

제약산업의 품질관리 시스템 최근 동향

Trend of Quality System



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- 의약품 개발
- 품질 위험 관리
- 의약품 품질관리 시스템

3. 사례 연구 (Case Studies)

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1. 개요 (Introduction)

- **의약품 품질의 목적**

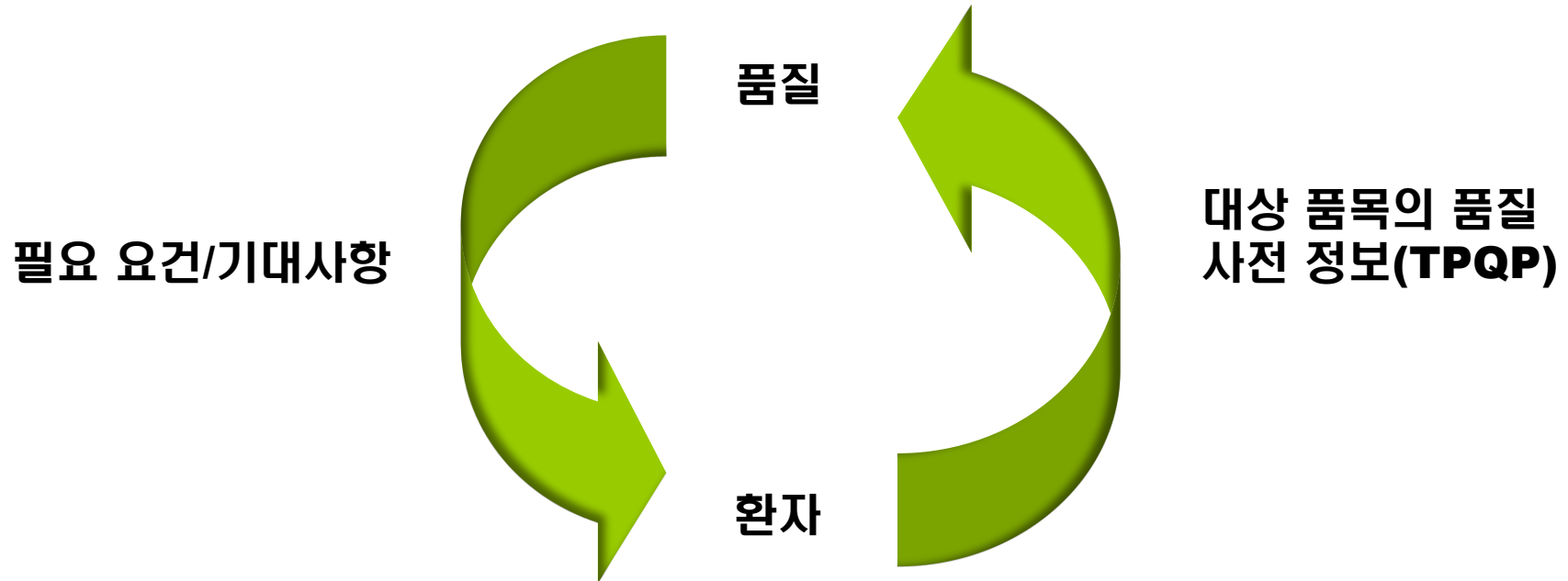
(Objectives of Pharmaceutical Quality)

- **의약품 품질 관리의 목표 (Desired states)**
- **ICH-Q series**



1. 개요 (Introduction)

의약품 품질의 목적



“Pharmaceutical quality란 환자에 대해 기대하는 약효를 나타내지 못하고, 위해 상황이 발생할 수 있는 위험(Risk)를 허용할 수 있는 정도로 관리하는 것을 의미한다.”

1. 개요 (Introduction)

의약품 품질관리의 목표 (Desired States)

- Pharmaceutical Quality의 바람직한 단계 또는 수준은 효과적인 제조 공정 설계를 통해 제품 품질이 확보되어야 한다
- 제품의 기준은 처방 및 공정의 요인들이 제품에 어떤 영향을 미치는가에 대한 충분한 이해를 토대로 설정되어야 한다
- *이렇게 확립된 품질관리 시스템은 지속적인 개선이 수행되고 실시간으로 품질을 보증할 수 있도록 하여야 한다.

FDA PAT Guideline

1. 개요 (Introduction)

ICH-Q series

- Q 1 – 안정성 시험 (Stability Testing)
- Q 2 – 시험법 밸리데이션 (Analytical Validation)
- Q 3 – 순도 (Impurities)
- Q 4 – 공정서 (Pharmacopoeias)
- Q 5 – 생물학적 제제 (Biotechnological Products)
- Q 6 – 시험 기준 (Specifications)
- Q 7 – 의약품 제조 관리 (Good Manufacturing Practice)
- Q 8 – 의약품 개발 (Pharmaceutical Development)**
- Q 9 – 품질 위험 관리 (Quality Risk Management)**
- Q 10 – 의약품 품질 시스템 (Pharmaceutical Quality System)**
- Q 11- 주성분 원료의 개발 및 제조**
(Development and Manufacture of Drug Substances)

**Just concept
paper**

2. 품질 관련 최근 지침 (Recent Quality Guidance)

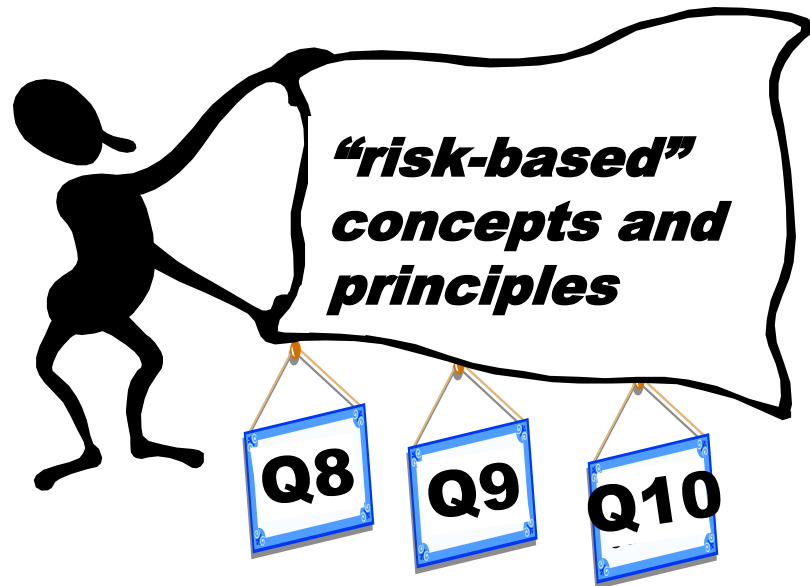
- 패러다임의 변화 (The New paradigm)
- 의약품 개발 (Pharmaceutical Development)
- 품질 위험 관리 (Quality Risk Management-QRM)
- 의약품 품질 시스템 (Pharmaceutical Quality System -PQS)



2. 품질관련 최근 지침 (Recent Quality Guidance)

패러다임의 변화 (The new paradigm)

- ICH Q series



의약품 개발 (Q8)

과거 : **Data transfer / Variable output**

현재 : **Knowledge transfer / Science based / Consistent output**

품질 위험 관리 (Q9)

과거 : **Used, however poorly defined**

현재 : **Opportunity to use structured process thinking**

의약품 품질 시스템 (Q10)

과거 : **GMP checklist**

향후 : **Quality Systems across product life cycle**

2. 품질관련 최근 지침 (Recent Quality Guidance)

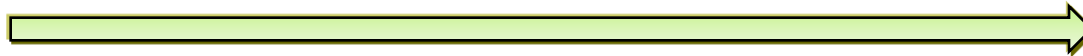
패러다임의 변화 (The new paradigm)

- ICH Q series & Product life cycle

제품 생명 주기



ICH Q8/Q8(R) - Pharmaceutical Development



PAT(Process Analytical Technology Guidance)



ICH Q9 – Quality Risk Management



ICH Q10 – Pharmaceutical Quality Systems



2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 개발 단계 (Pharmaceutical Development)

- Quality by Design (QbD) 정의

위험분석을 포함한 과학적 근거를 바탕으로 해당 제품 및 공정에 대한 충분한 이해를 통해 의약품을 개발하는 접근 방법

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 개발 단계 (Pharmaceutical Development)

Quality by Design의 특징

Current

- 실험적
- 결과 중심
- 회고적
- **Test to document quality**
- 제품 자체를 고려한 기준 설정
- 변동 인자에 대한 이해 미흡

