Pharmaceutical Development

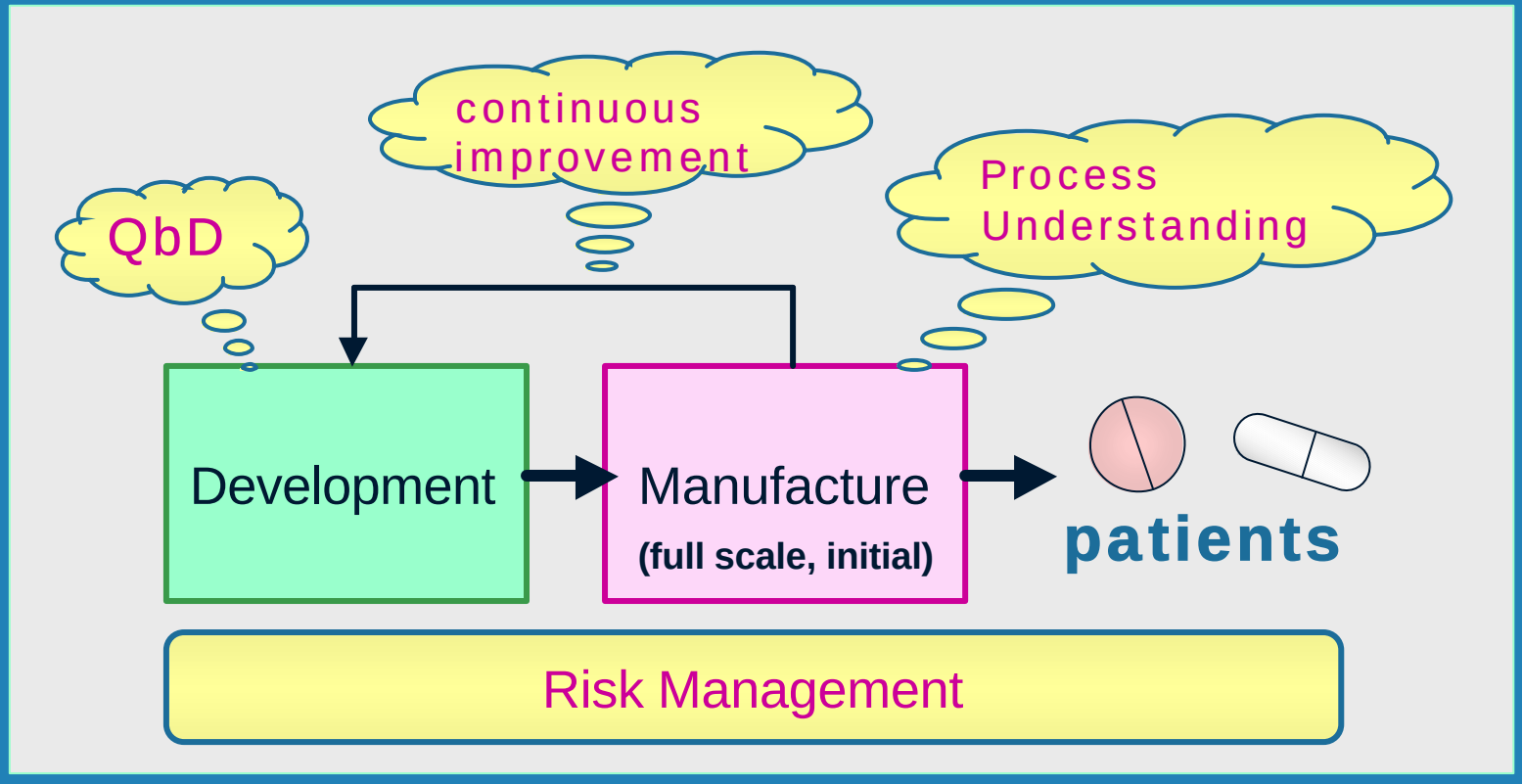
- Japanese Industry's Perspectives -

Akira Kato

Formulation Research Labs
Eisai Co., Ltd.

