

Optimise time and resource utilisation through effective contracting of a third party

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Outline of my presentation

- ◆ Stages in the development, licensing and modification of a licensed biological product
- ◆ Typical characteristics of these stages
- ◆ Points to consider for choosing the right CDO or CMO
- ◆ Improving the interaction between sponsor and contractor



Time to market and financial consequences

	<u>Years</u>	<u>Cost (M\$)</u>
◆ Research phase	2.4	4.9
◆ Process development	2.0	16.1
◆ Preparation of experimental products	2.2	17
◆ Upscaling and manufacturing	2.1	20
◆ Registration and launch	<u>1.3</u>	<u>3</u>
	10.0	61

from: Struck (1996) and Gregersen (1997)



Research phase

- ◆ Definition active component
- ◆ Product (= active component) characterisation
- ◆ Pre-formulation
- ◆ Development cell line
- ◆ Characterisation cell line
- ◆ Regulatory and quality issues



Process Development

- ◆ Process development
- ◆ Formulation
- ◆ Analyses
- ◆ Stability
- ◆ Pre-clinical studies
- ◆ Regulatory and quality issues



Preparation of experimental products for clinical evaluation

- ◆ Pilot scale production
- ◆ Formulation
- ◆ Analyses
- ◆ Stability
- ◆ Material for phase I and II trials
- ◆ Regulatory and quality issues



Upscaling Production Process

- ◆ Scaling up production process
- ◆ Analyses
- ◆ Stability
- ◆ Technology transfer to production department
- ◆ Quality issues



Manufacture at the ultimate production scale

- ◆ Full scale production
- ◆ Process validation
- ◆ Analyses
- ◆ Stability
- ◆ Material for phase III trial
- ◆ EU: MAA
US : PLA (NDA)