Q8

QbD

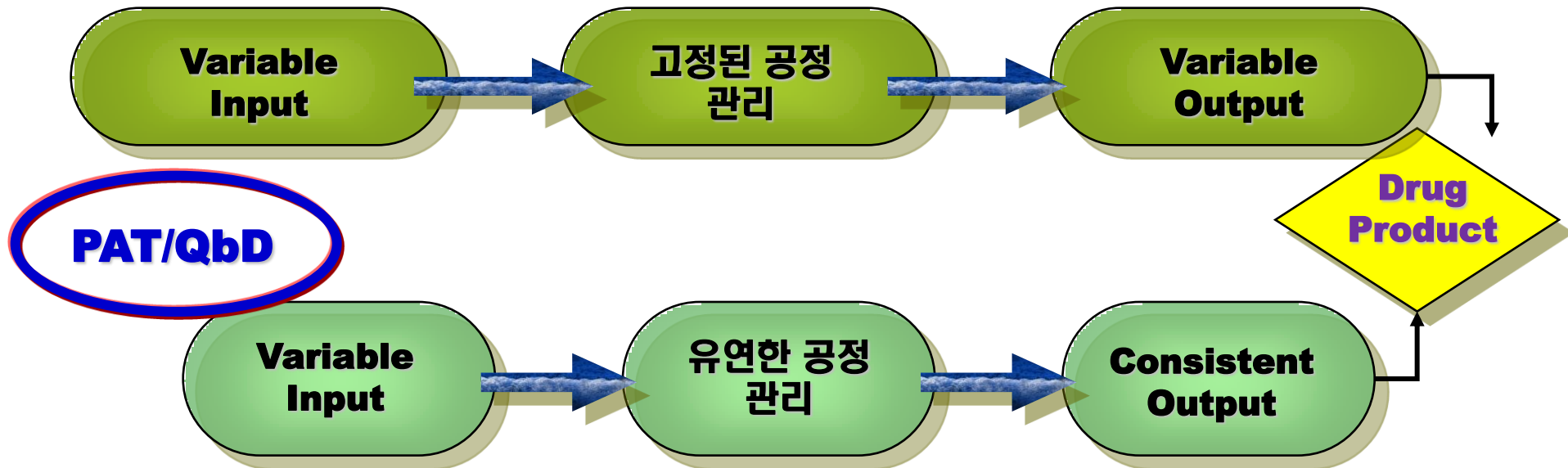
- 체계적
- 지식 정보 중심
- 예측적
- 과학적이고 위험 기반
- 환자에 기대사항을 고려한 기준 설정
- **Design Space**를 통한 변동 인자 파악

2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 개발 (Pharmaceutical Development)

- Quality by Design (QbD) 개념

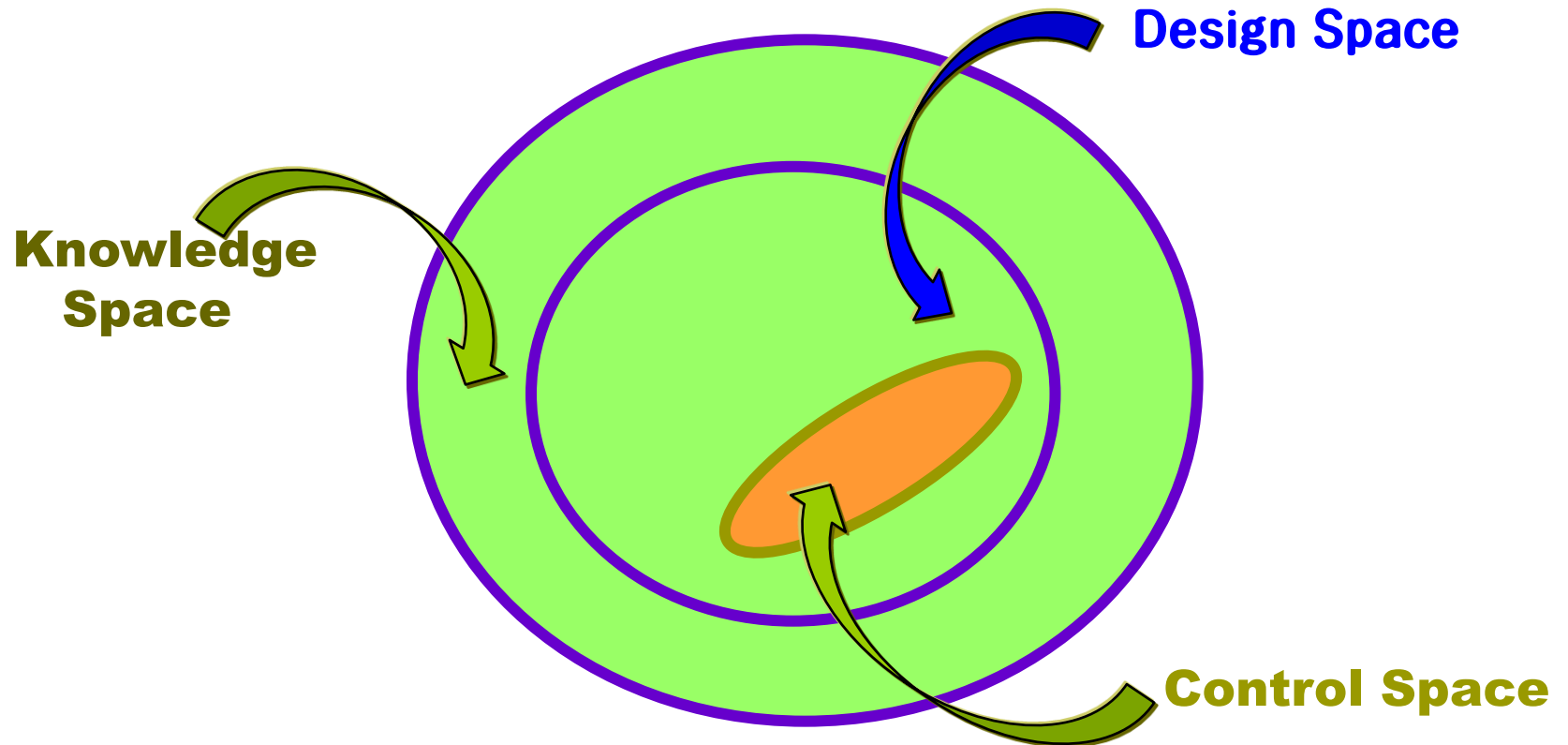
Now (GMP)



2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 개발 (Pharmaceutical Development)

- Quality by Design (QbD) 개념



2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 개발 (Pharmaceutical Development)

- Quality by Design (QbD) 절차



2. 품질관련 최근 지침 (Recent Quality Guidance)

품질 위험 관리 (Quality risk management -QRM)

.위험관리의 이점



2. 품질관련 최근 지침 (Recent Quality Guidance)

품질 위험 관리 (Quality risk management -QRM)

. 개념



Quality

현수준 파악

Degree to which a set of inherent properties of a product, system or process **fulfills requirements**

Risk

위험 평가

combination of the **probability** of occurrence of harm and the **severity** of that harm

Management

시스템 개선 관리

Systematic **process** for the **assessment, control, communication and review** of risks to the quality of the drug (medicinal) product **across the product lifecycle**

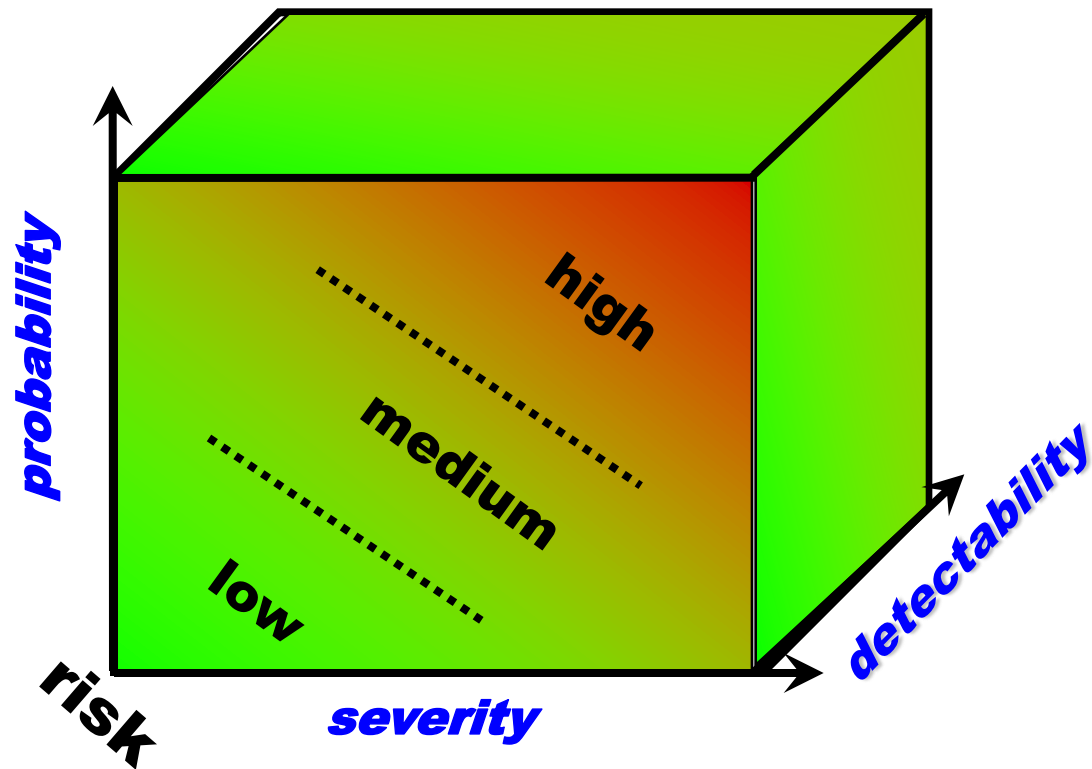
Yuhan Corporation

2. 품질관련 최근 지침 (Recent Quality Guidance)

