



# Developing a Strong Business Case for QbD Implementation Within a Contract Manufacturing Company

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DSM Biologics

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**Bio**  
**BusinessEvent**

Connecting Science to Business

Unlimited. **DSM**



# Agenda

- Introduction to DSM Biologics
- Quality by Design
- Integration QbD
  - Theory
  - Practice and Challenges
- Conclusion





## Message

“Quality by Design  
is an excellent tool  
for CMO and Sponsor”



# DSM Biologics



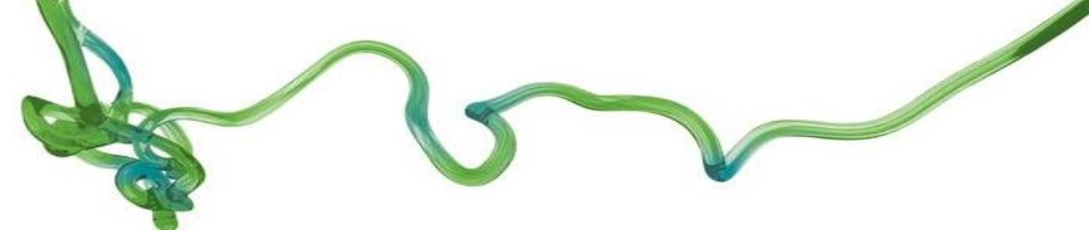
## DSM Biologics contract manufacturing

- DSM Biologics is part of DSM, a global player in the field of Life Sciences & Material Sciences
  - Technology driven for nutritional, high end plastics & pharma industry
  - Servicing the Pharma- and Biotech industry from development to commercial supply
    - small molecules, biopharmaceuticals and fill & finish



# DSM Biologics contract manufacturing

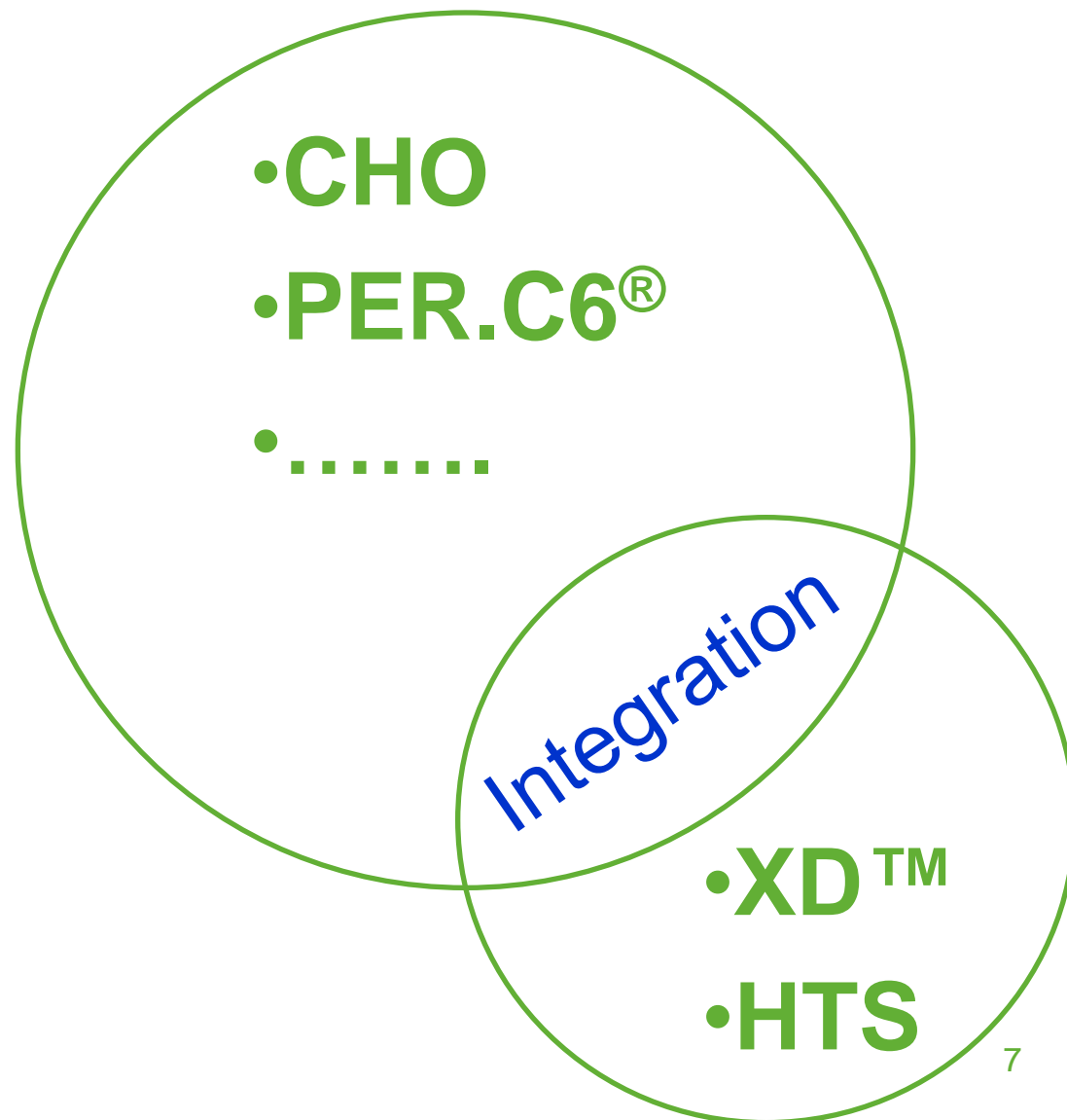
- Development and cGMP manufacturing facility located in Groningen, the Netherlands
  
- Over 20 years experience
- Pre-IND products
- Phase I, II, III and marketed products
  
- Flexible manufacturing platforms
  - Single use technologies, including Single Use Bioreactors
  - Per.C6® Platform
  - Intensified platform processes incl. XD®



# DSM Biologics Mission

**Manufacturing Services**

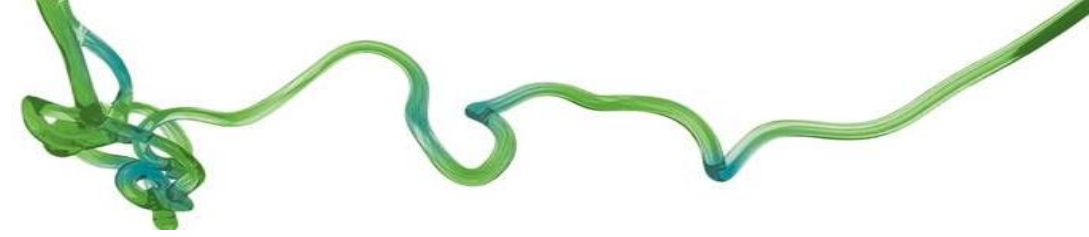
**Technologies**



- XD®
- PER.C6®
- HTS



# Quality by Design



# The Theory

- QbD is a **systematic approach** to attaining desirable quality through careful evaluation of all attributes that characterize product quality from early development through the entire product lifecycle.
- The components of QbD — **knowledge capture, risk management and quality systems** — can deliver a number of benefits to the sponsor and the contractor, and ultimately benefit the patient.
- A QbD orientation can provide a formal framework that makes it easier to leverage existing knowledge capital.
- QbD gives the contractor numerous opportunities to add value to the sponsors process.