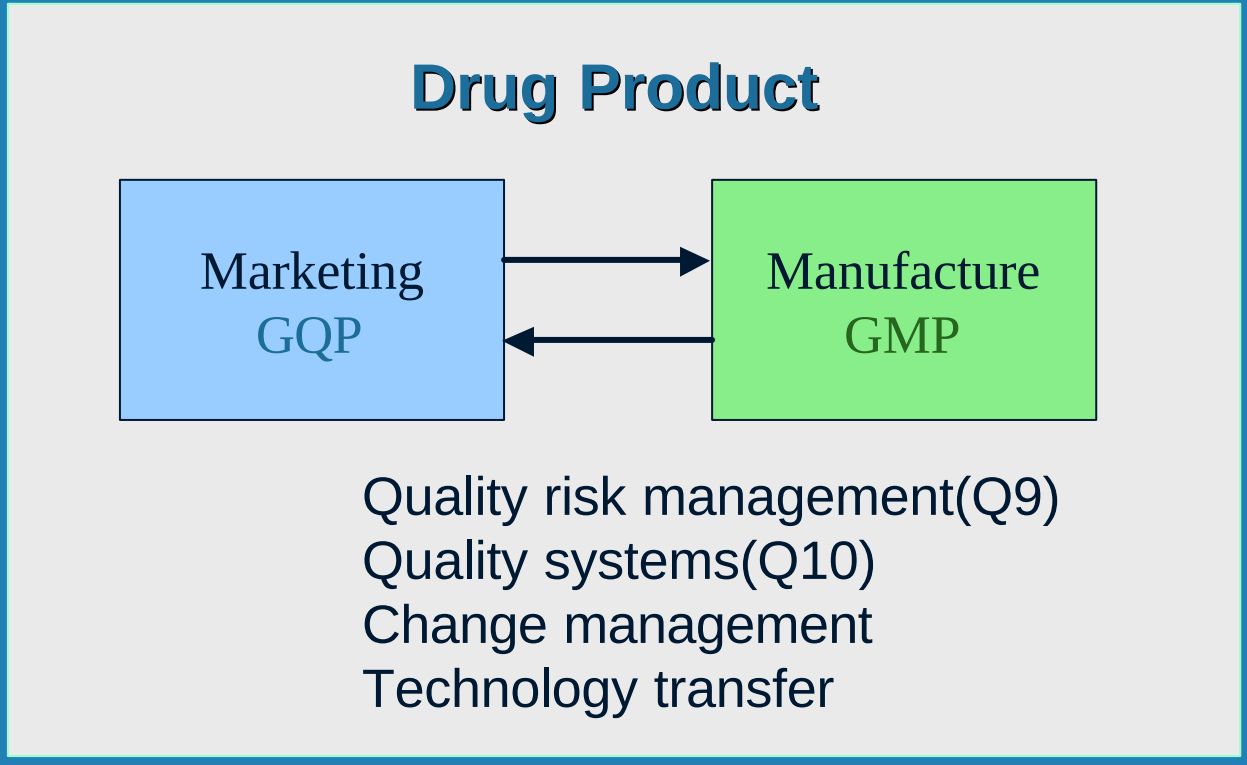
Desired State after Change of Law

1. to supply very high quality product



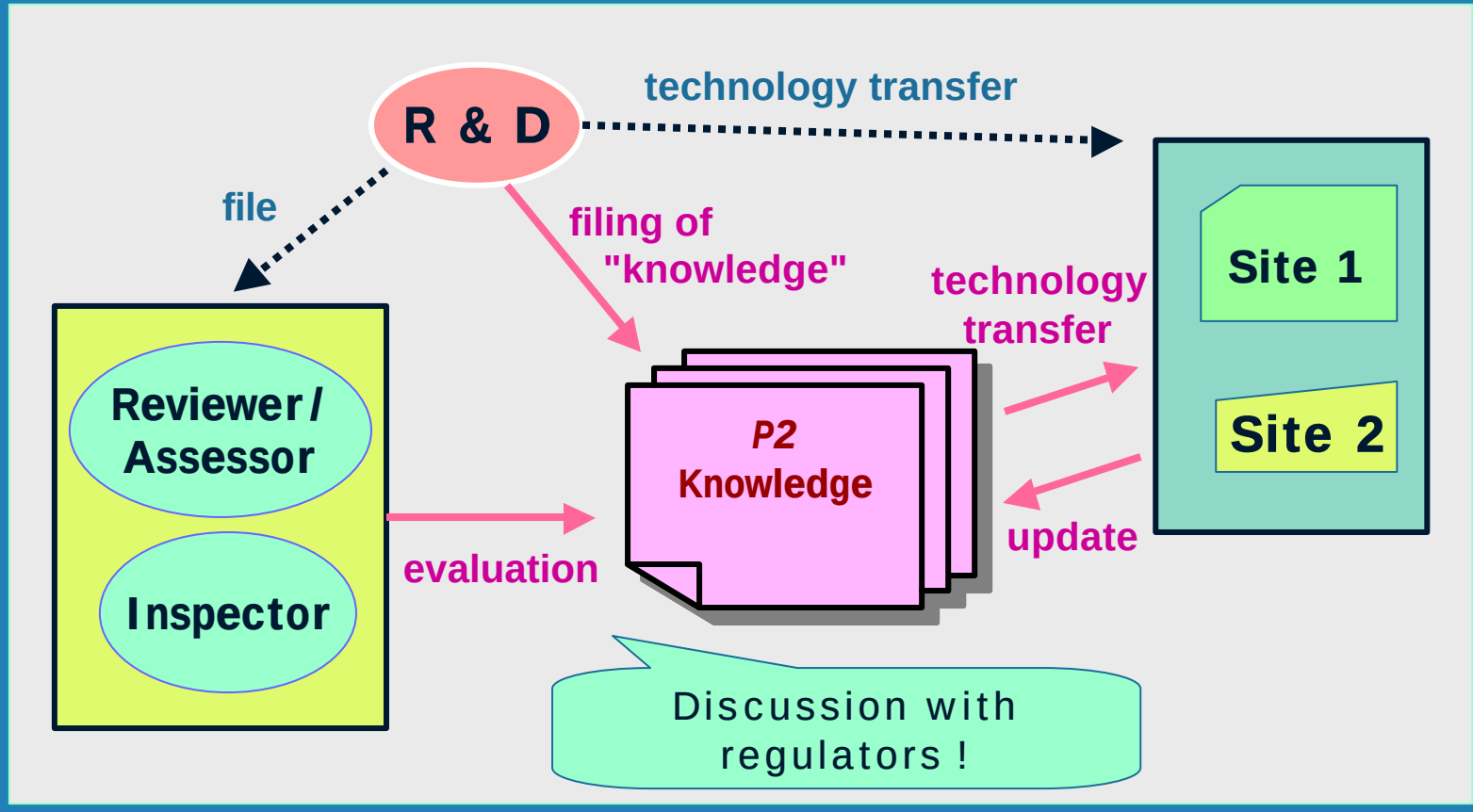
Desired State

2. to establish quality system

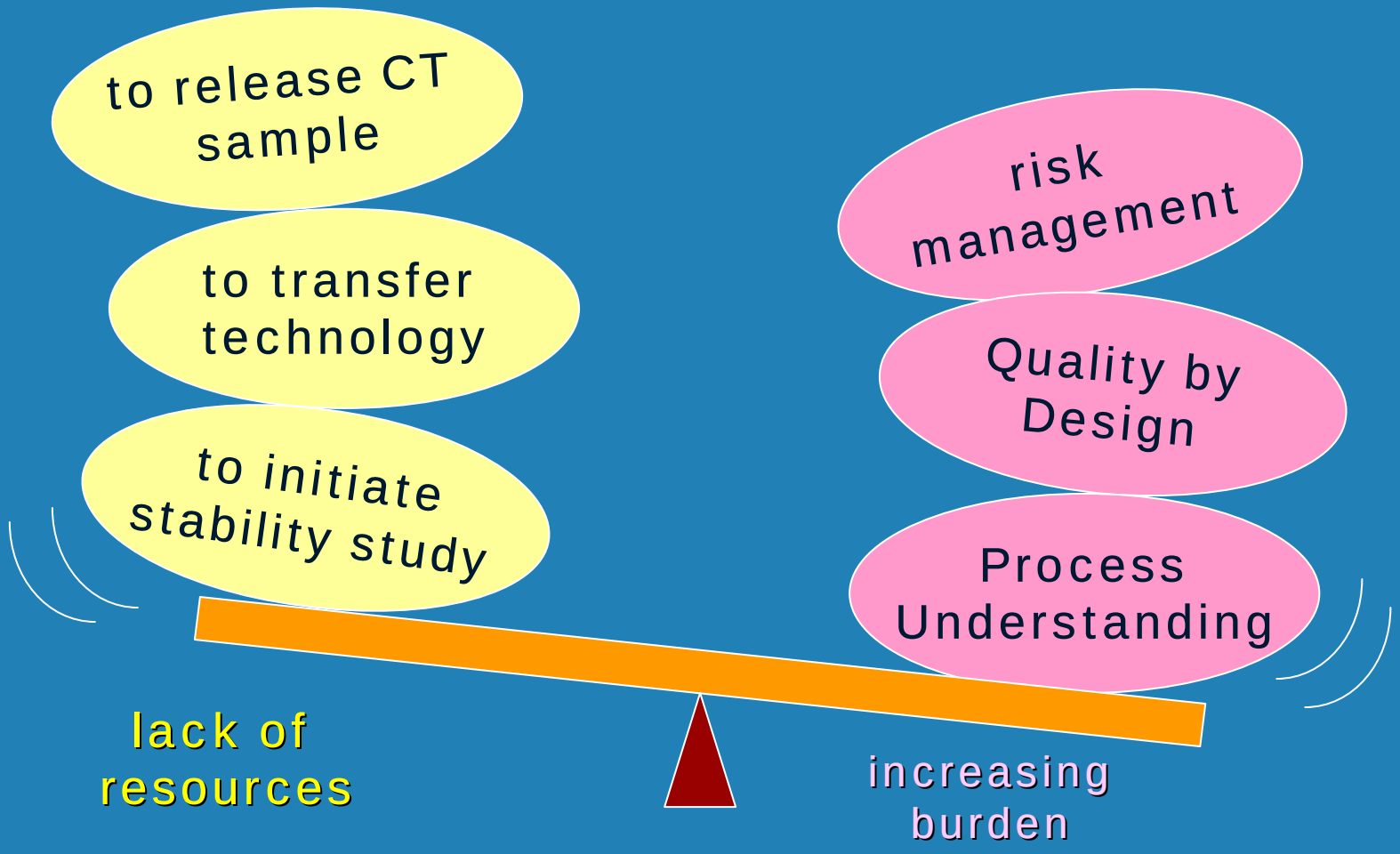


Desired State

3. to share more information



Formulator's Dilemma



Important Process

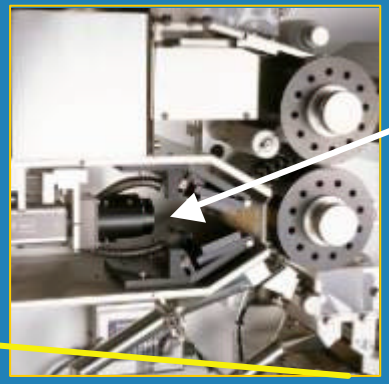
1. to focus on Critical Risks
2. to manage Risks
3. to translate into Knowledge
4. to conduct Risk Communication
   eg. tolerable level

Points to Consider

1. "Quality"
   - "Quality" and Technology
2. Standard formulation and QbD
   - Expert System
3. Optional vs Mandatory
   - BA/BE during development

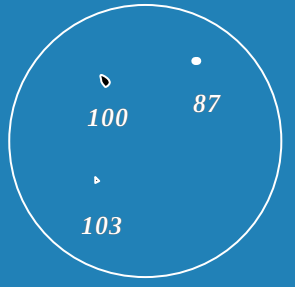
1. "Quality" (cosmetic issue)