품질 위험 관리 (Quality risk management -QRM)

.위험 평가 인자

- 1) 가능성(빈도)
Probability
- 2) 심각성 (Severity)
- 3) 검출 능력
(Detectability)



2. 품질관련 최근 지침 (Recent Quality Guidance)

품질 위험 관리 (Quality risk management -QRM)

. 접근 방법 (Methodology)

1. 시스템적 위험 (시설 및 작업자 관점)

e.g., interfaces, operators risk, environment, components such as equipment, IT, design elements

2. 시스템적 위험 (조직 및 구조적 관점)

e.g., Quality systems, controls, measurements, documentation, regulatory compliance

3. 공정 위험

e.g., process operations and quality parameters

4 제품 위험 (safety & efficacy)

e.g., quality attributes: measured data according to specifications

2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 품질 시스템 (Pharmaceutical quality system)

개념

대상 제품의 품질, 공정 능력을 일관되도록 하고, 일련의 관리 사항을 지속적으로 개선할 수 있도록 한다는 것이며, 이는 제조 관리 시스템을 포괄하는 개념이다.

“The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded”

The Quality System is the foundation for the drug manufacturing systems. Quality system model integrates manufacturing systems

2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 품질 시스템 (Pharmaceutical quality system)

주요 항목

1. 문서관리 (Documentation)

2. 교육 및 훈련 (Training and education)

3. 외주 및 원자재 관리 (Outsourced activities / purchased materials)

4. 품질 관리 전략 (Control Strategy)

Use quality risk management to establish using parameters and attributes and related facility and equipment operating conditions

5. 모니터링 및 개선 조치 (Monitoring / Handling Quality Defects (CAPA))

The level of effort of the investigation should be commensurate with the level of risk. Result should be product and process improvements

2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 품질 시스템 (Pharmaceutical quality system)

주요 항목

6. 실사 (Auditing / Inspection)

For regulators

For companies

7. 정기적 평가 (Periodic review)

8. 변경 관리 (Change management / change control)

Level and formality commensurate with risk

-Effect of the change on the overall process and product

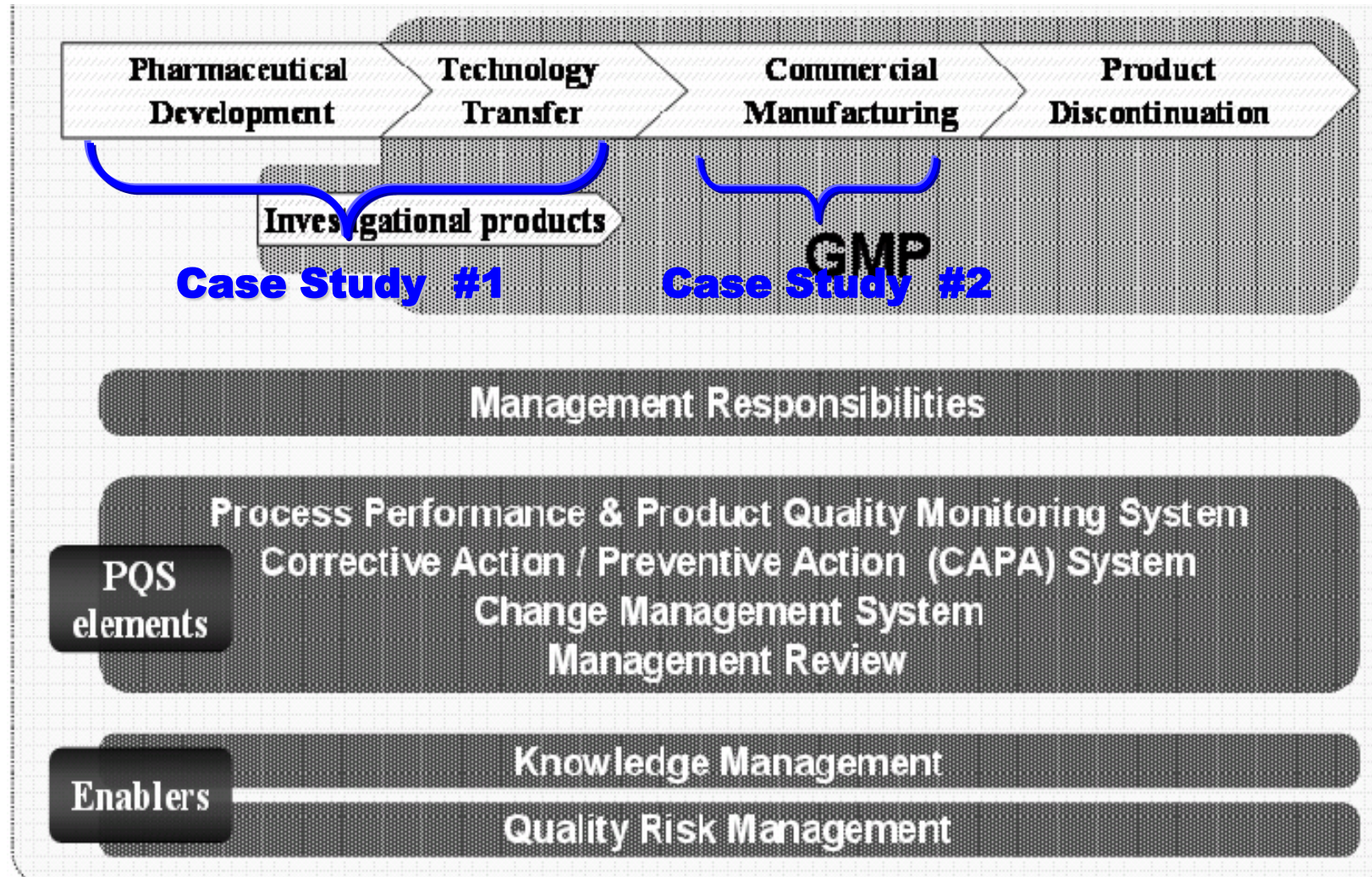
-Effect on validation

-Evaluation of the change upon implementation

9. 지속적 개선 (Continual improvement)

2. 품질관련 최근 지침 (Recent Quality Guidance)

의약품 품질 시스템 (Pharmaceutical quality system)



3. 사례 연구 (Case Studies)

- **Case Study #1 – 개발 단계 의약품**
- **Case Study #2 – 기존 의약품**



3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

Quality Target Product Profile (QTPP)

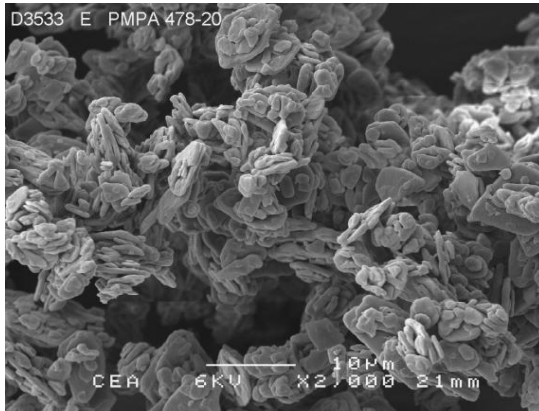
- 고용량 제품 (High drug loading)
- 주성분 A 와 B 와 상호 물리화학적 상호 작용 정보
Potential for physical and chemical Interactions between API A and API B
- API A에 대한 이전 제제 연구 자료 없음.
 - Justify widening of API A particle size specification
- 생체 이용률 관련 정보 (Bio-equivalency)

3. 사례 연구 (Case Studies -#1)