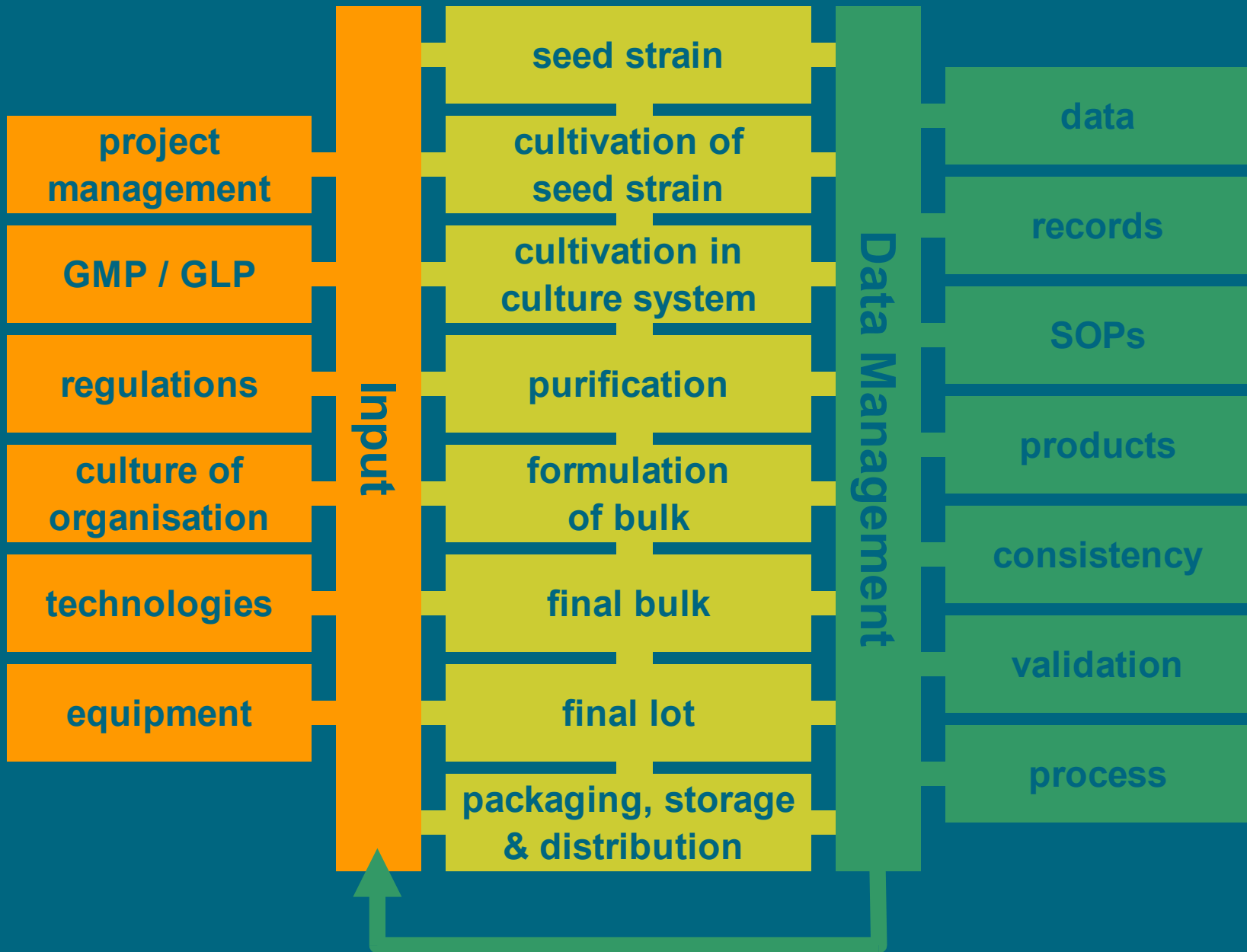


'Modification' of a licensed process

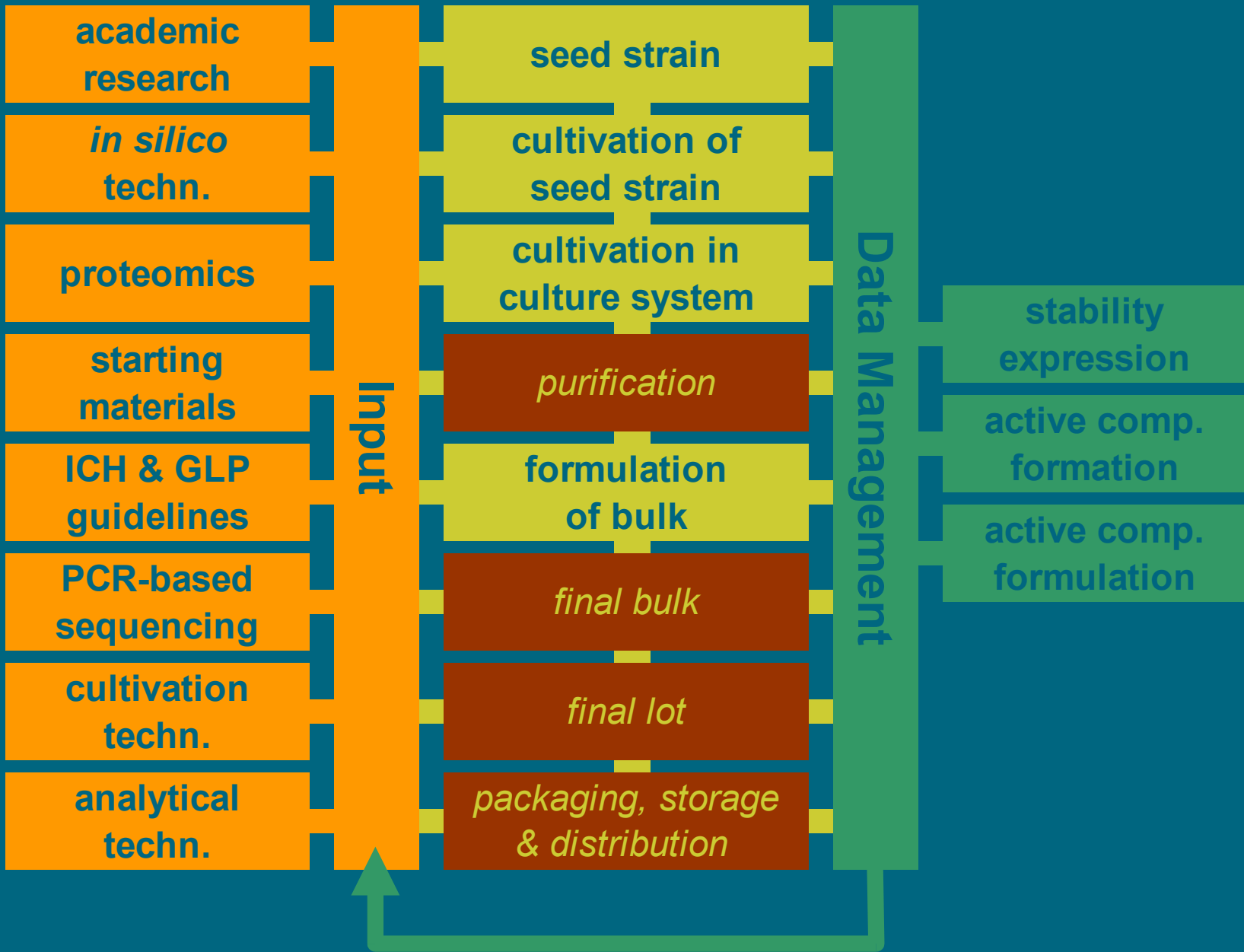
- ◆ Establish comparability of the product manufactured by the licensed and the new process
- ◆ Regulatory and quality issues _



General Process



Research Phase:



Research Phase

Regulatory issues:

- ◆ GLP: CFR title 21; part 58

- ◆ ICH guidelines

 - seed strain: Q5B

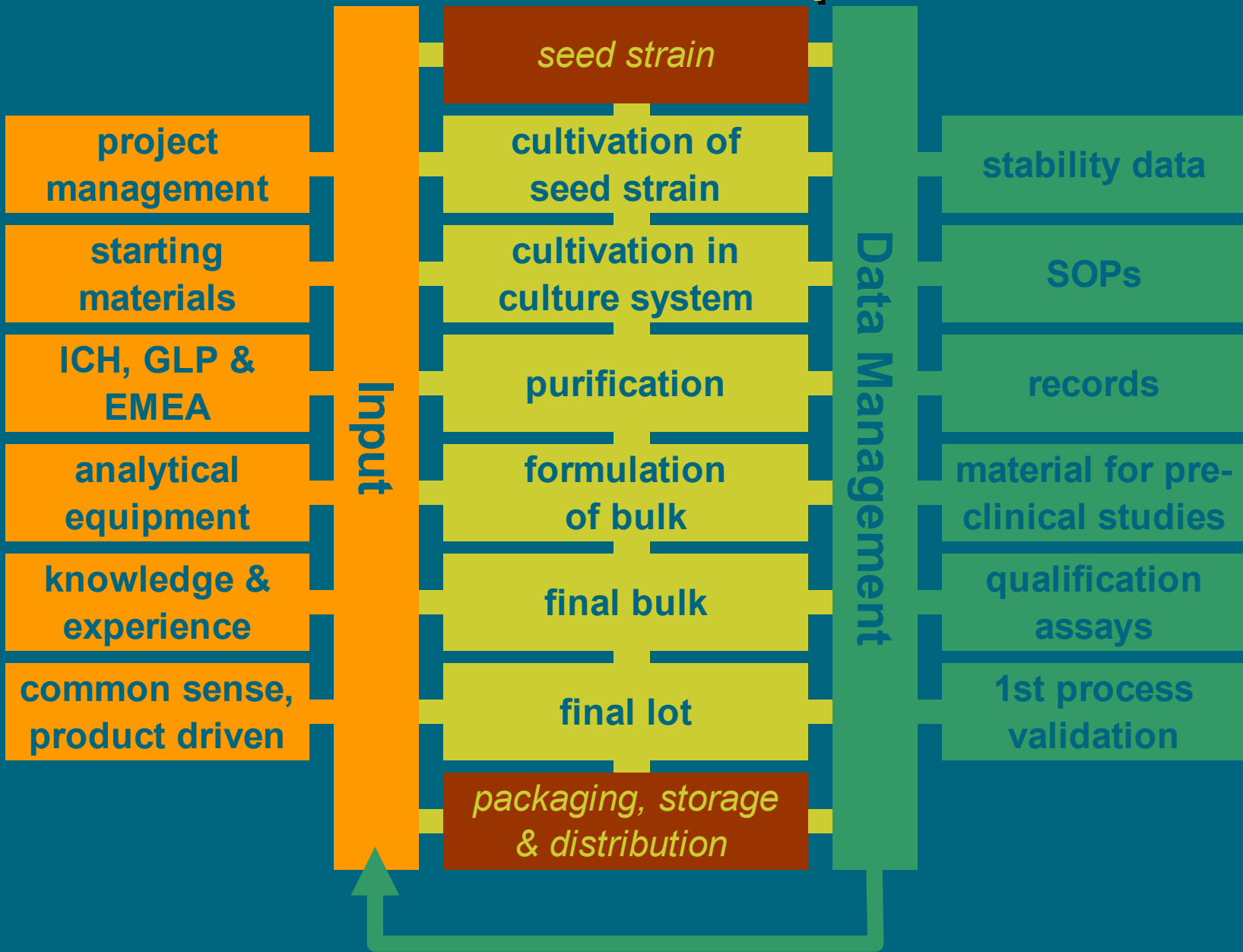
 - cultivation of seed strain: Q5B; Q5D

 - cultivation in cult. System: Q5B; Q5D

 - formulation of bulk: Q2B; Q5D; Q6B



Process Development:



Process Development

Regulatory issues:

◆ GLP: CRF title 21; part 58

◆ EMEA: CPMP/QWP/155/96

CPMP/BWP/4310/00

◆ ICH guidelines

cultivation in cult. System: Q5D

purification: Q5C; Q6B

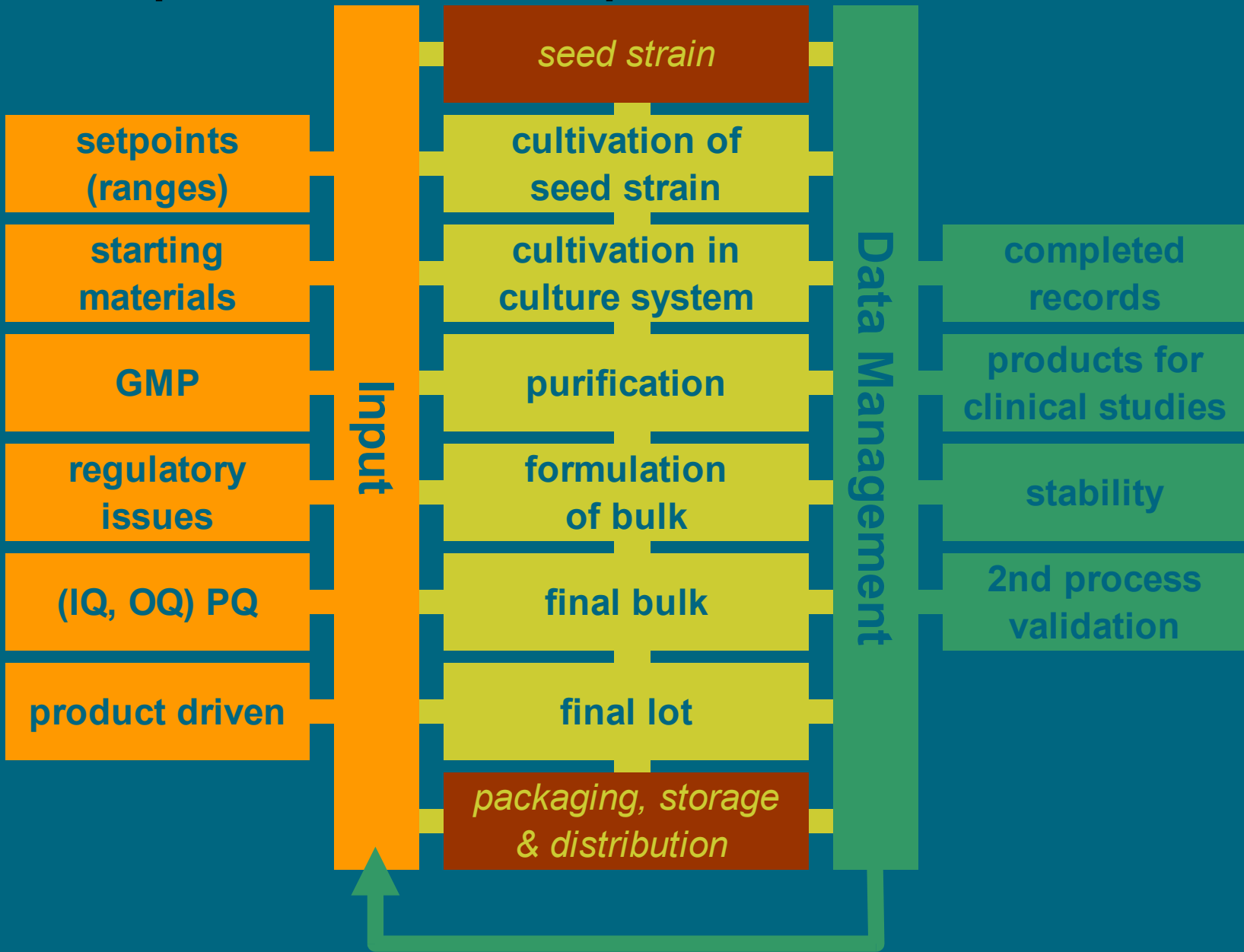
formulation bulk: Q2A/B; Q5C; Q6B

final bulk: Q2A/B; Q5C; Q6B

final lot: Q2A/B; Q5C; Q6B



Preparation of Experimental Products:



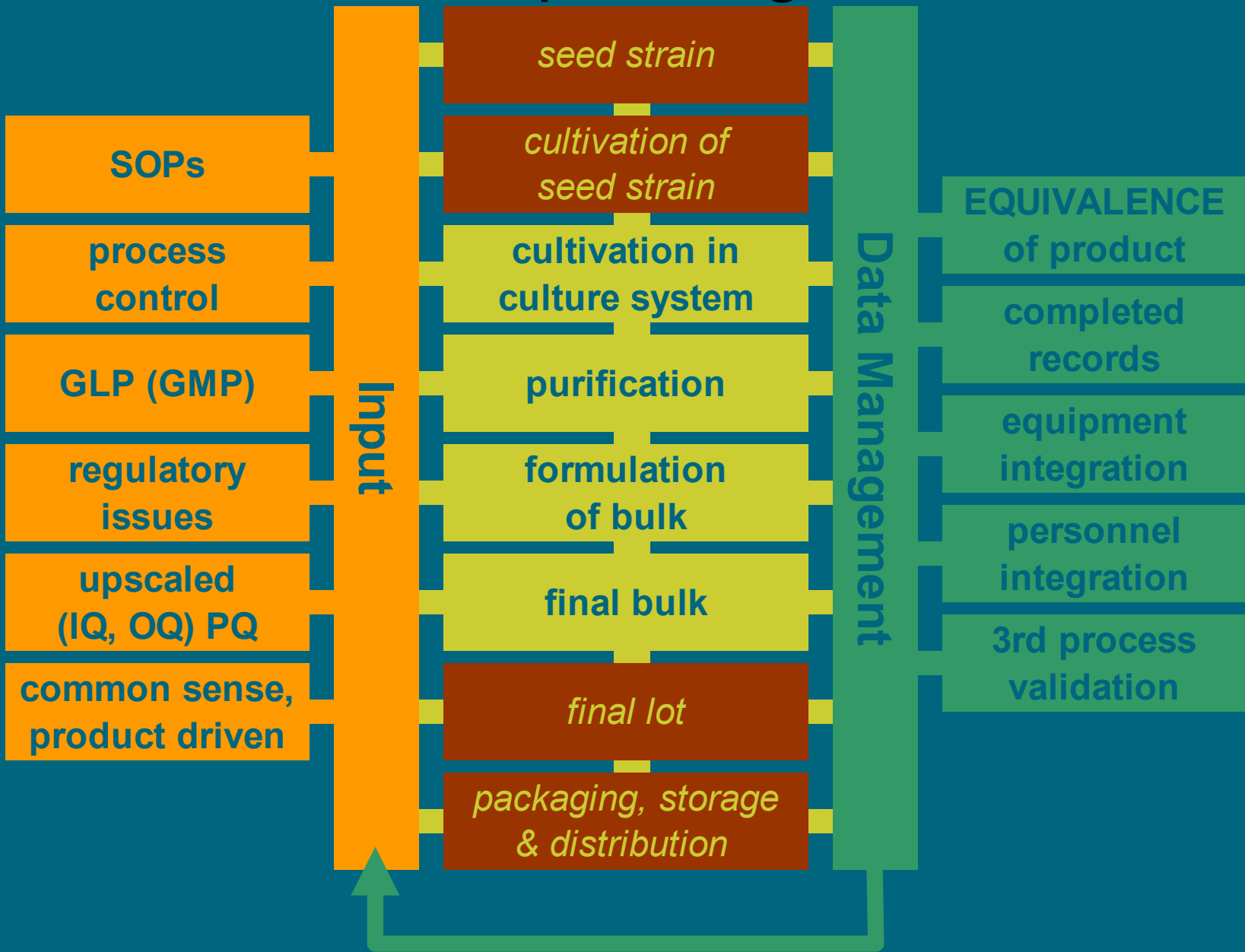
Preparation of Experimental Products

Regulatory issues

- ◆ GMP: Eudralex vol. 4; annex 13
- ◆ EU: Clinical trial directives 2001/20/EC
- ◆ US: CFR title 21; part 312 (IND)
- ◆ ICH guidelines
 - purification Q5A
 - formulation of bulk Q5C; Q6B
 - final bulk Q5C; Q6B
 - final lot Q5C; Q6B



Upscaling:



Upscaling

Regulatory issues

- ◆ GLP: CRF title 21; part 58

- ◆ ICH guidelines

 - formulation of bulk

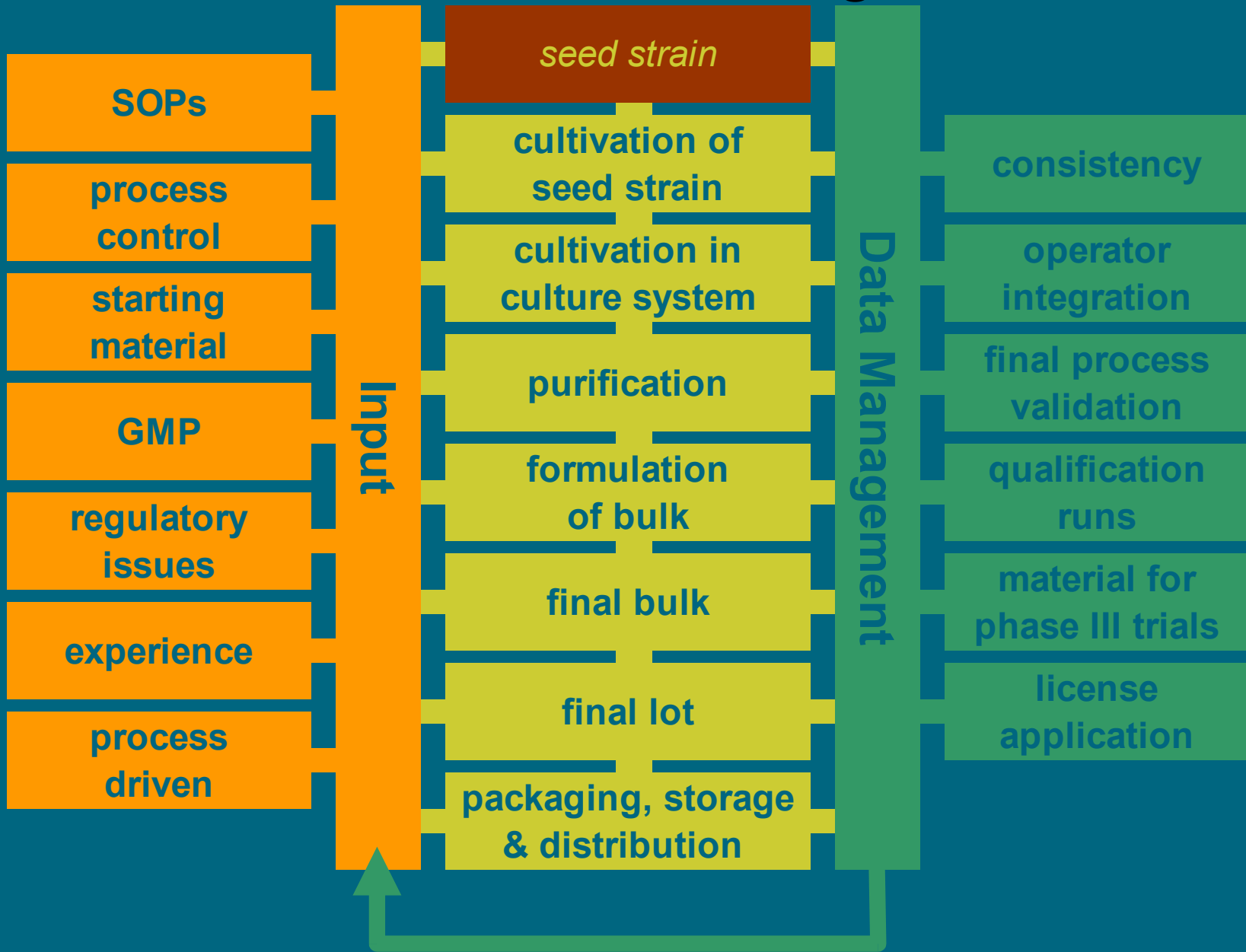
Q5C; Q6B

 - final bulk

Q5C; Q6B



Manufacturing:



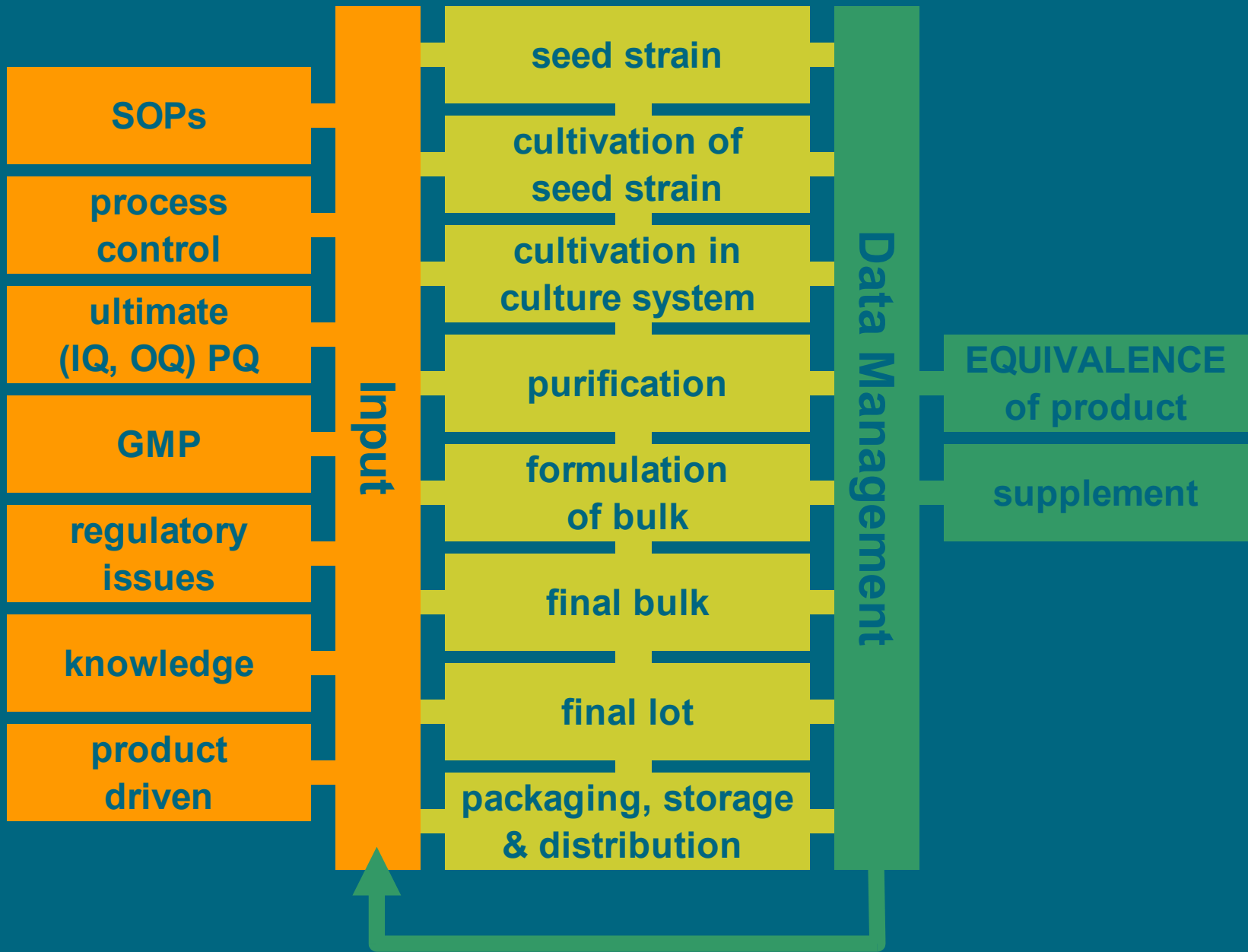
Manufacturing

Regulatory issues

- ◆ GMP: Eudralex vol. 4; annex 13
- ◆ EU: Eudralex volume 1
- ◆ US: CFR title 21; part 601
- ◆ ICH guidelines
 - purification Q5A
 - formulation of bulk Q5C; Q6B
 - final bulk Q5C; Q6B
 - final lot Q5C; Q6B



