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A practical approach for implementing product lifecycle and control strategy for API manufacturing processes

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DISCLAIMER

The information presented here reflects the view of the presenter and not the views of QBiotics Limited or PharmOut

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AGENDA

1. Product life cycle concept
2. Ingredients
3. Definition phase
4. Process development and knowledge management
5. Implanting control strategy
6. Challenges

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PRODUCT LIFE CYCLE CONCEPT

Linking target product profile, process development and process qualification to demonstrate sustainable quality, safety and efficacy.

Process lifecycle

- Process design
- Process qualification
- Continuous process verification

Approach

- Traditional
- Enhance
- Hybrid

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PRODUCT LIFE CYCLE CONCEPT

"Mind-set is really what it is all about."

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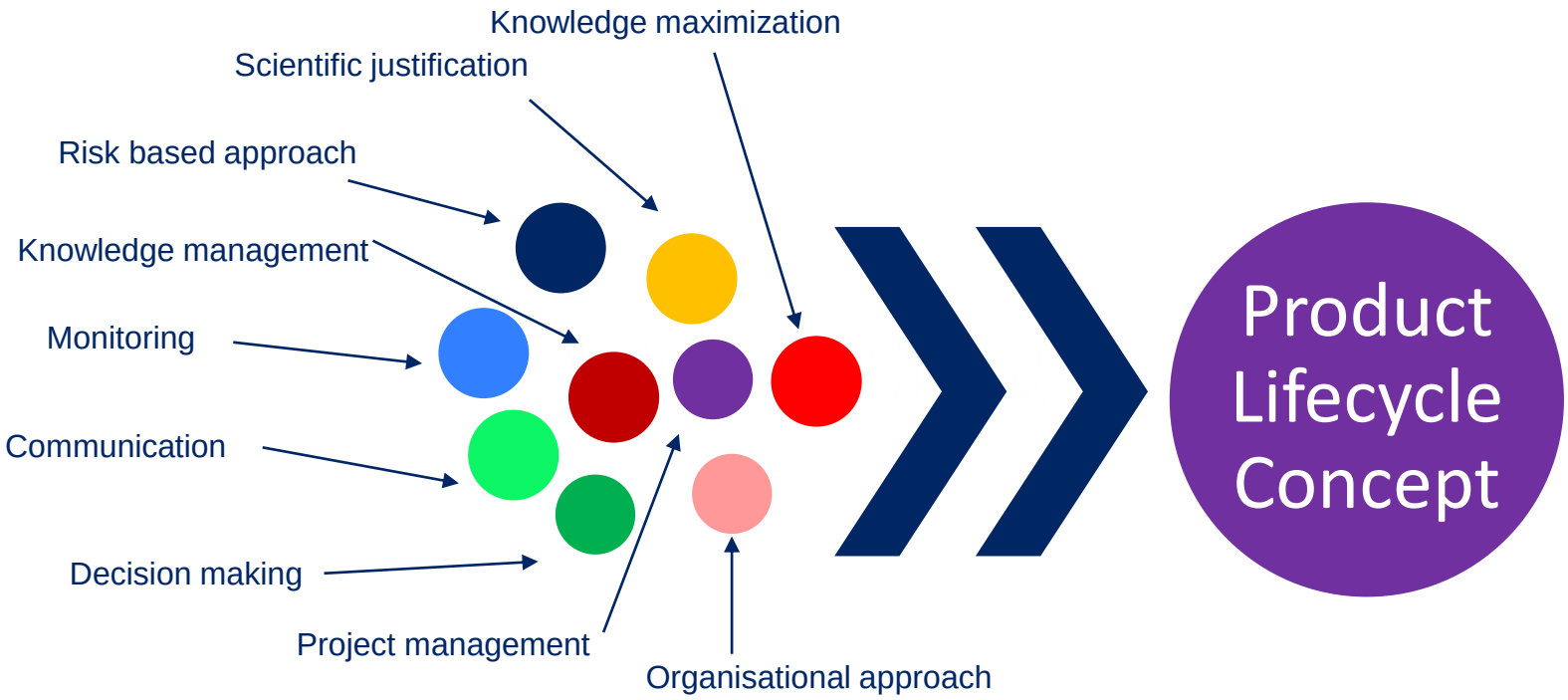
INGREDIENTS



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PRODUCT LIFE CYCLE CONCEPT

"If you fail to plan, you are planning to fail."