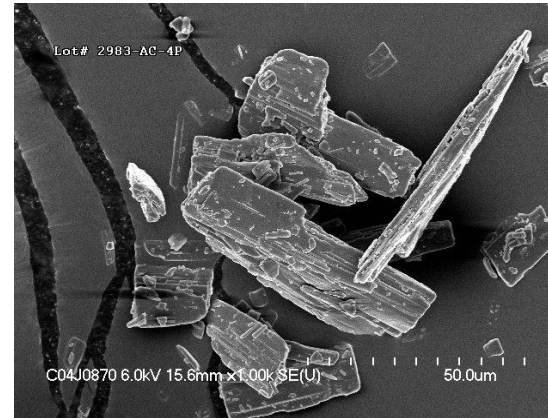
1. 제제 개발 (Formulation Development Challenges)

Quality Target Product Profile (QTPP)

입자 형상



API A



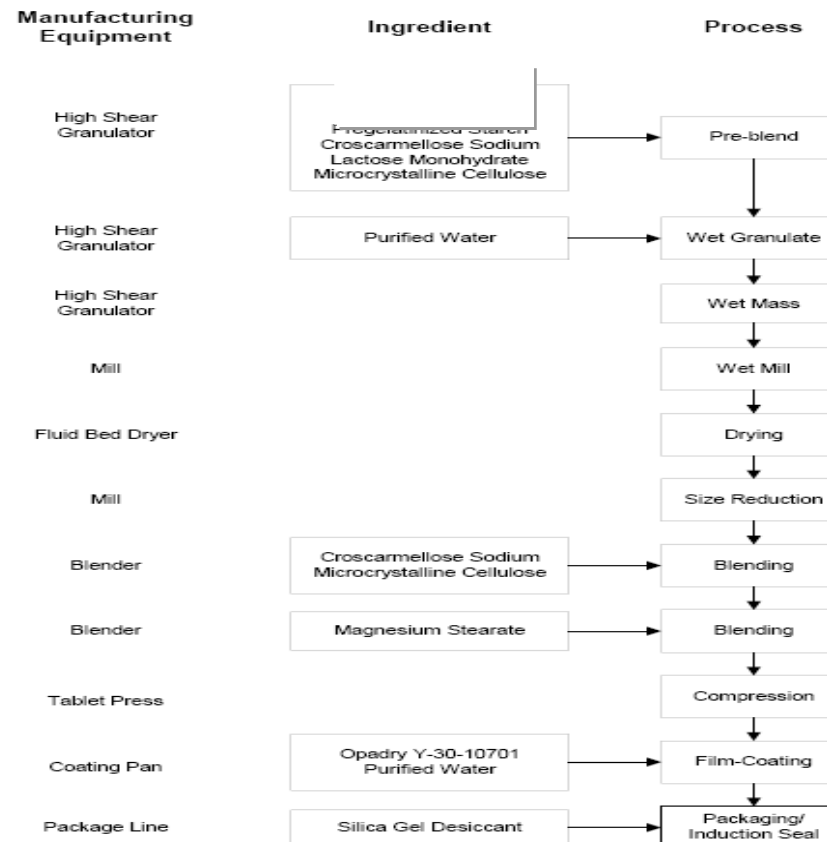
API B

3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

Quality Target Product Profile (QTPP)

공정 흐름도



3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

Quality Target Product Profile (QTPP)

실온에서 습식과립 시간에 따른 안정성

Wet Granulation Storage Time (days)	API A			API B	
	% Total Imp./Deg	% Related compound	% Label Strength	% Total Imp./Deg.	% Label Strength
0	0.39	0.22	102	0.01	101
1	0.44	0.26	100	0.02	99
2	0.45	0.28	100	0.03	100
5	0.58	0.43	100	0.05	98

3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

Critical Quality Attributes (CQA)

완제 포장에서의 안정성 검토

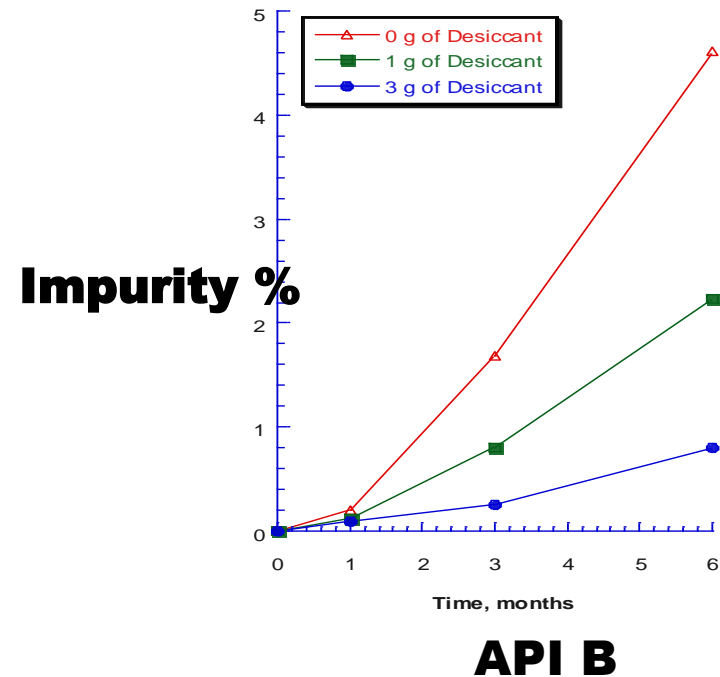
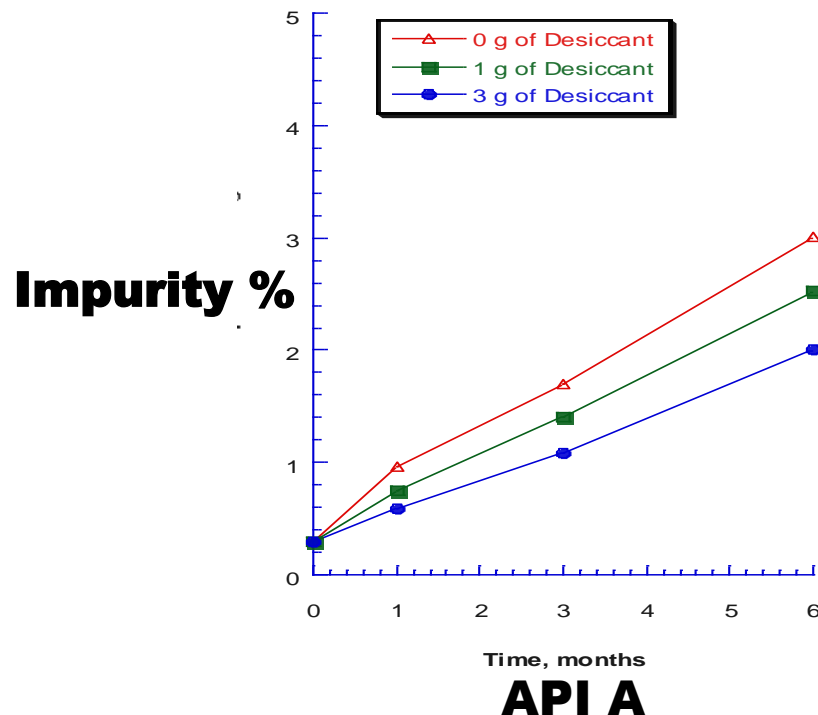
- **Selection of primary packaging configuration**
- **75 mL high density polyethylene (HDPE) bottle**
- **30 tablets per bottle**
- **Induction sealed polypropylene cap**
- **0, 1, and 3 g desiccant**
- **40°C/75% RH storage conditions**

3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

시험 계획 (DOE for Design Space)

제습제 투입량에 따른 주성분 A 와 B의 Impurity 영향



3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

Quality Target Product Profile (QTPP)