# Manufacturing Platform: Modular unit operations

DSM Biologics Manufacturing Platform

Platform building blocks

Process



# Value creator: XD<sup>®</sup> Technology

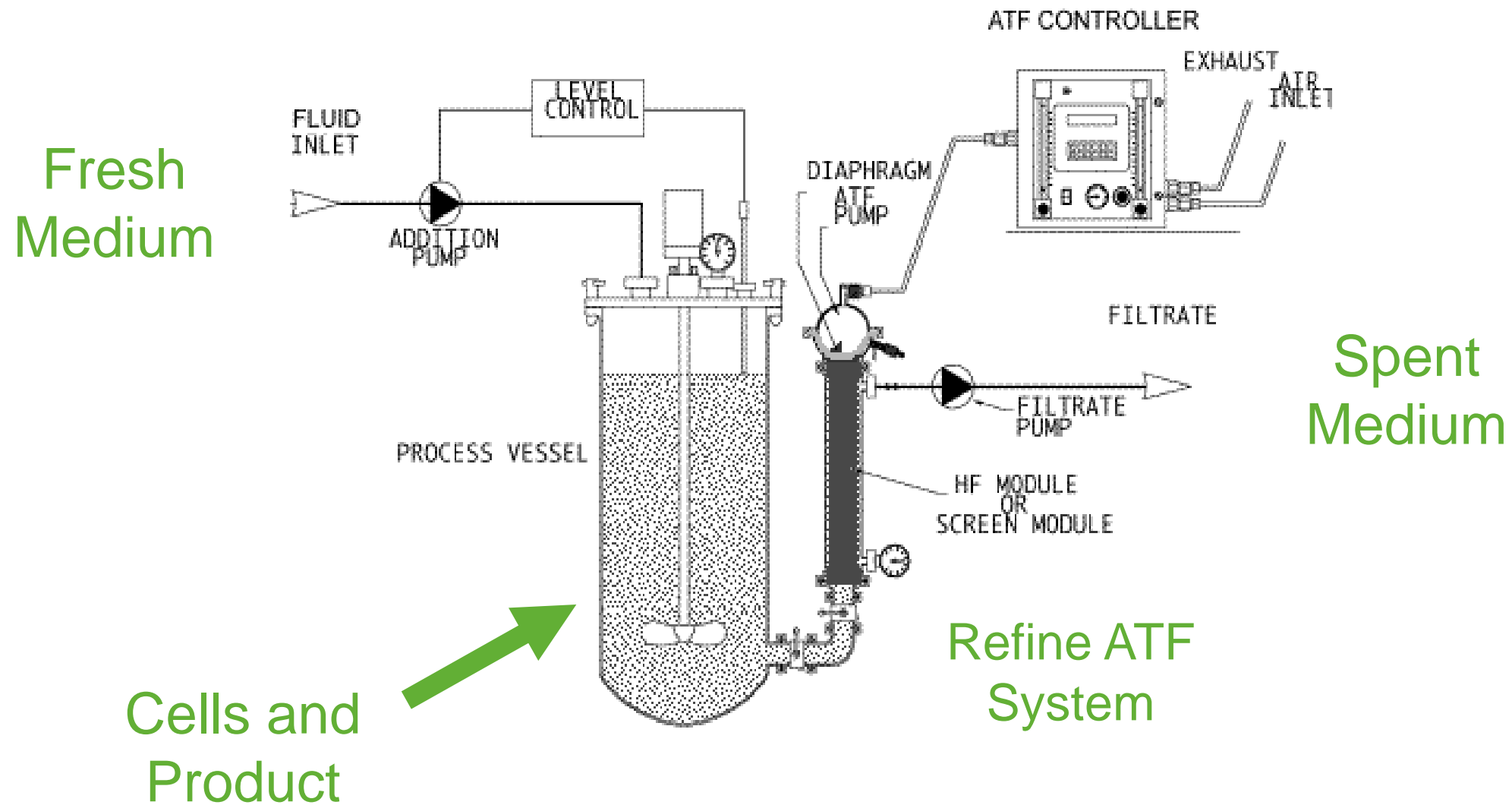


Image from [www.magellaninstruments.com](http://www.magellaninstruments.com)