Video-monitoring

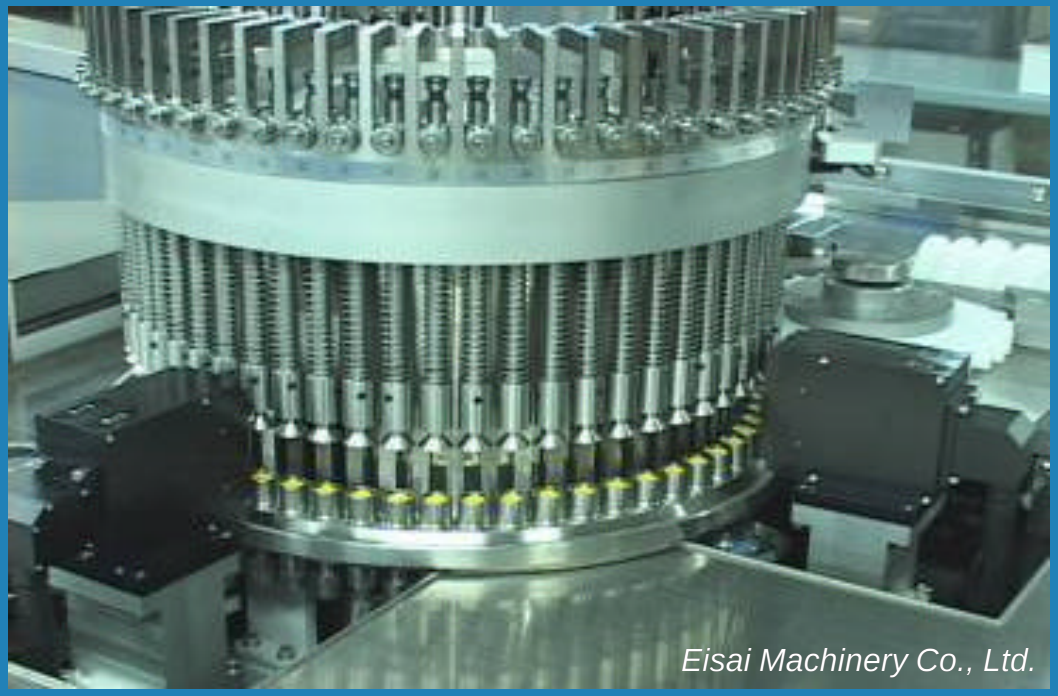


sensor camera

image

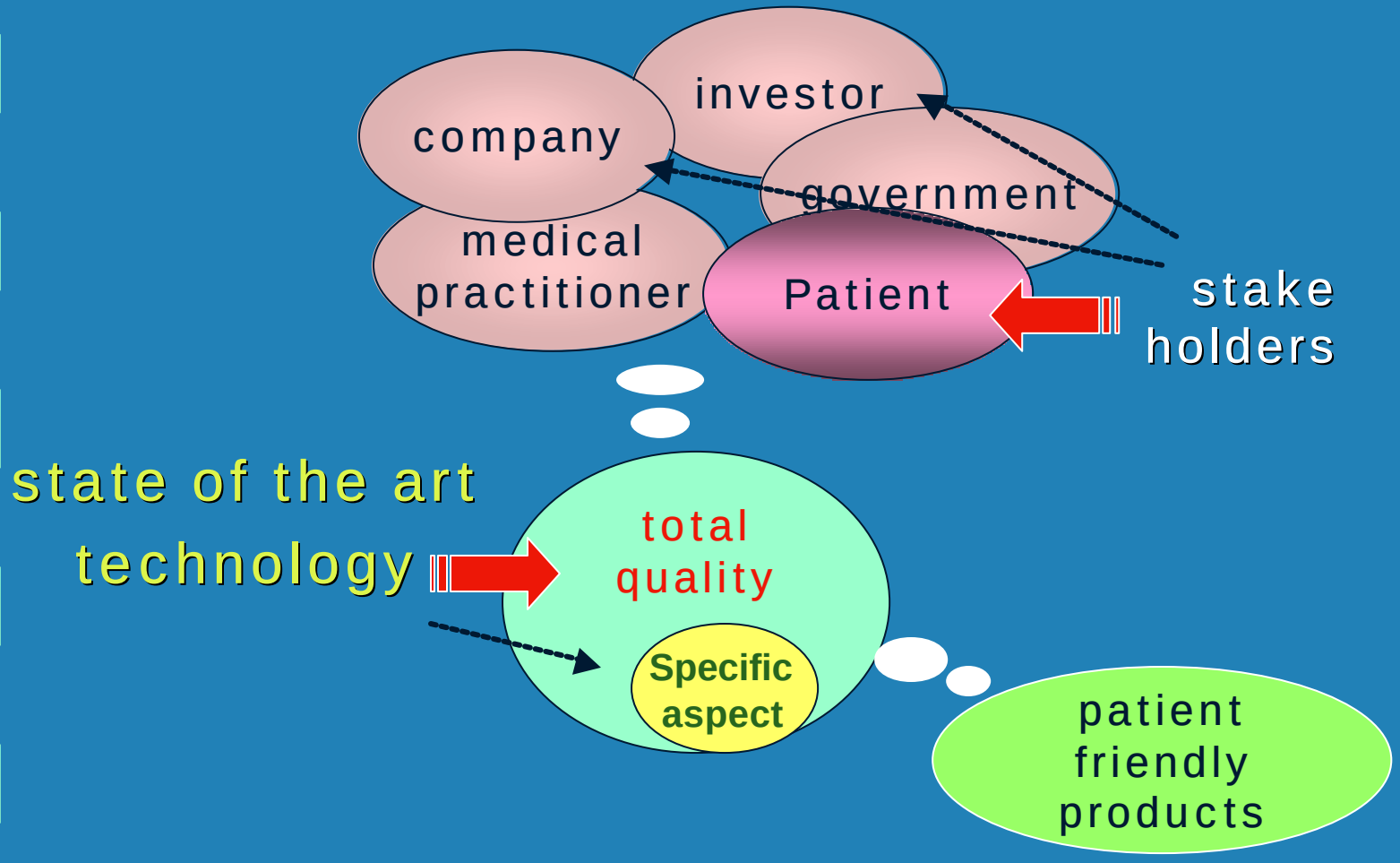


"Quality" (cosmetic issue)