제조 단위 Scale-up 검토

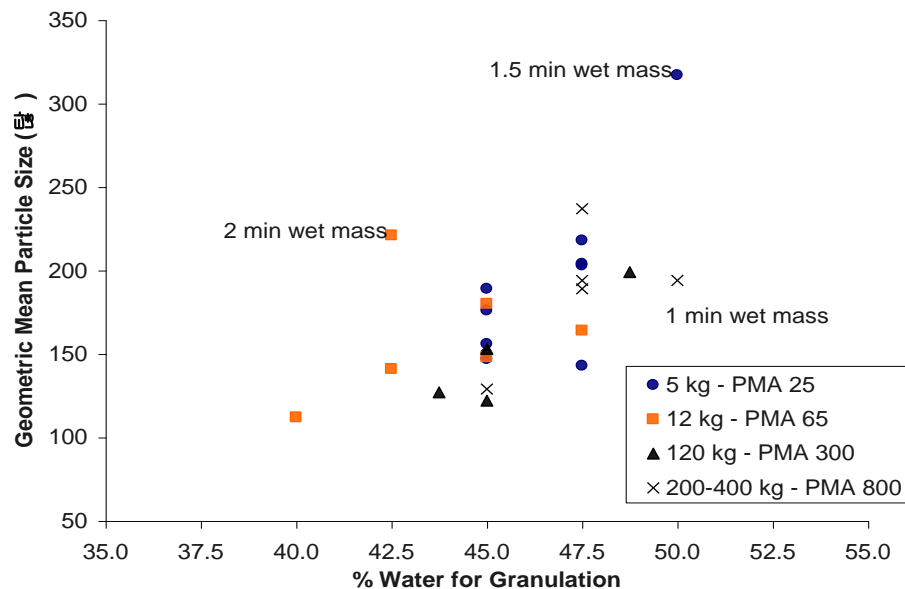
Manufacturing Process Parameter	Range Evaluated for Development Batches	Range Evaluated for Primary Stability Batches	Range Evaluated for Scale-Up Batches
Theoretical Batch Size	2 to 12 kg	120 kg	200-400 kg
Water for Granulation	40 to 47.5%	42.5 to 50%	45 to 50%
Water Addition Time	3 to 6 minutes	5 to 7 minutes	5 minutes
Wet Massing Time	60 to 120 seconds	30 to 60 seconds	60 seconds