Benjamin Franklin

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IMPLEMENTING LIFECYCLE AND CONTROL STRATEGY

Definition phase

Bigger picture!	Example
The source of active material	Plant (whole, leaf, fruit seed etc.) Percentage of active and related substance
Target compound (the molecule)	Structure Solubility Polymorphism Chirality
Target patients	Human Veterinary medicine
Potential dosage form	Oral Topical Injectable
Target product profile	Identity, strength, purity, potency, safety and other Critical Quality Attributes (CQA)
Process Analytical Technology	Off-line, at-line on-line IR, NMR, HPLC, GC, MSMS
Demand vs process scalability	Grams, Kg, Tons

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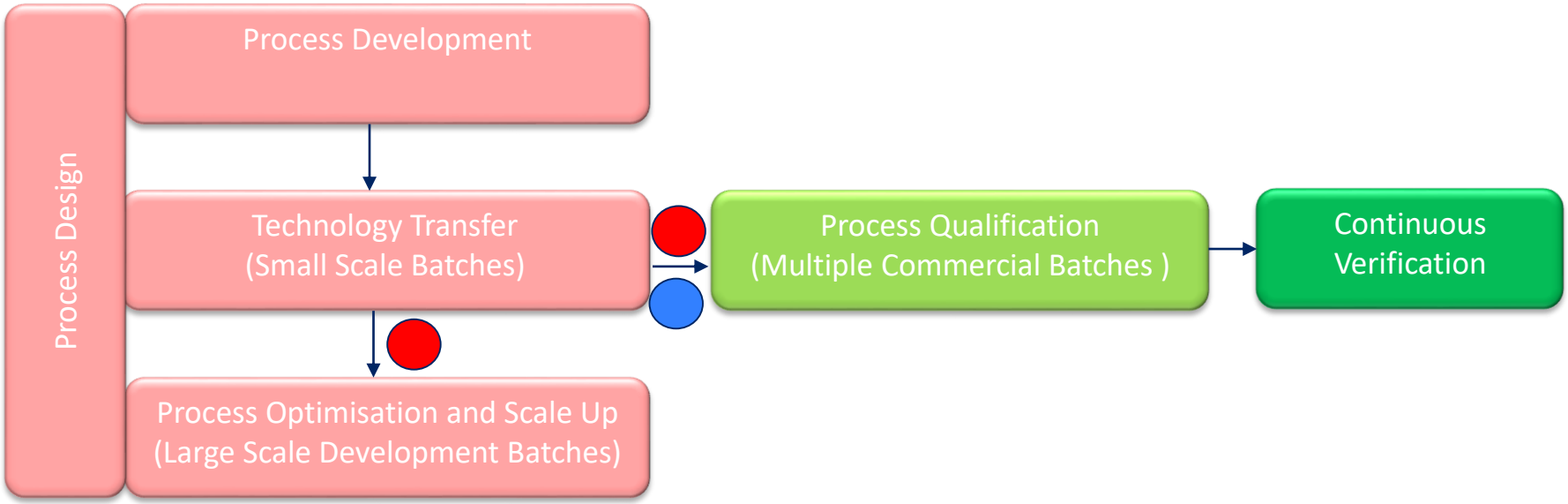
Process Validation Lifecycle Approach