Vial / ampoule inspection machine

Technology of the Future



2. Standard formulation and QbD

1. Computer aided formulation development

Microsoft Access for Windows

2. for IR tablet through fluid bed granulation

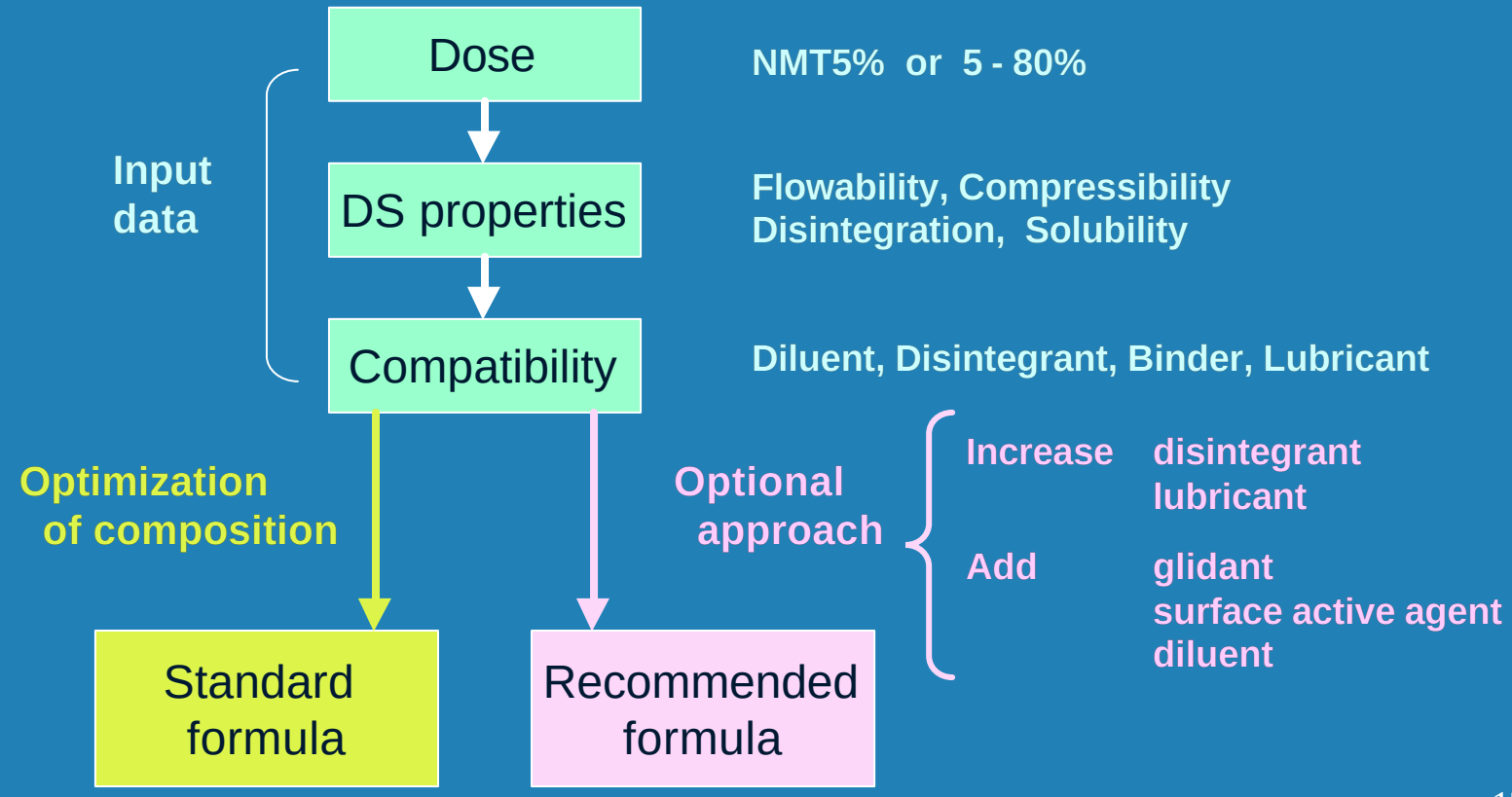
Japanese formulator's preference

3. Collaboration with University

Professor Hashida, Kyoto Univ. (leader)