3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

DOE for Design Space

습식과립 시간 및 정제수 투입량에 따른 과립 성상 영향 검토

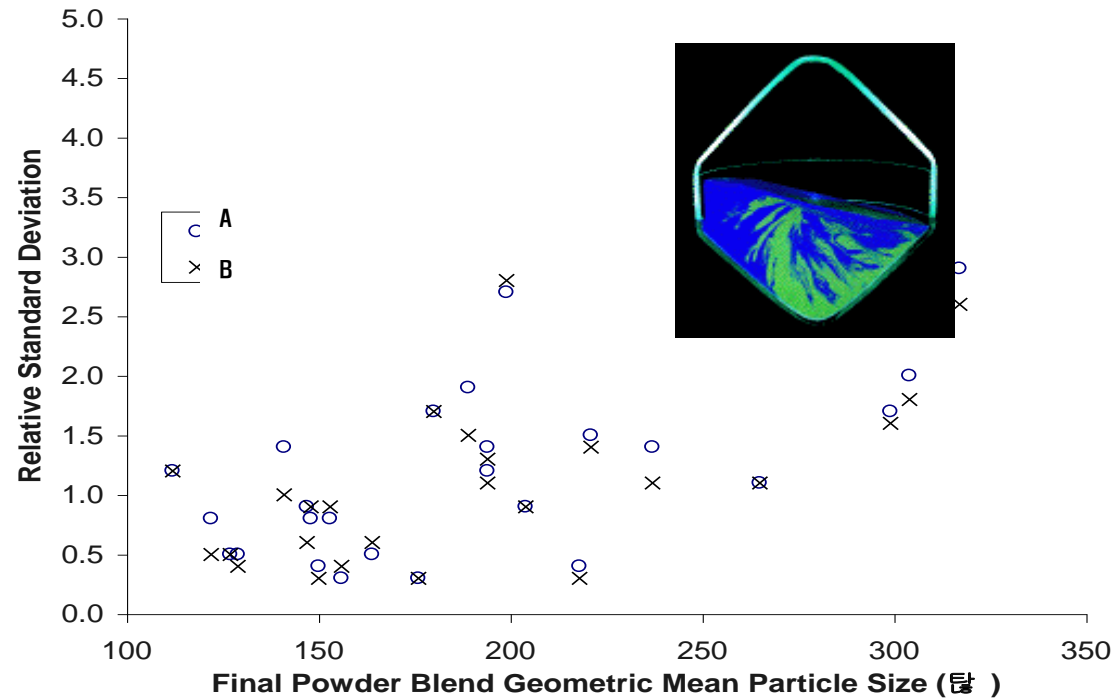


3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

DOE for Design Space

최종 혼합시 입자 분포에 따른 혼합도 영향성 검토

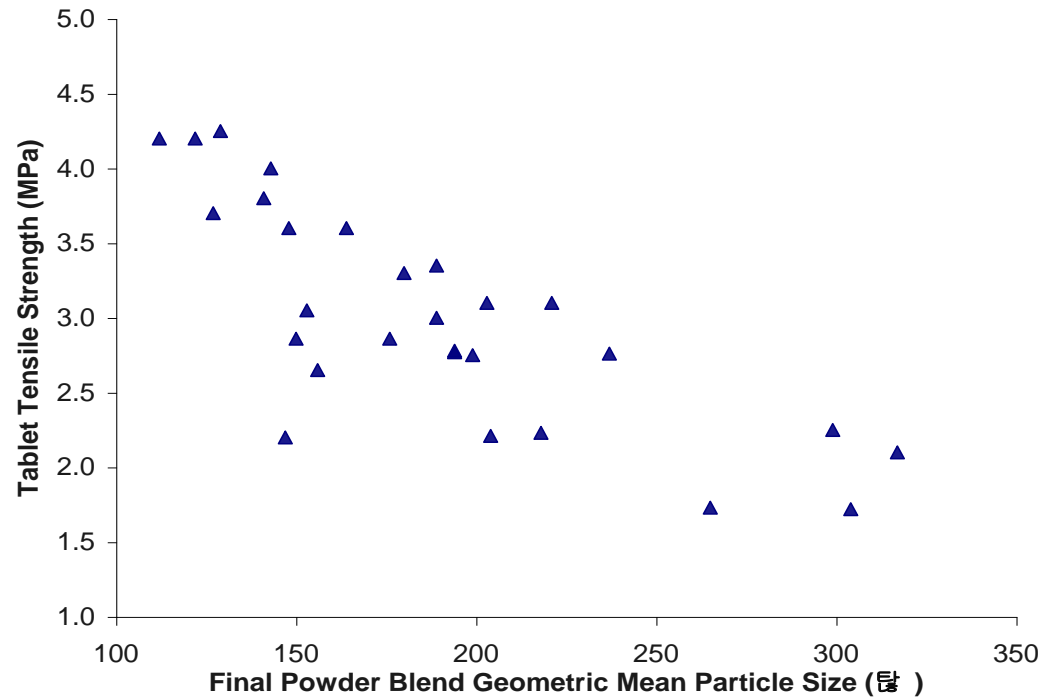


3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

DOE for Design Space

최종 혼합 시 입자도와 정제 경도와 의 영향성 검토

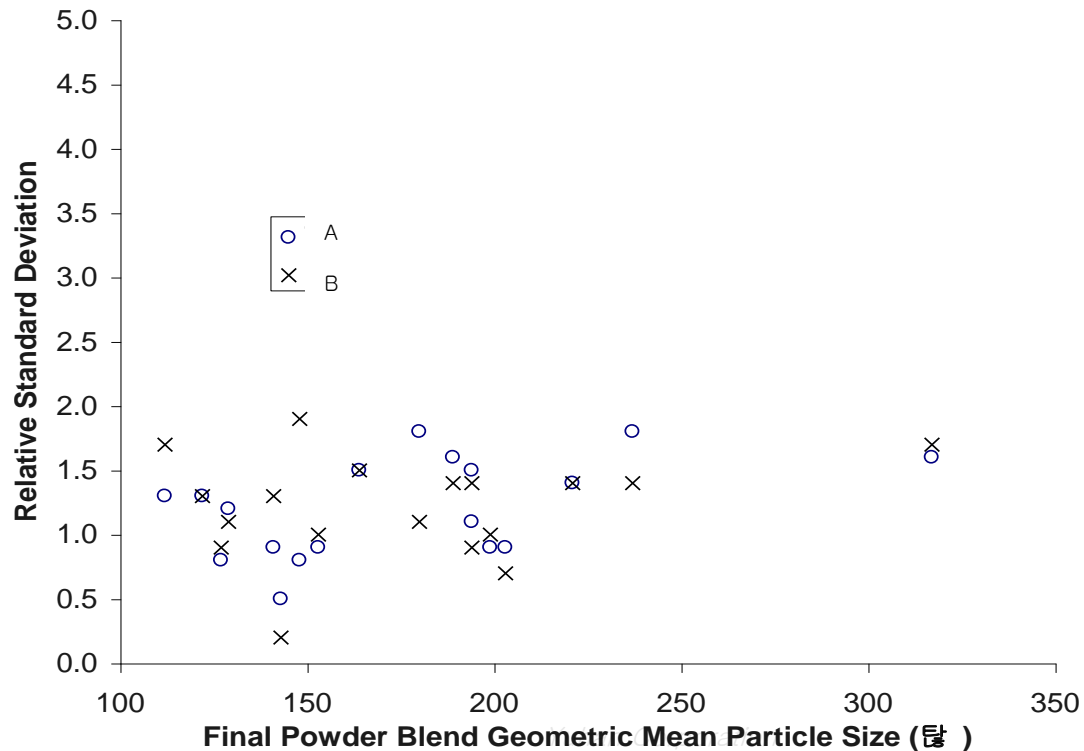


3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

DOE for Design Space

최종 혼합 시 입자도와 정제의 제제 균일성 검토

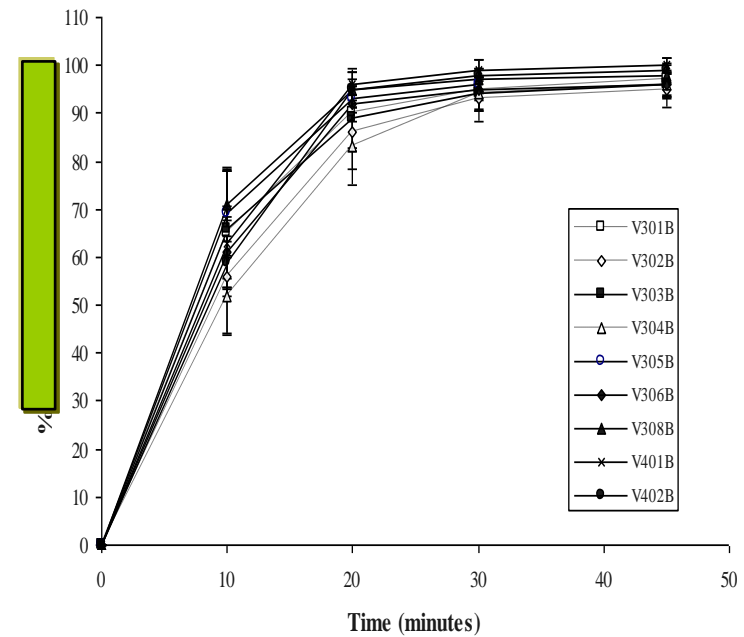
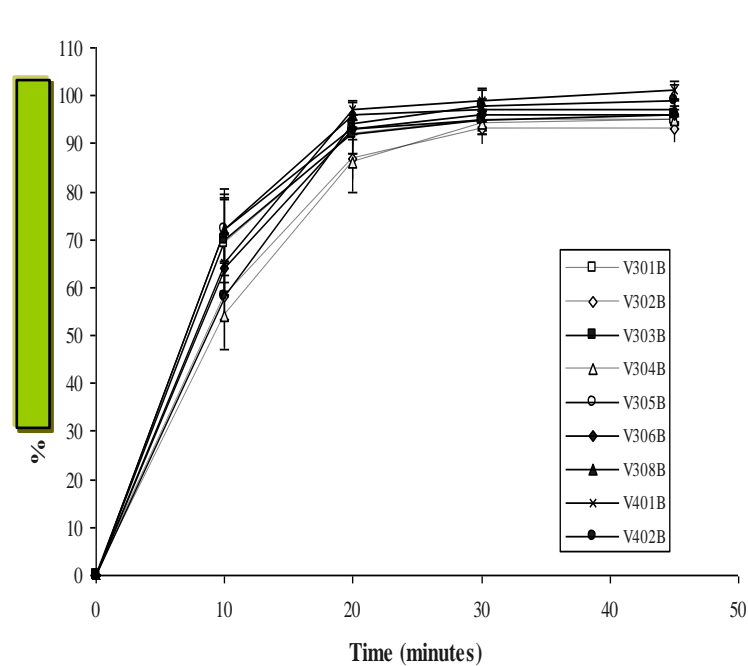


3. 사례 연구 (Case Studies -#1)

1. 제제 개발 (Formulation Development Challenges)

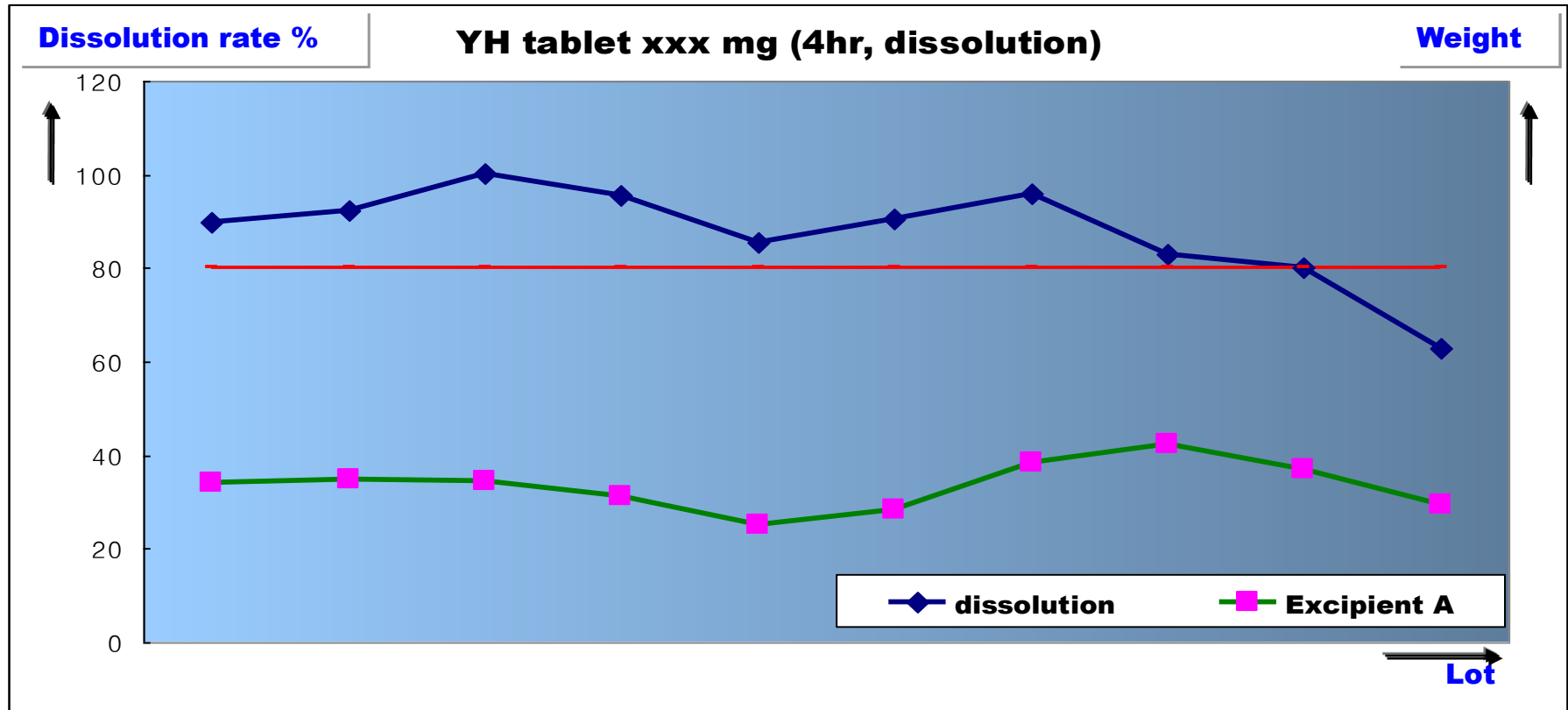
DOE for Design Space

제조단위 Scale-up에 따른 각 조건별 용출 영향 검토



3. 사례 연구 Case Studies (#2)

기존 제제 (*design space for existing products*)



- 용출률 결과 (4 hrs, water 37℃)

1) dissolution rate result → **Unstable & variability**

2) **Excipient A affect dissolution rate** of tablet

3. 사례 연구 Case Studies (#2)

기존 제제 (*design space for existing products*)

Tablet	Characteristics / Requirements	Translation into Quality Target Product Profile (QTPP)
Dose	xxx mg	Assay & Uniformity
Extended Release	For 4hr , Extended Release	Dissolution Rate 30min : 5~30%, 60min : 20~50%, 240 min : more than 80%
Apprearance	Film coated tablet , HDPE bottle packaging	
Description and hardness	Robust tablet able to withstand transport and handling.	
Expired period	Stable for 24 month	

- 해당 제품의 주요 품질 인자 (CQAs)

1)용출률, 2)마손도, 3)안정성

- Tablet CQAs : 사전 정보 (연간 품질평가, 제품 시험 자료, 안정성 자료)를 통한 결정

3. 사례 연구Case Studies (#2)

