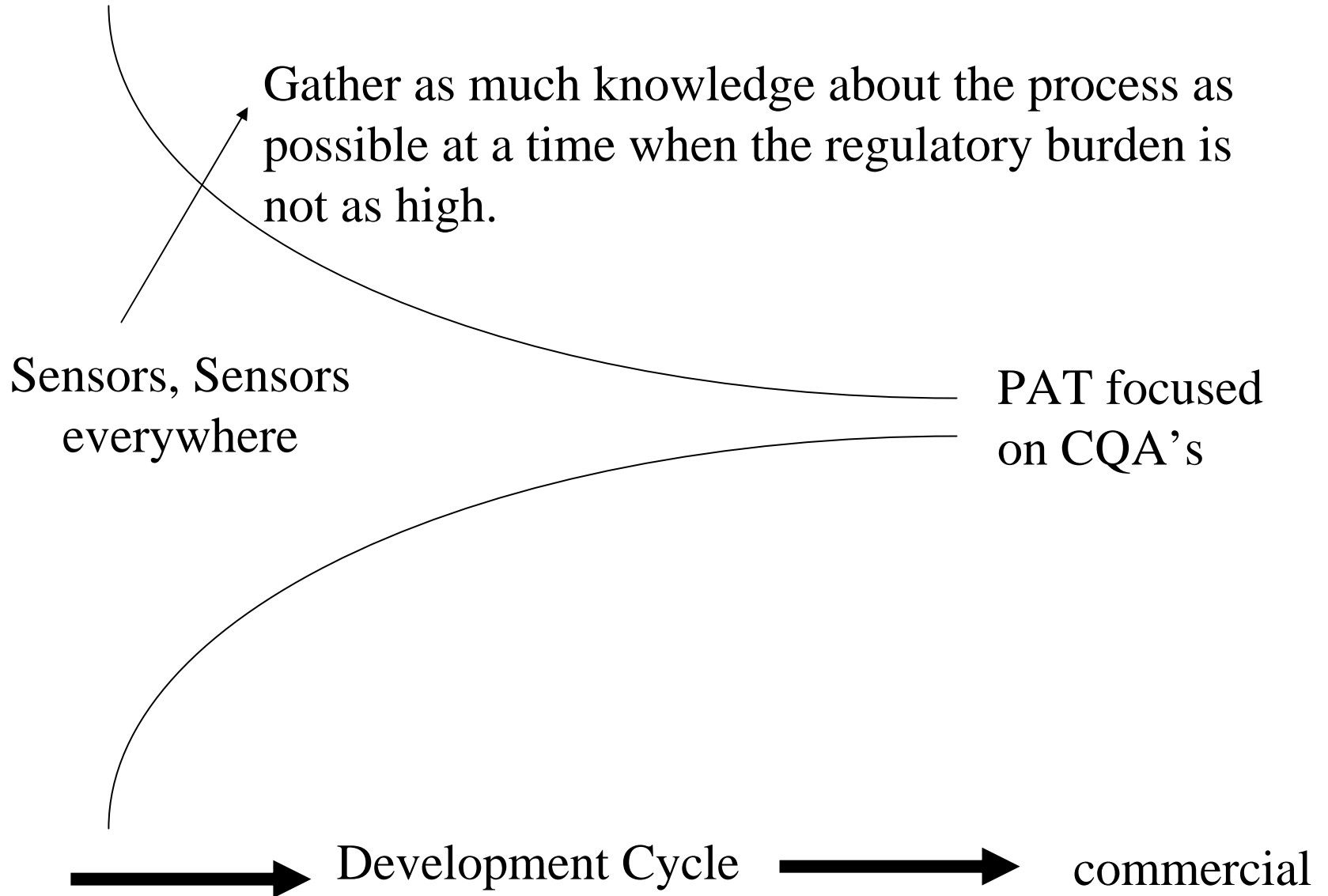
http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm

Search PAT on www.fda.gov

Same Approach Applies

- What properties of the product are truly impacting the quality attribute.
 - Eg. Particle size for absorption, moisture for degradation products, etc.
- Where are those properties best assessed?
 - Is the best assessment location amenable to PAT
- How are those properties best assessed?
 - Are the PAT tools available, cost effective to implement and maintain
- What are meaningful limits?
 - The database gets much larger when using PAT. How do you evaluate the data and set limits.

PAT in Development



What Constitutes PAT

- Complex instrumentation: NIR, Raman, FTIR, etc.
- Common underutilized data:
 - Press information
 - Exhaust temps, humidity
 - Granulator speeds, power
 - Air flows
 - Etc.

Why Use PAT

- Necessary to prevent costly batch failures
- Eliminate costly laboratory tests
- Speed manufacturing timeline (real-time release)
- Fun to play with the fancy instruments
- others

What does the QbD Initiative Mean for the Analytical Scientist?

- Close relationship between functional areas (analytical development, formulation/process development, drug metabolism, API development, safety assessment, clinical research, CMC)
- Broader technical skills and a good understanding of the analytical state of the art
- Focus on the big picture/end game (not a box checking mentality)
- Truly implementing QbD has the potential to provide a deeper scientific understanding of products and drive long-term efficiencies