= Risk Assessment

= Method Validation

Process Development and Knowledge Management

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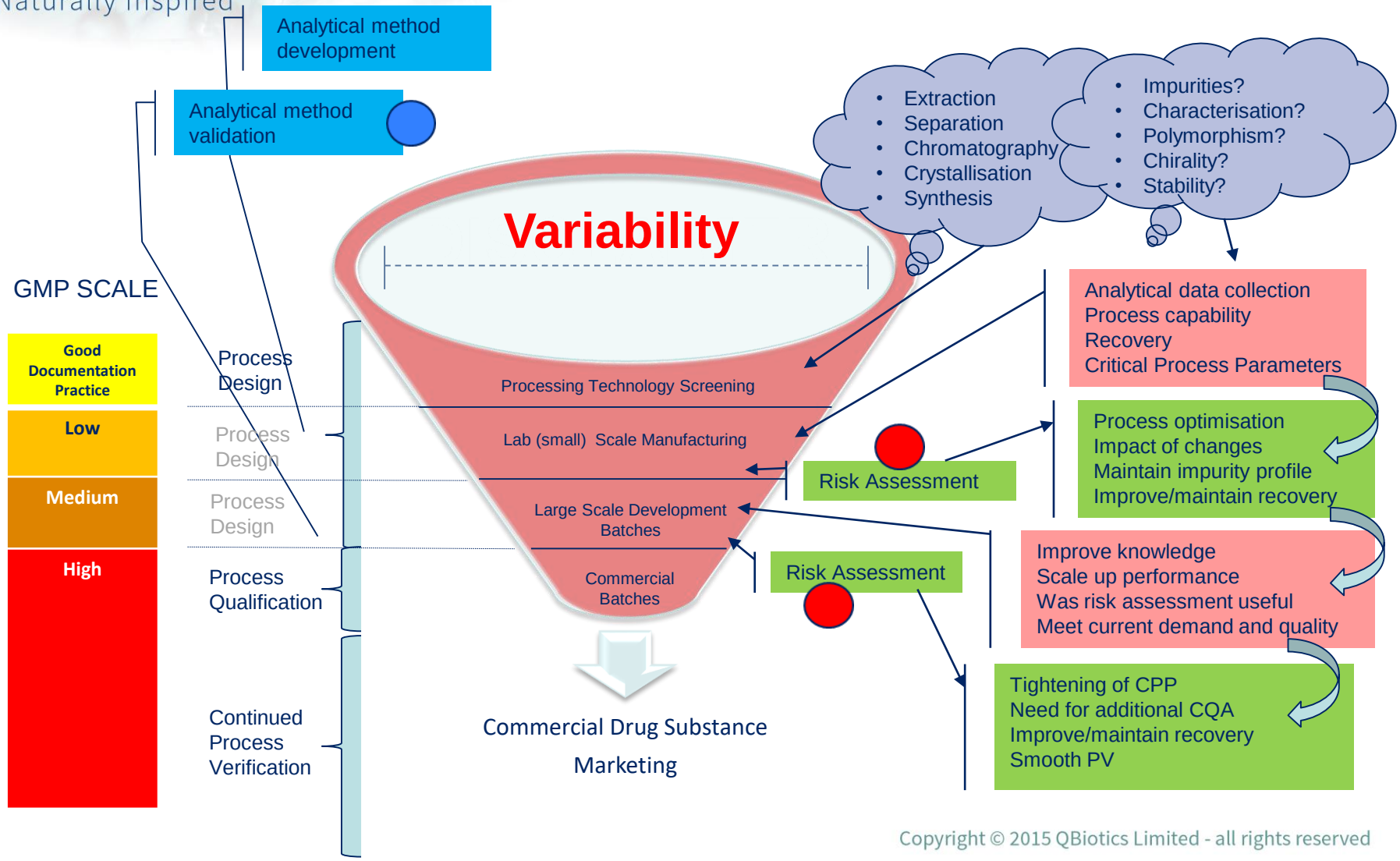

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PRODUCT LIFE CYCLE CONCEPT

It is always cheaper to do the job right the first time.