기존 제제 (*design space for existing products*)

Quality risk assessment - YH xxx mg tablet

	High								
	Medium								
	Low								
	Raw material variability	Wet granulation	Drying	Oscillating	Blending	Blending (Lubrication)	Tabletting	Coating	Packaging
Dissolution	High	Medium	Low	High	Low	Low	Medium	Low	Low
Disintegration	High	Low	Low	High	Low	Medium	High	Low	Low
hardness	Medium	Medium	Low	High	Low	Medium	High	Medium	Low
Friability	Medium	Medium	Low	High	Low	Medium	High	Medium	Low
Capping	Low	Medium	Low	High	Low	Medium	High	Low	Low
sticking	Low	Low	Low	High	Low	Low	Low	Low	Low
assy	Low	Low	Low	High	Low	Low	Low	Low	Low
uniformity	Low	Low	Low	High	Low	Low	Low	Low	Low
Impurity	Low	Low	High	Low	Low	Low	Low	Low	Low
stability	Low	Low	High	Low	Low	Low	Low	Low	Low

위험 분석 : 주요 품질 인자에 대한 위험 영향성 검토

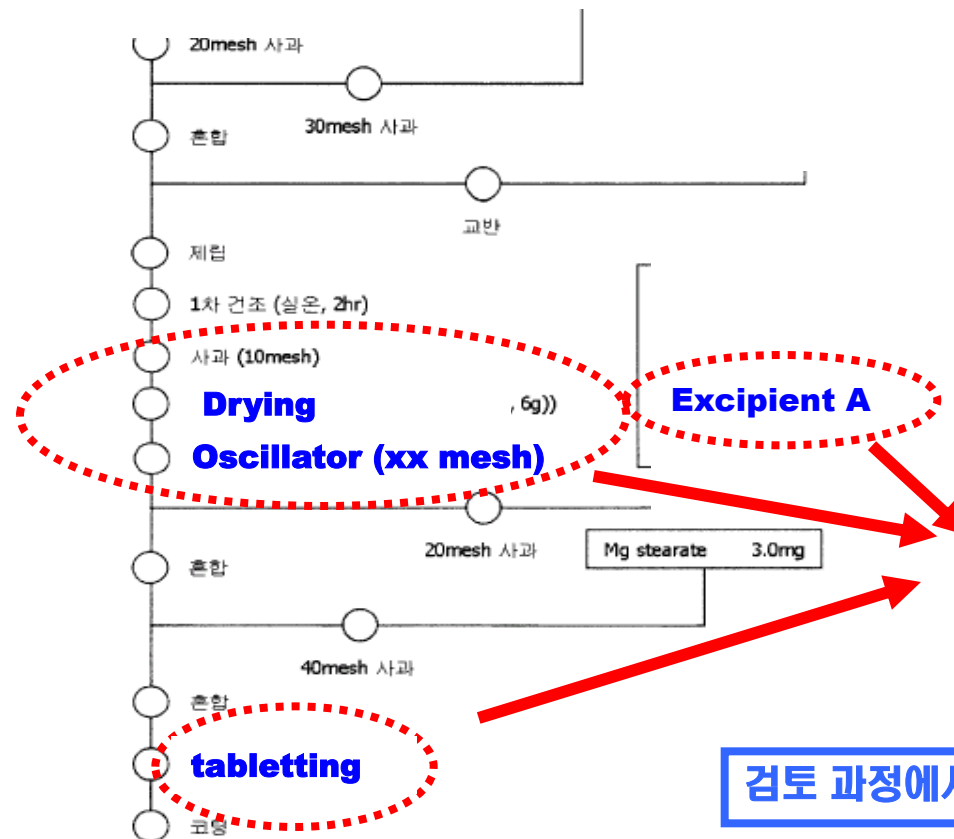
- using prior knowledge : Annual product review, Trend analysis, stability test.. etc

- Lab scale test

* 주요 관리 인자 : 1) 제립 입자 크기, 2)정제 경도 3) 건조 온도 4) 원료 성상의 변동성

3. 사례 연구 Case Studies (#2)

기존 제제 (*design space for existing products*)



주요 공정 관리 인자.

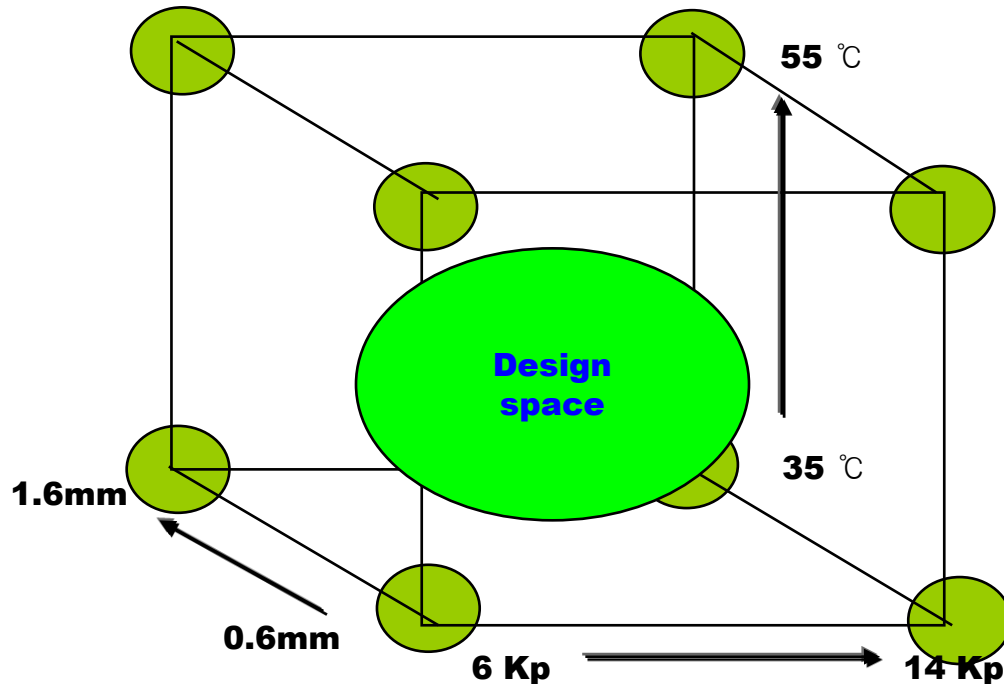
- Design of experiment

1. Particle size
2. Hardness
3. Drying temperature
4. Excipient A

검토 과정에서 첨가제 A는 B로 변경하여 고정 시킴

3. 사례 연구 Case Studies (#2)

기존 제제 (*design space for existing products*)



1. 각 인자 별 상호 연관성

- 1) Particle size : 0.6~1.6mm Fitz mill
- 2) Hardness : 6 ~ 14 KP
- 3) Drying temperature : 35 ~ 55 °C