# XD<sup>®</sup> combines the benefits of fed batch and perfusion processes

## XD<sup>®</sup> Process



### Cell Culture Mode of Manufacturing

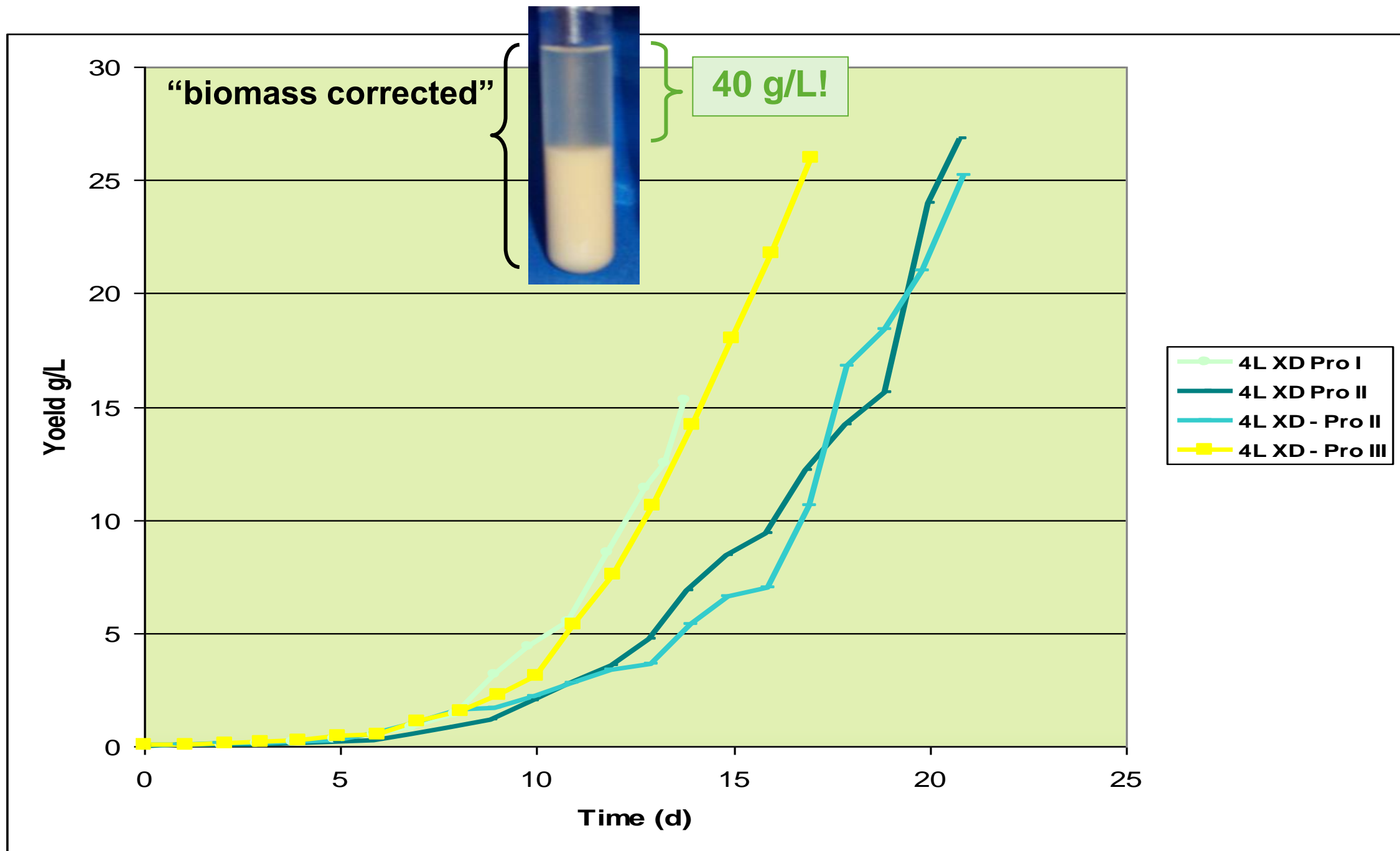
**Fed Batch**  
Feed concentrate  
Build up Metabolites  
Osmo increase  
Changing environment  
Reducing cell viabilities  
Concentrated Harvest  
batch identification

**XD<sup>®</sup>**  
Medium Feed  
Wash out Metabolites  
No Osmo increase  
Constant environment  
High cell viabilities  
Concentrated Harvest  
batch identification

**Perfusion**  
Medium Feed  
Wash out Metabolites  
No Osmo increase  
Constant environment  
High cell viabilities  
Dilute harvest  
Large harvest