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EXAMPLE CONTROL STRATEGY

Raw Material_ Plant Origin

Processing Technology Screening	Lab (small) Scale Manufacturing	Large Scale Development Batches	Commercial Batches
• Physical Appearance • Compare with reference photo	• Physical Appearance • Compare with reference photo • TLC/ HPTLC identification	• Physical Appearance • Compare with reference photo • HPTLC identification • Assay (Report results)	• Physical Appearance • Compare with botanically certified standard • HPTLC identification or HPLC finger printing • Assay (> X %) • Moisture content

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EXAMPLE CONTROL STRATEGY

API Starting Material and Intermediates

Processing Technology Screening	Lab (small) Scale Manufacturing	Large Scale Development Batches	Commercial Batches
• Physical Appearance • HPLC Purity % (report results)	• Physical Appearance • Purity % (report results) • HPLC finger print	• Physical Appearance • Identification by HPLC • Assay (report results) • Report impurities that appeared in small scale final API (no acceptance criteria)	• Physical Appearance • Identification by HPLC • Assay (report results) • Critical Impurities (NMT X %) • Moisture content

How many "intermediate products" ???

What is API starting material ??

CQA of the "intermediate products and API starting material" ???

Monitor variation

Potential acceptance criteria for intermediate API starting material??

Factors that causes variation

Risks of API starting material and intermediate not meeting its specification??

Control variation

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EXAMPLE CONTROL STRATEGY

Process Control

Processing Technology Screening	Lab (small) Scale Manufacturing	Large Scale Development Batches	Commercial Batches
• Record everything!	• Test everything! • Collect, data for **CPP** such as temperature, time, pH, pressure, vacuum etc. • Recovery and process efficiency for each step. • Study reprocessing capabilities 	• Reduce in process testing • Include meaningful in process testing • Introduce upper and lower range for temperature, time, pH, pressure, vacuum etc • Finalise reprocessing pathways 	• Finalised in-process specification and acceptance criteria • Tightened range of CPP • Implement reprocessing policy and procedures

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EXAMPLE CONTROL STRATEGY

Drug Substance

Processing Technology Screening	Lab (small) Scale Manufacturing	Large Scale Development Batches	Commercial Batches
• Physical Appearance • HPLC Purity % (report results)	• Physical Appearance • Identification FTIR, HPLC • Assay % (report results) • Impurities (all impurities, Report result) • Moisture content • More testing is better	• Physical Appearance • Identification FTIR, HPLC • Assay % (report results) • Impurities (all impurities , Report result) • Moisture content (Report result) • Elemental impurities (USP) • Residual solvents (Report result) • Micro (USP) • Endotoxin (Report result)	• Physical Appearance • Identification FTIR, HPLC • Assay % (> X %) • Specified Impurities (≤ X % impurities , above identification threshold or degradation impurities) • Unspecified Impurities (≤ X % impurities , above Reportable • Moisture content (Report result) • Elemental impurities (USP) • Residual solvents (Report result) • Micro (USP) • Endotoxin (Report result) • Residue on ignition

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PRODUCT LIFE CYCLE CONCEPT

Process Qualification

Processing Technology Screening	Lab (small) Scale Manufacturing	Large Scale Development Batches	Commercial Batches

• Too far	• Team building
	• Training
		• Planning
		  • Timing
		  • No of batches
		• Batch record fine tuning
		• Master plan and Protocol
			• Testing high risk CQA and CPP
			• Smooth Execution of PVP
			• Continued verification protocol and metrics
			• APQR
			• Quality metrics

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CHALLENGES

- Understanding source of variability and degree of variation
- Linking the impact of variation to the CQA of the product
- Controlling variation while maintaining sustainable yield
- Balancing quality and commercial viability
- Collaboration of multidisciplinary functions such as R&D, clinical, quality, regulatory
- Time
- Resources
- Organisational culture and mindset

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PRODUCT LIFE CYCLE CONCEPT

"Those who **fail** to learn from the past are doomed to repeat it."

Sir Winston Churchill

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Thank you for your attention

Questions....?