Scientists of 13 Japanese Pharmaceutical Companies

Decision Tree



Output

Name	A		B	
Formulation	**Ingredient**	**mg/Tablet**	**Ingredient**	**mg/Tablet**
API	A	100 (50%)	B	100 (50%)
Diluent 1	Lactose	2 (1%)	Lactose	23 (11.5%)
Diluent 2	MCC	40 (20%)		
Disintegrant (Intra)	Corn Starch	40 (20%)	Corn Starch	60 (30%)
Disintegrant (Inter)	Corn Starch	10 (5%)	CMC Ca	10 (5%)
Binder	HPC	6 (3%)	HPC	6 (3%)
Lubricant	St-Mg	2 (1%)	St-Mg	1 (0.5%)
Others				
Total Weight		200		200
FB Granulator, Batch Size	FD-5S, 3.76kg		MP-01, 1kg	
Spray Rate	69g/min		14g/min	
Granule Density (Tapped, Loose)	0.50, 0.54		0.413, 0.529	
Angle of Repose (°)	34		38	
Particle Size Distribution (%) +30/+50/+70/+100/ 140/200/-200	0.8/12.6/28.0/24.8/ 16.8/7.2/9.8		0.4/9.2/16.9/12.9/ 23.6/17.1/19.8	
Tablet	Correct 12HUK, 2 kg		Correct 12HUK, 5 kg	
Tooling	8.0mm (Convex), x6		8.0mm (Convex), x12	
Hardness	6.5 kg		6.2 kg	
Friability	0.14%		0.10%	
Weight (CV%)	0.51%		0.90%	
Capping	No		No	
Disintegration (min)	6.6		5.5	
Dissolution (Test Media)	10':48, 20':89, 30':98 (Water)		15': 90, 30':100 (Water)	

structured approach?

3. BE vs 'Assessing BE'

BA/BE during development

- BE is to assure therapeutic equivalence. but BA/BE guidelines say BE study is necessary even before establishing efficacy and safety,

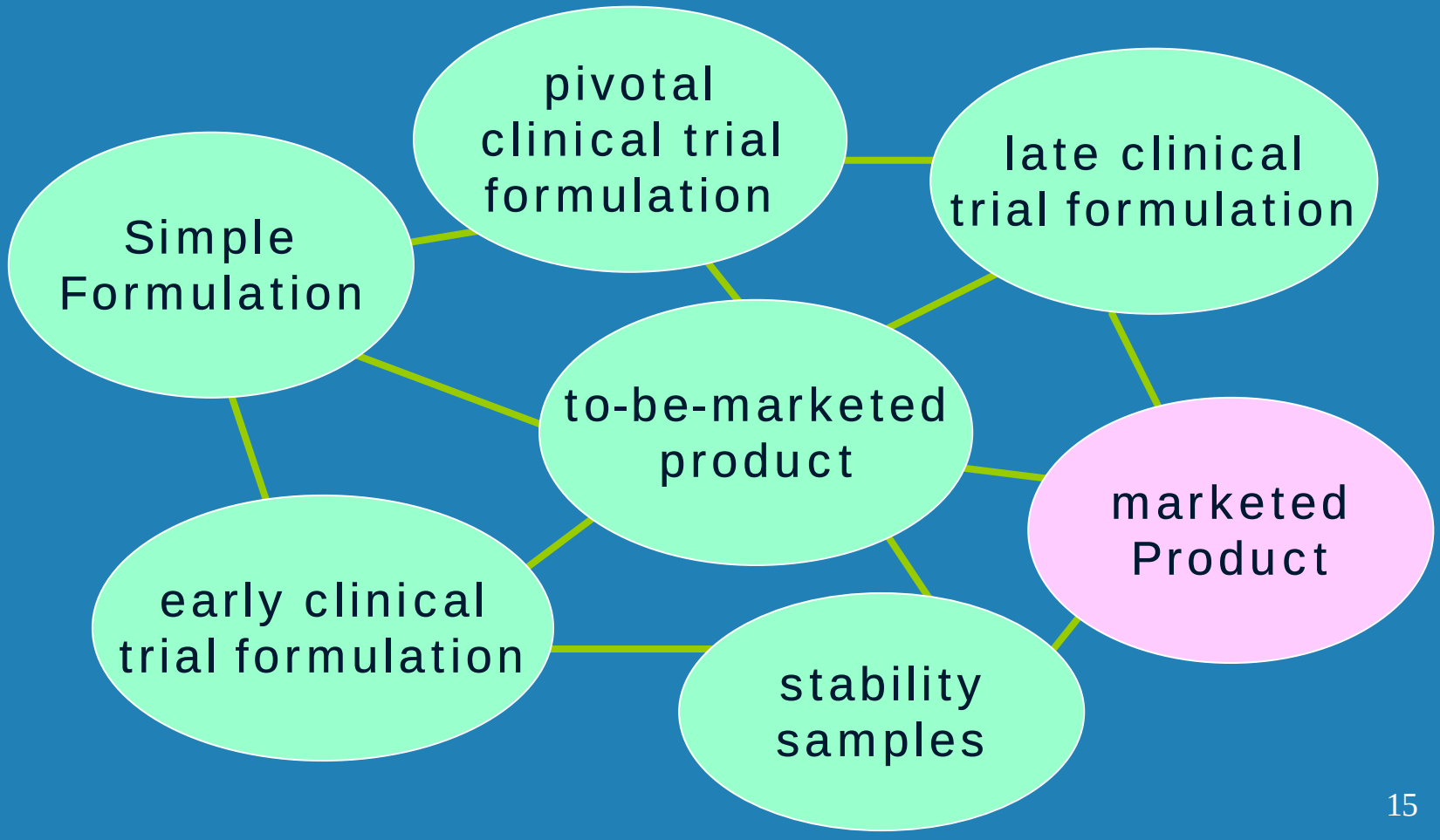
  leading to regulatory uncertainty.