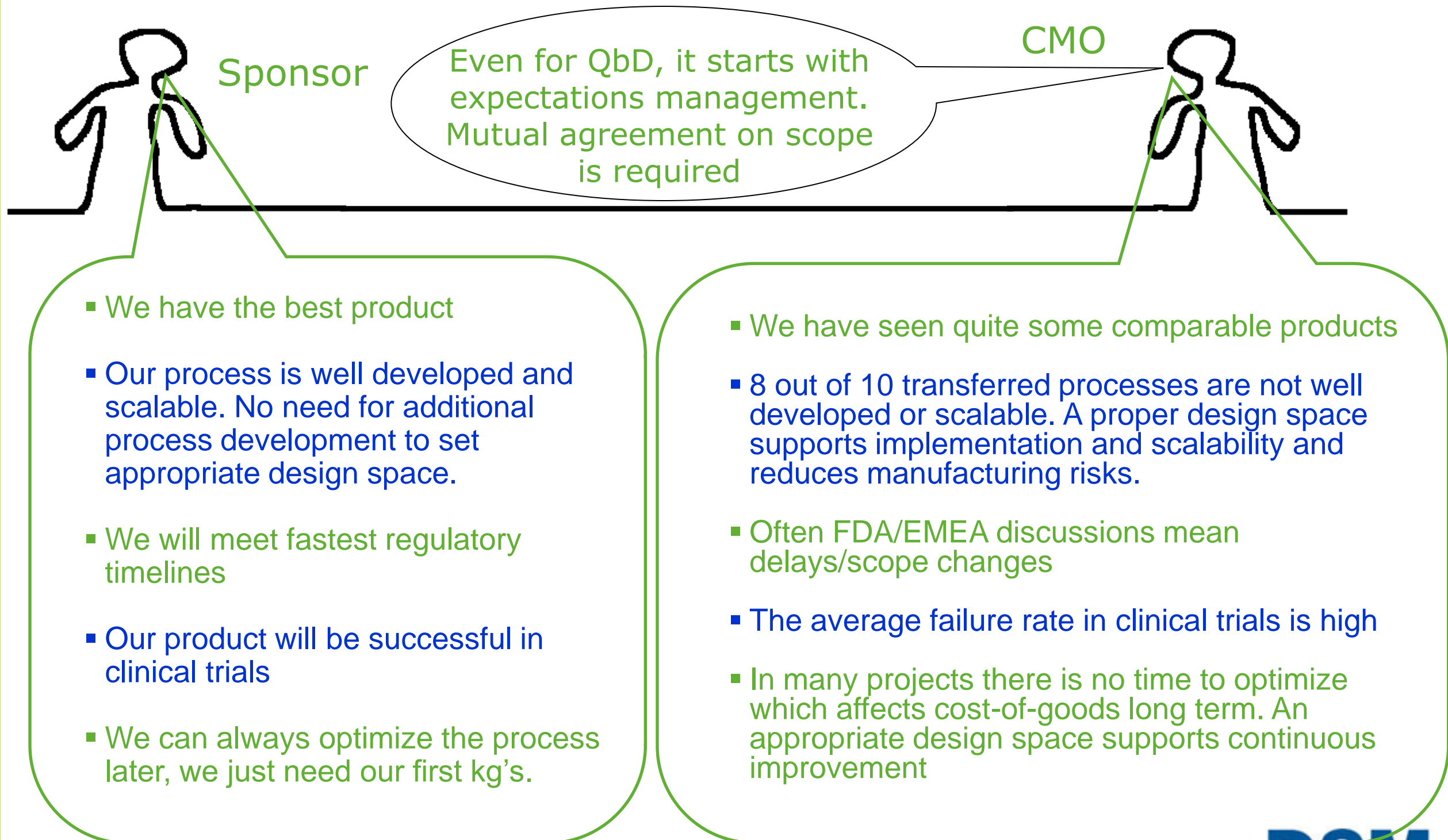


# Productivity of PER.C6<sup>®</sup> using XD<sup>®</sup>



# The Practice

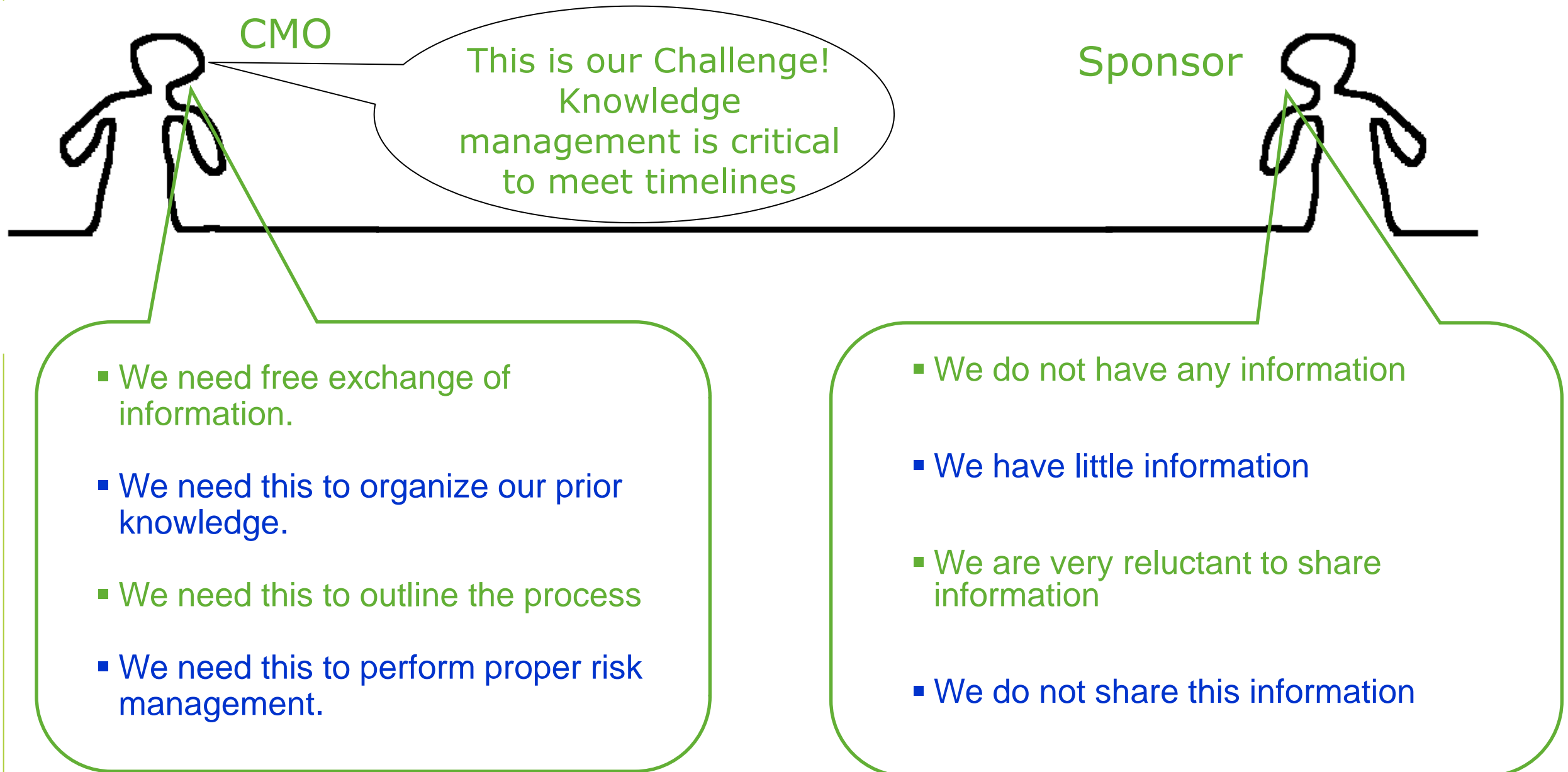
## Expectations management

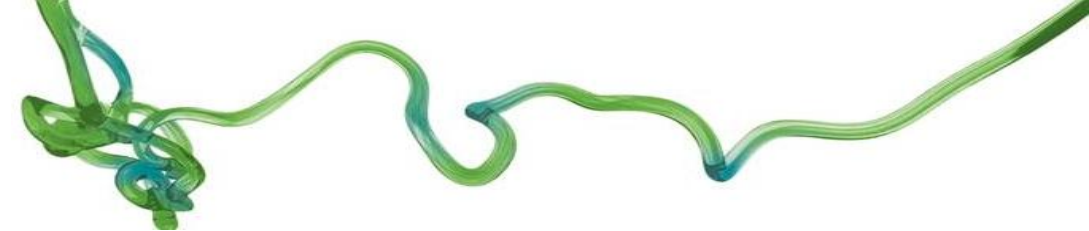




# The Practice

## Knowledge management





# The Practice

realism





## Summary

It is important to share knowledge bi-directional

Risks should be identified and communicated

Applying Quality by Design potentially increases success-rate.