Modification of Licensed Product:



Modification of Licensed Product

Regulatory issues

- ◆ GMP: Eudralex vol. 4; annex 13
- ◆ EU: Eudralex vol. 2A; chapter 5
CPMP/BWP/3207/00
- ◆ US: CFR title 21; part 601.12
- ◆ ICH guidelines
 - seed strain Q5B
 - cultivation of seed strain Q5B; Q5D
 - cultivation in cult. system Q5D
 - purification Q5A
 - formulation of bulk Q5C; Q6B
 - final bulk & final lot Q5C; Q6B



Terms for outsourcing

- ◆ Research Phase *Academia?*
- ◆ Process Development PDO/niche player
- ◆ Preparation of experimental products CMO/niche player
- ◆ Upscaling PDO or CMO/niche player
- ◆ Manufacturing CMO
- ◆ Modification of Licensed Product CMO



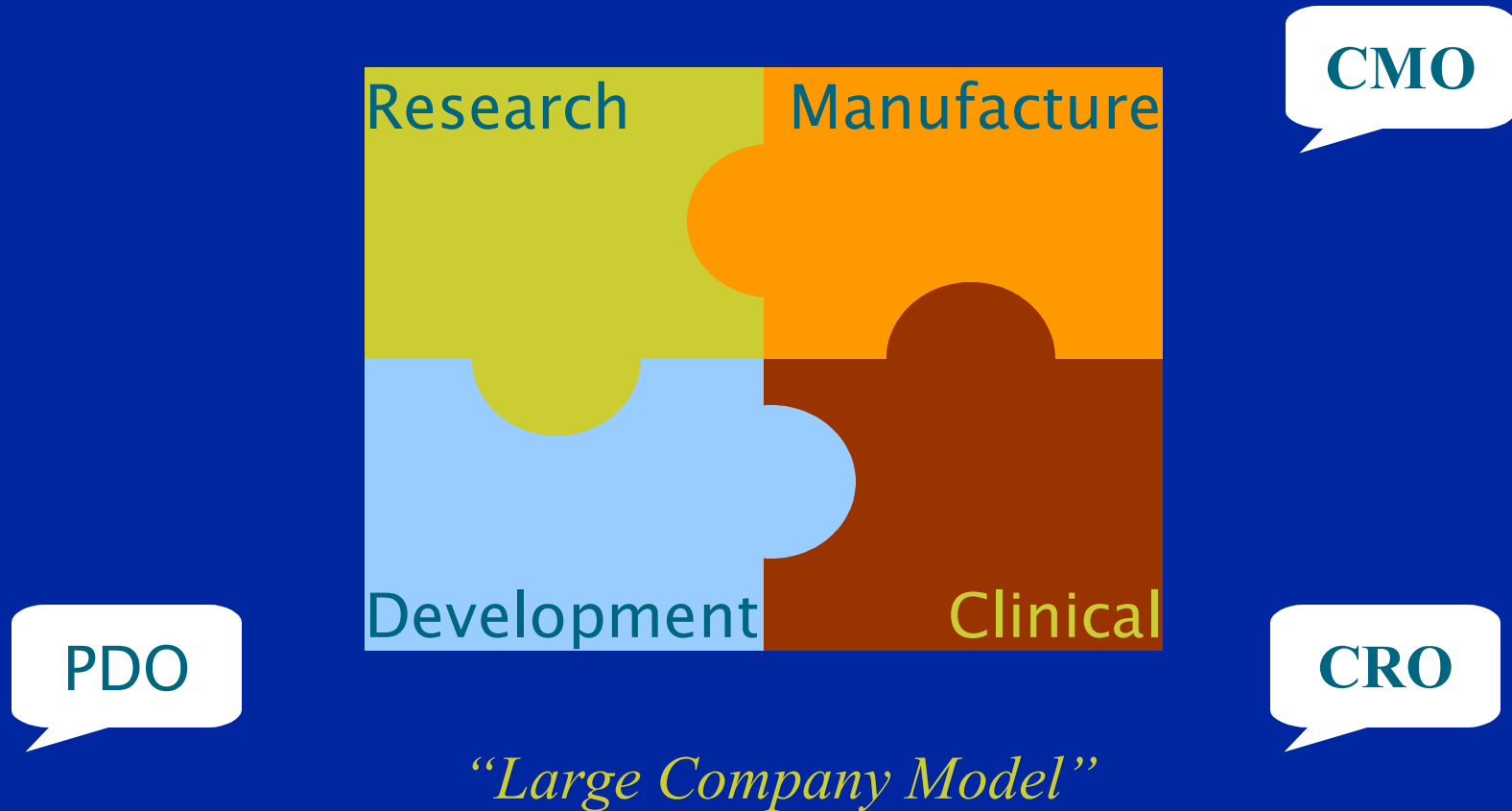
Changing world

- ◆ Genomics; proteomics (biologics)
- ◆ Combinational chemistry (drugs)
- ◆ Mergers, changing priorities, competition
- ◆ Development of new drug delivery systems
- ◆ Emergence of virtual pharmaceutical companies