- active working group in JPMA
- presentation of idea

  Proposal of assessing BE procedures during drug development;

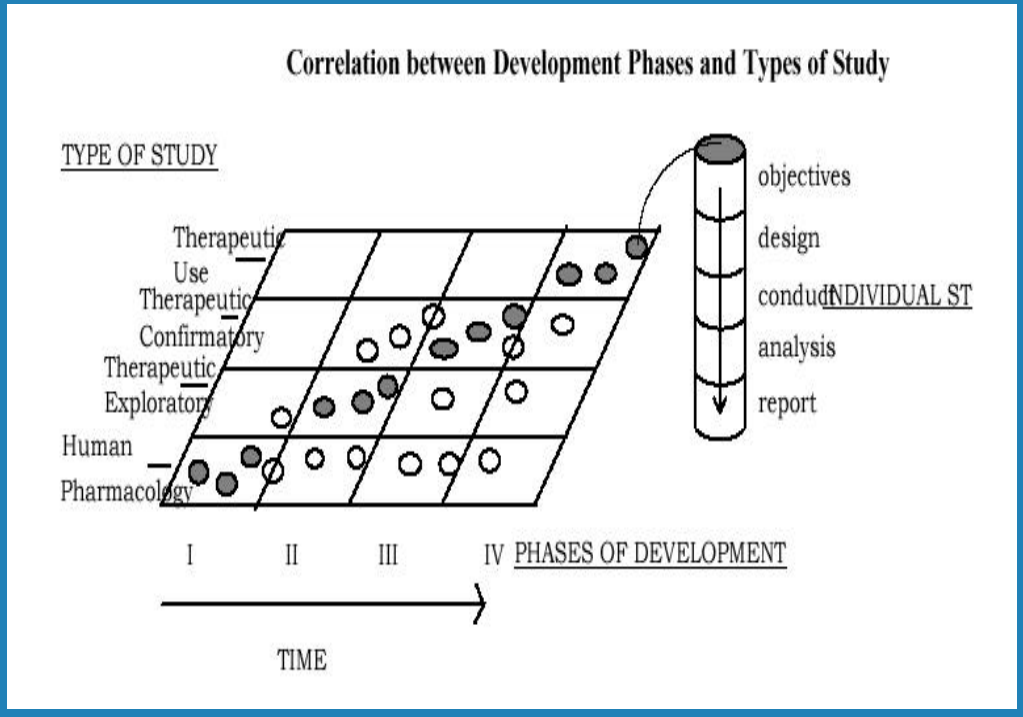
  Pharmaceutical Quality Forum: 1st Symposium

Formulations during Development



Changes during development

Proposed procedures to link formulations



Before dose finding

→ Dissolution and/or BA

Before Phase III

→ BA comparison study

During and after Phase III

→ BE study

ICH E8 "General Considerations for Clinical Trials"
3.1.3 Phases of Clinical Development

Q8 ICH process

- Nov 2004 — Step 2 : Q8 draft
- 1Q 2005 — Translation
- 1～2Q 2005 — Public Comment
  (Your input is crucial.)
- 2Q 2005 — ICH Brussels meeting