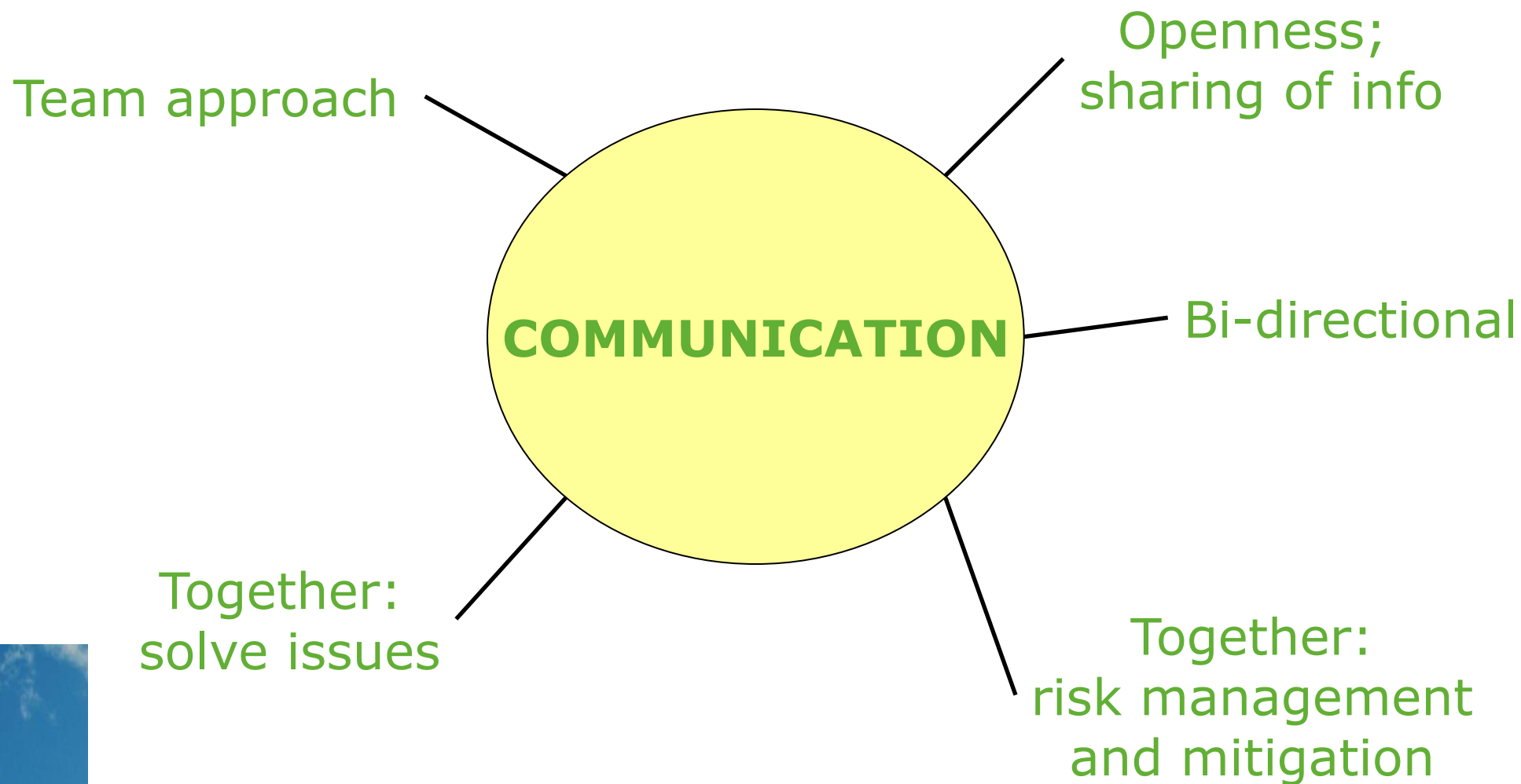


# Integration QbD and CMO



# The Theory

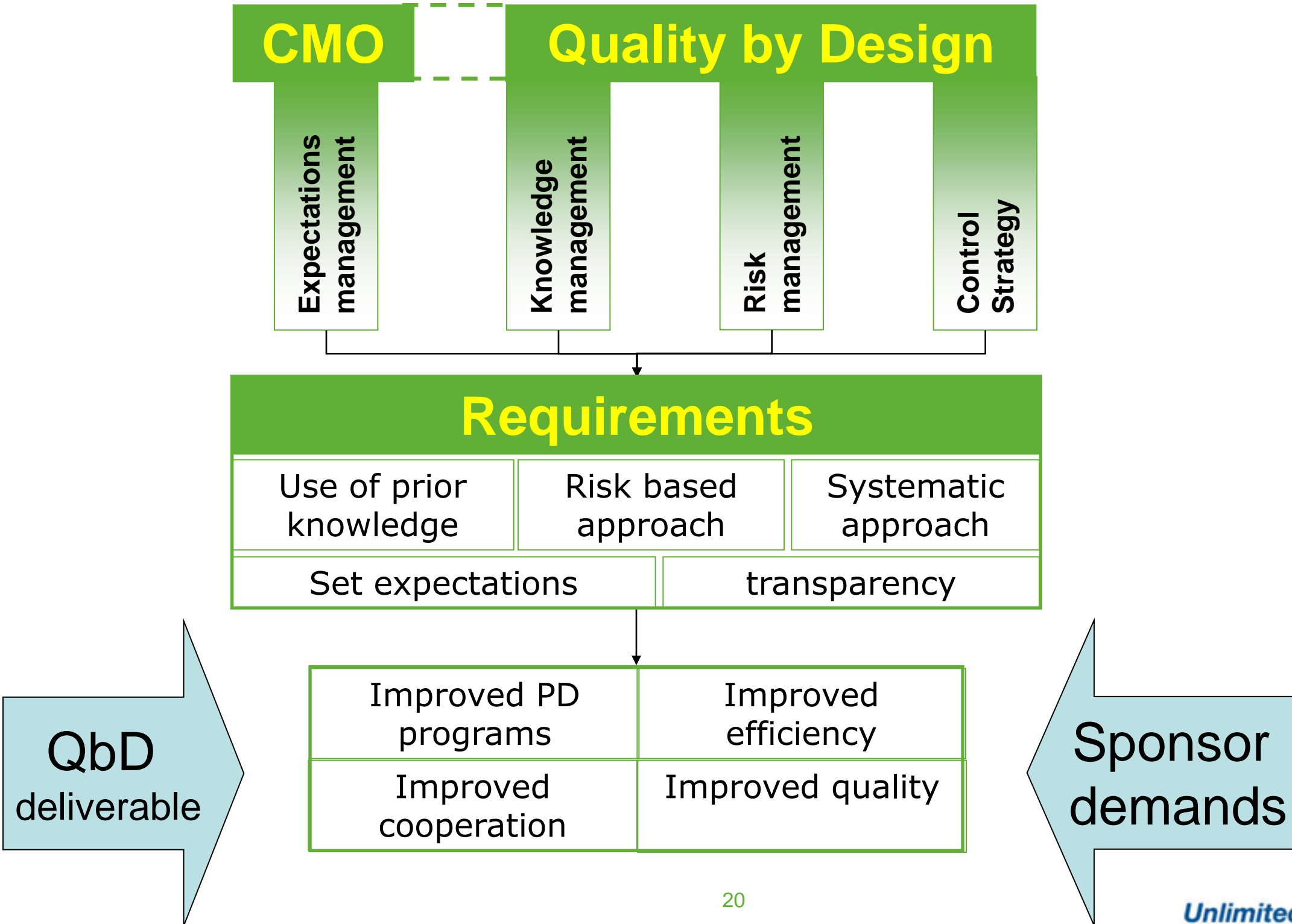
Integration of QbD and CMO





# The Theory

Integration of QbD and CMO





# The Practice

## Integration of QbD and CMO

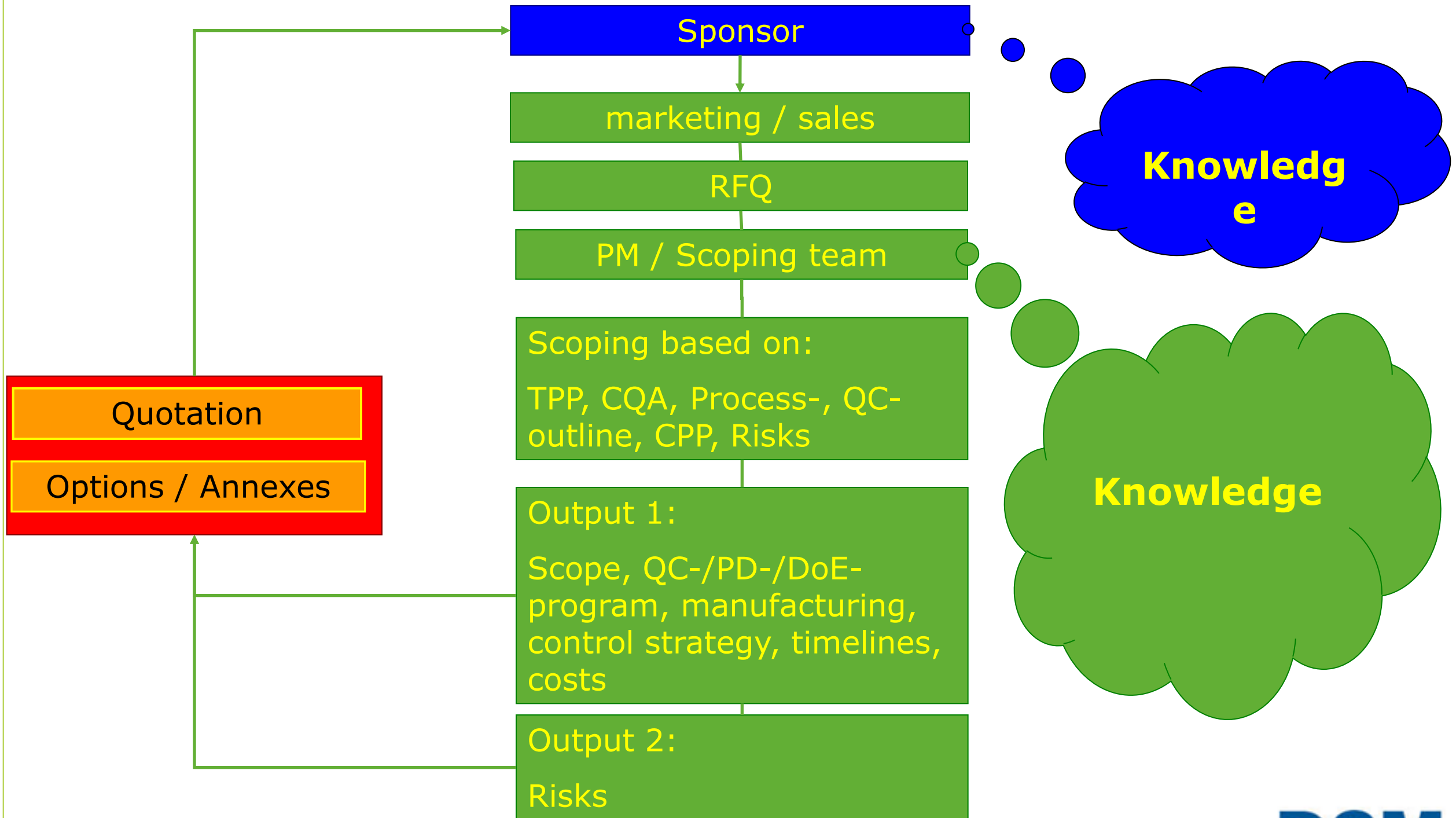
For (potential) customers we divide a project in 2 phases:

- Pre-contract phase (prospecting phase)
- Execution phase





# Quality by design starts in prospecting phase





## Prospecting Phase Deliverable

Quotation covering main scope, costs and timelines

Risk identification which assesses potential additional work to mitigate identified risks