*“Optimise time and resource utilisation
for cost reduction”*



Creating a New Biological



Creating a New Biological - Outsourcing



“Small Company Model”



Creating a New Biological - Outsourcing

Academia?

CMO

Research

Manufacture

Development

Clinical

PDO

CRO

“Virtual Company Model”



Three types of PDOs and CMOs

- ◆ Dedicated contractor
- ◆ Excess capacity contractor
- ◆ Drug delivery company (*niche player*)



Outline of a request for a quotation

- ◆ Introduction
- ◆ Manufacturing volumes and schedule
- ◆ Manufacturing requirements
- ◆ Quality control requirements
- ◆ Validation requirements
- ◆ Stability
- ◆ Supplied to the contractor
- ◆ Appendix

from: Klein (2001)



Stages of contract manufacturing partnerships

- ◆ Linkage
- ◆ Negotiation
- ◆ Development
- ◆ Implementation
- ◆ Maintenance
- ◆ Disengagement

from: Messing (2000)



Evaluating Potential CMOs (1)

Credibility

- ◆ Company history & track record
- ◆ Operations
- ◆ Personnel

Capability

- ◆ Facilities
- ◆ Equipment
- ◆ Deliverables

from: Jawadekar (2001)



Evaluating Potential CMOs (2)

Capacity

- ◆ Facility and equipment
- ◆ Personnel

Cost

- ◆ Project/Personnel
- ◆ Benchmarking

from: Jawadekar (2001)



Should you one-stop shop ?

- ◆ Process development, formulation, pilot scale production, control and packaging
- ◆ Upscaling, manufacture at the ultimate scale including final lot, control and packaging
- ◆ Pilot scale production, control and clinical testing

Advantage: speed the development process,
reduce the need for in house process development
and facilitate regulatory activities

from: Miller (1999)



Major ingredients for the goal of the sponsor

- ◆ Assemble a core team
- ◆ Collaborate
- ◆ Clarify expectations
- ◆ Create a proposal
- ◆ Select project managers
- ◆ Facilitate open communication
- ◆ Stay on tracks
- ◆ Enjoy the rewards

from: Baltezor et al. (2001)



Trust: the secret of success for PDOs and CMOs

- ◆ Seamless relationship
- ◆ Communication
- ◆ Communication failures
- ◆ Warning signs
- ◆ The evolving sponsor-contractor relationship

from: Vardzal (2000)



Data Management - Technology Transfer

- ◆ Central Database for
 - ◆ Research
 - ◆ Process Development
 - ◆ Preparation of Experimental Products
 - ◆ Upscaling & Manufacturing
 - ◆ Registration & Launch
 - ◆ Modification of Licensed Product
- ◆ Linking
 - ◆ Batches
 - ◆ Experiments
 - ◆ Materials
 - ◆ Products



Data Management - Technology Transfer

- ◆ Storing
 - ◆ All Relevant Data
 - ◆ Records
 - ◆ Documents
 - ◆ SOPs
 - ◆ Guidelines
- ◆ Safety
 - ◆ Various Levels of Authorisation
 - ◆ Electronic signatures for Data, Documents and Complete Activities
 - ◆ Automated Backup Procedures



Data Management - EDNA

The screenshot displays the EDNA software interface. On the left is a hierarchical tree structure. The main window contains a table with the following columns: ID, Name, Date, and Description. Below this table is a detailed view of a selected record, showing fields for Document ID, Name, Author, and Date.

ID	Name	Date	Description
290000	W. J. J. J. J.	2000-09-01	Prevalence of... (text truncated)
290001	W. J. J. J. J.	2000-09-01	Prevalence of... (text truncated)
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Document ID	Name	Author	Date
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290001_01_02	W. J. J. J. J.	W. J. J. J. J.	2000-09-01
290001_01_03	W. J. J. J. J.	W. J. J. J. J.	2000-09-01

Activities

Categories

Data, Records & Documents



Data Management - EDNA

- ◆ All Necessary Tools for Data Management
- ◆ Extended Search Capabilities
- ◆ Encrypted Documents
- ◆ Use of several Remote Databases (*outsourcing*)



- ◆ Product of Nephaso: www.nephaso.com



Conclusions

- ◆ Outsourcing is a fact
- ◆ Realise and accept the advantages of outsourcing
- ◆ Clear objectives and good data management are the major ingredients for success of outsourcing



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