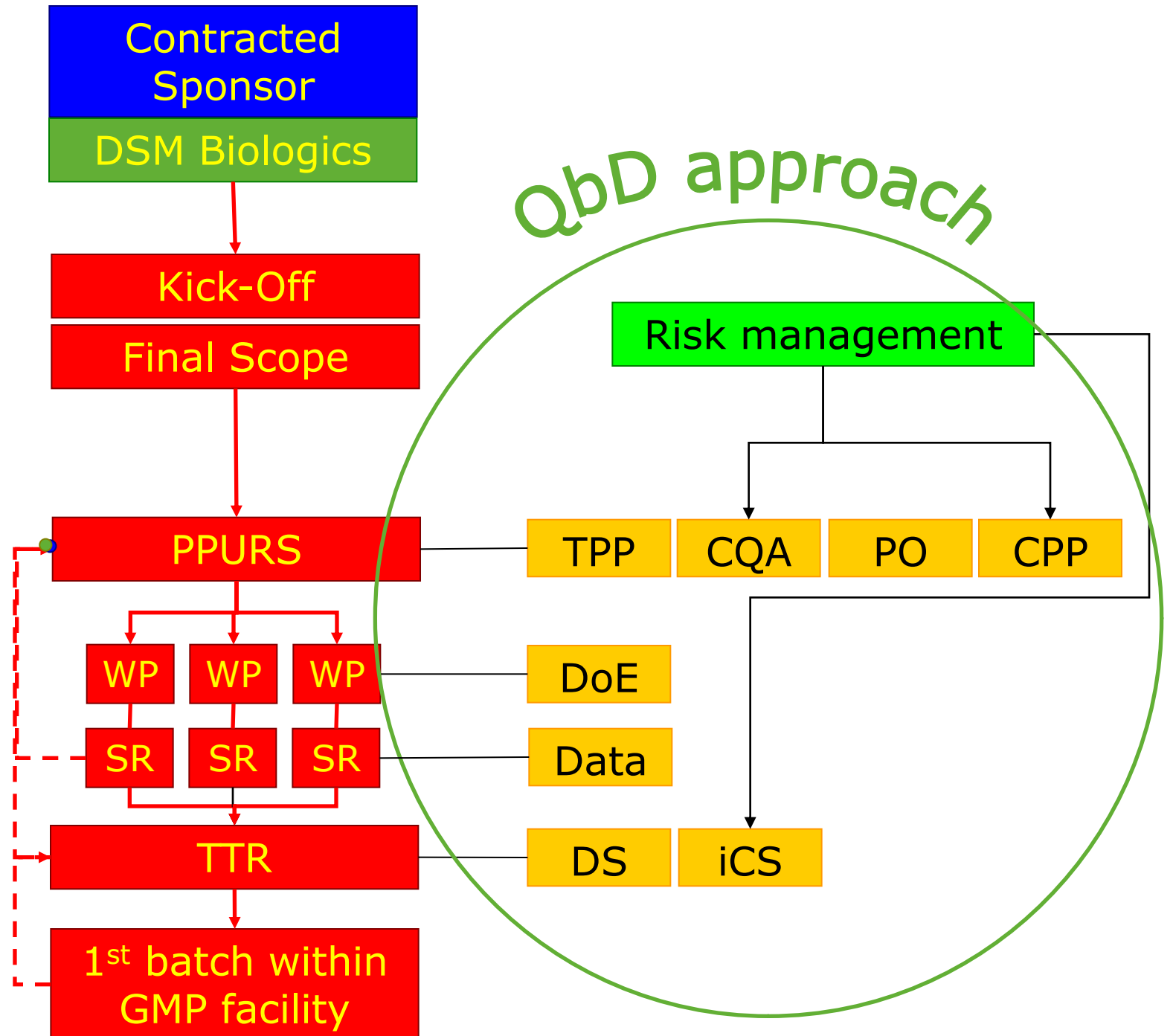


# Quality by design continuous in execution phase

Process Development

Sponsor knowledge

CMO knowledge



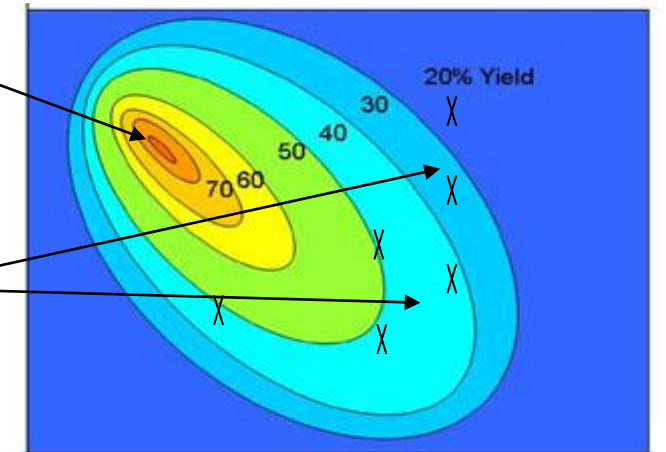
# QbD in execution phase / Process Development

## Downstream Processing

- Identified bottleneck
- Column chromatography

Process optimum

Tested conditions



- Finding the Process Optimum through testing with lab-scale columns

- Limited amount of experiments possible
- Not always the optimum found
- Time consuming
- Large quantity of material necessary from upstream



# QbD in execution phase / Process Development

## Downstream Processing

Solution found in technology and QbD:

High Throughput Screening (HTS)

Systematic, knowledge and risk management, efficient,

- Mini-Columns in 96-well-format
- 96 experiments in one time

- Resin scouting
- Process Condition Screening:
  - Loading conditions, pH & conductivity
  - Elution conditions
  - Intermediate wash step development



# QbD in execution phase / Process Development

## Downstream Processing



### HTS resin screening: an example

	1	2	3	4	5	6	7	8	9	10	11	12
20 mM Tris, 1 M (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , pH 7.5					++				++	++		
20 mM Tris, 1 M (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , pH 8.0				+		++						
20 mM Tris, 1.5 M (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , pH 7.5	+				++			++	+	++		
20 mM Tris, 1 M (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , pH 8.0					++				++		++	
20 mM Tris, 1 M (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , pH 8.5					++		++	++	++			
20 mM Tris, 0.5 M NaCl, pH 7.5	+											
20 mM Tris, 1.0 M NaCl, pH 7.5	++						+					
20 mM Tris, 1.5 M NaCl, pH 7.5								++	++		++	

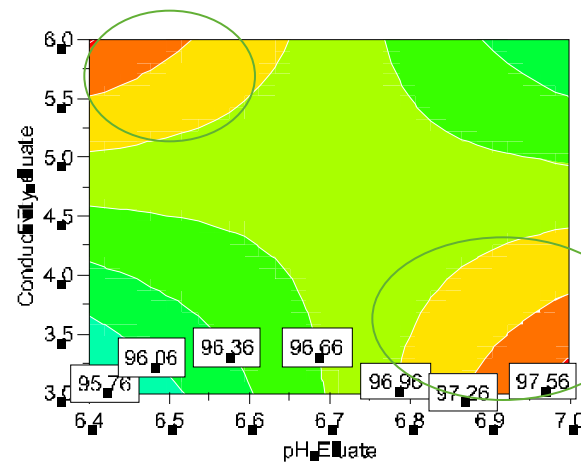
	Butyl Sep 4 FF	Butyl S-Sep. 6 FF	Phenyl Sep. 6 FF HS	Phenyl sep. 6 FF LS	Phenyl Sep. HP	Toyopearl Ether-650M	Toyopearl PPG-600M	Toyopearl Phenyl-650M	Toyopearl phenyl-650C	Toyopearl Butyl-650M	Macrorep methyl	Macrorep t-butyl
A					++				++	++		
B				+		++						
C	+				++			++	+	++		
D					++				++		++	
E					++		++	++	++			
F	+											
G	++						+					
H								++	++		++	

# QbD in execution phase / Process Development

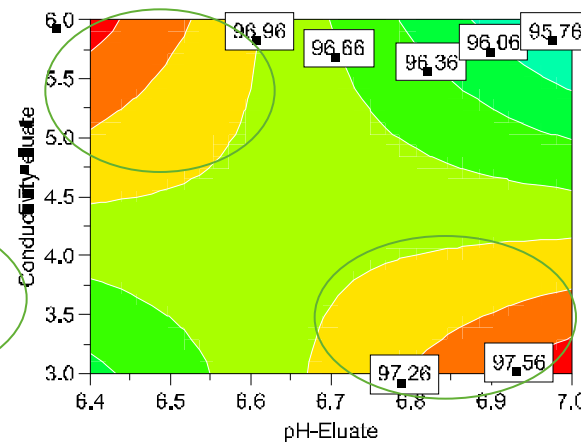
## Downstream Processing

### HTS resin screening: example: difficult to purify protein

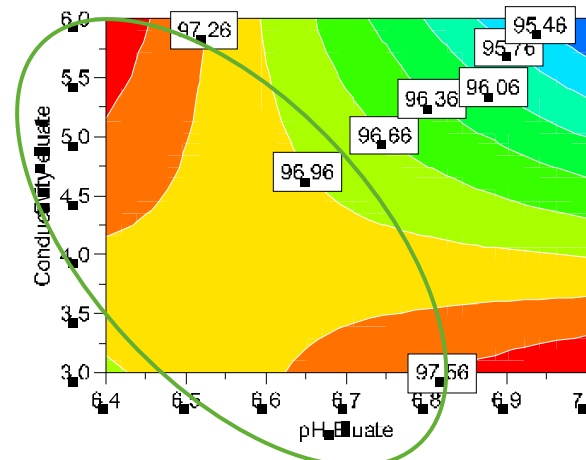
pH load  
5.5



5.0



4.5



 : > 97 % purity

- Identification of robust operating ranges
- Combine with **Design of Experiments**



# Process development Deliverable

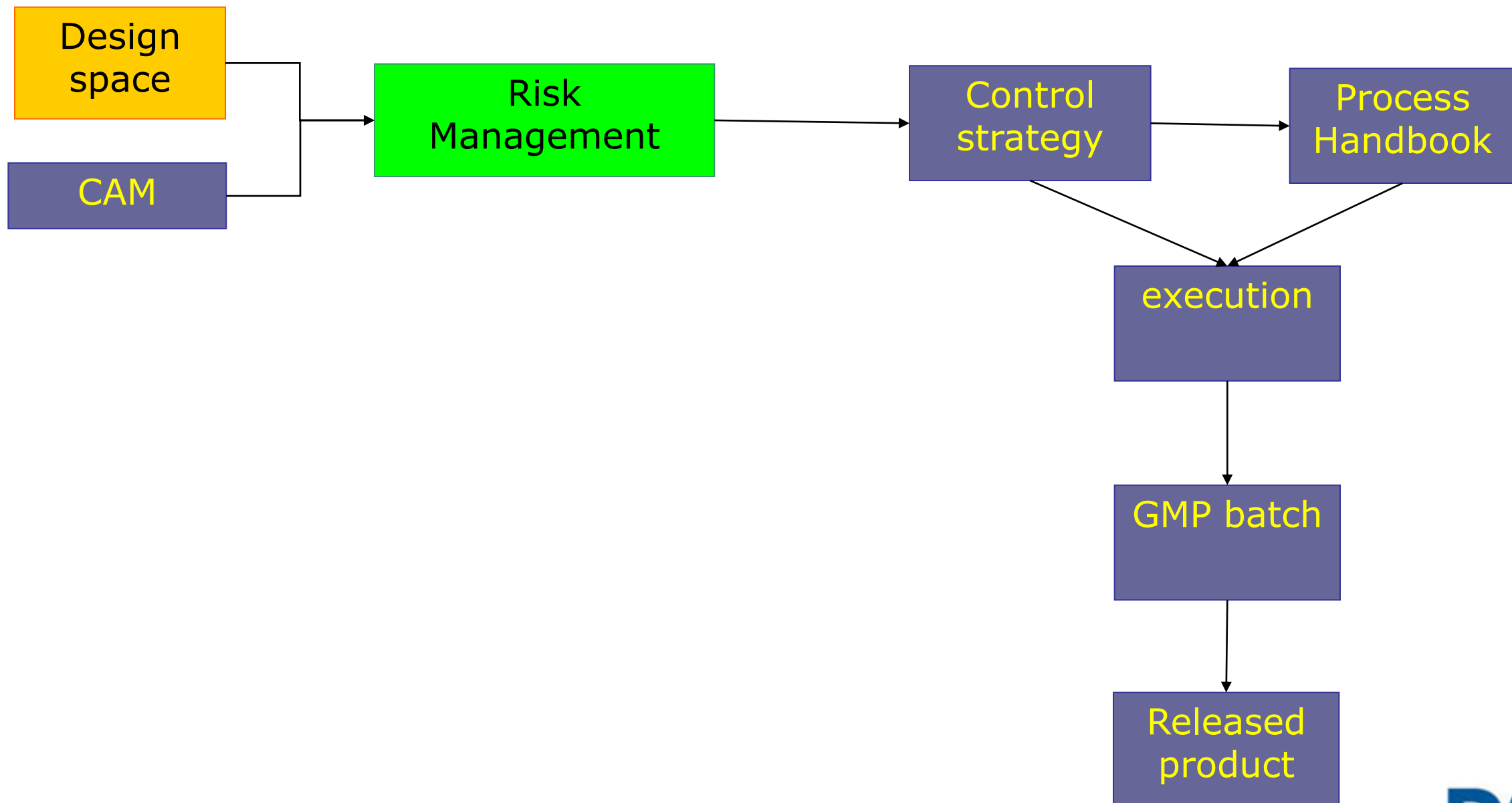
Documented evidence for:

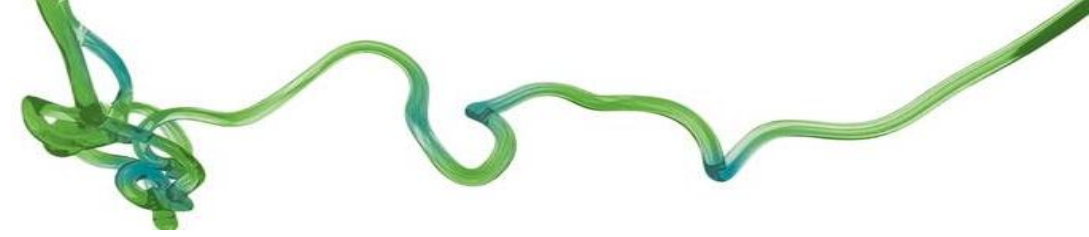
- Robust process evaluated against PPURS
- Robust product quality evaluated against PPURS
- Robust Design Space
- Robust Proof for Scalability of Process
  
- Initial Control Strategy for Manufacturing



# Quality by design continuous in execution phase

Manufacturing





# Manufacturing Deliverable

Robust and reproducible process and product quality

Detailed process handbook describing:

- Process History

- Process outline

- Product profile

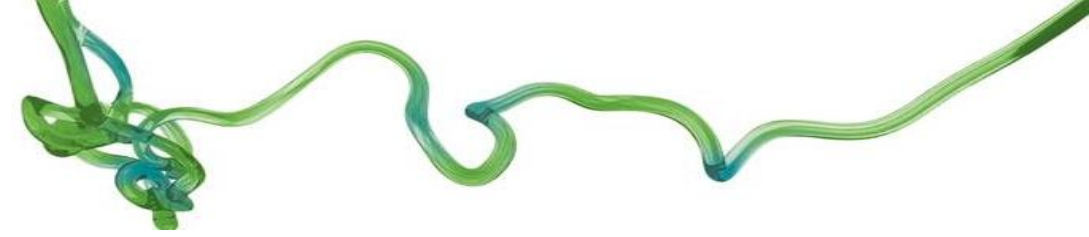
- Design space

- Control parameters

- Control Strategy



# Conclusions



# Conclusions

## Quality by Design

Structural

Transparent

Product and  
Process  
understanding

Product and  
Process Quality

Continuous  
improvements

Benefits for  
sponsor and CMO

DSM Biologics:  
Experienced partner  
Audited by regulatory  
agencies

- Short timelines
- Delivery-on-time
- Cost effective
- Validation
- Meeting the demand
- Security of supply over the product life time



THANK YOU