2. 결과 분석

-> establishment of design space

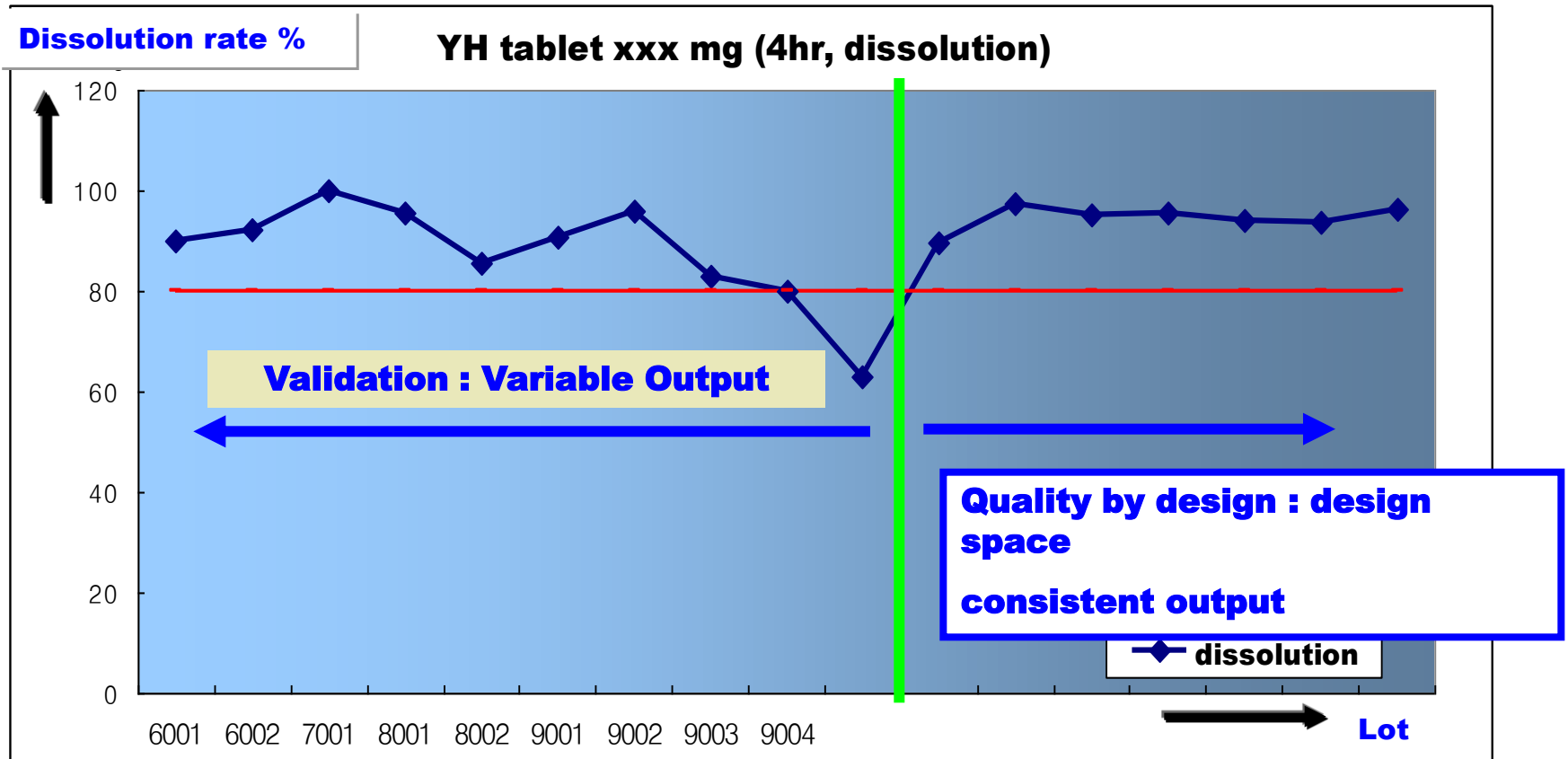


YH tablet ; 관리 조건

- 1) 제립 조건 -> Fitz mill 0.8mm
Particle size ↓ ; improve dissolution
- 2) 경도 8 Kp -> 12 Kp
Hardness ↑ ; improve friability
- 3) 건조 온도 50 °C -> 40 °C
temp ↓ ; improve stability

3. 사례 연구 Case Studies (#2)

기존 제제 (*design space for existing products*)

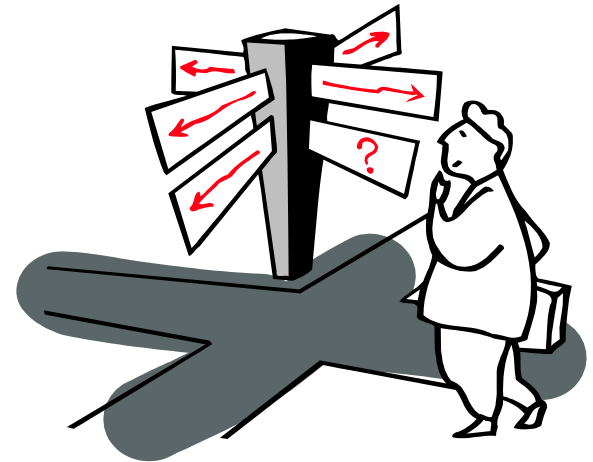


- **Quality by design (design space) apply to YH tablet**

안정적인 용출률 결과

4. 결론 (Conclusion)

- 품질 접근 방법 (Quality – Old & New approach)
- 품질 동향 요약 – ICH Q series
- 기본 목표 (Main purpose)
- 고려 사항 (Consideration)



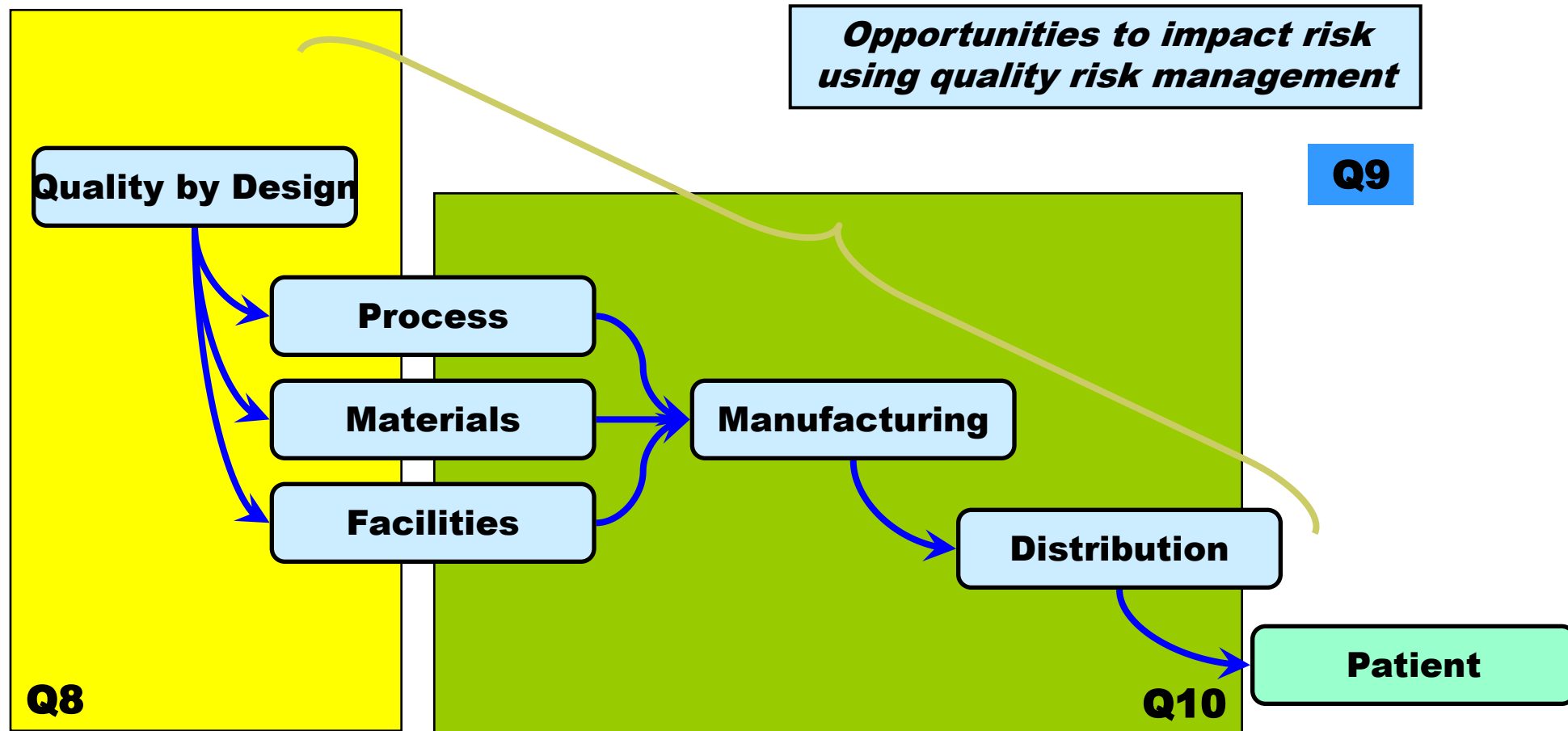
4. 결론 (Conclusions)

품질 접근 방법 (Quality - Old & New approach)

	과거	현재	비교
일반적 개념	Quality decisions divorced from science and risk evaluation. Adherence to filing commitments.	Quality decisions and filing commitments based on <u>Process Understanding</u> and <u>Risk Management</u> . Quality by Design.	<u>Design Space</u> concept introduced to integrate process knowledge with regulatory evaluation.
품질 관점	Post-factum sampling and quality testing. Process Validation.	Management of variability Process control focused on critical attributes. <u>Continuous Quality Verification</u> .	Quality by design definition applied. Measure critical process parameters to control output product quality.
시스템 관점	Systems designed to inhibit changes & minimize business risks. Discourages improvement & innovation.	Changes managed within company's quality system. <u>Real time batch release</u> feasible.	Regulators and industry place higher reliance / trust / understanding on systems. Multidisciplinary evaluation and decision making.
규제 관점	Compliance focus. Changes require prior approval.	Regulatory scrutiny adjusted to level of Process Understanding. Continuous improvement allowed within Design Space.	Requires mechanisms to communicate Process Understanding data

4. 결론 (Conclusions)

품질 동향 요약 - ICH Q series



4. 결론 (Conclusions)

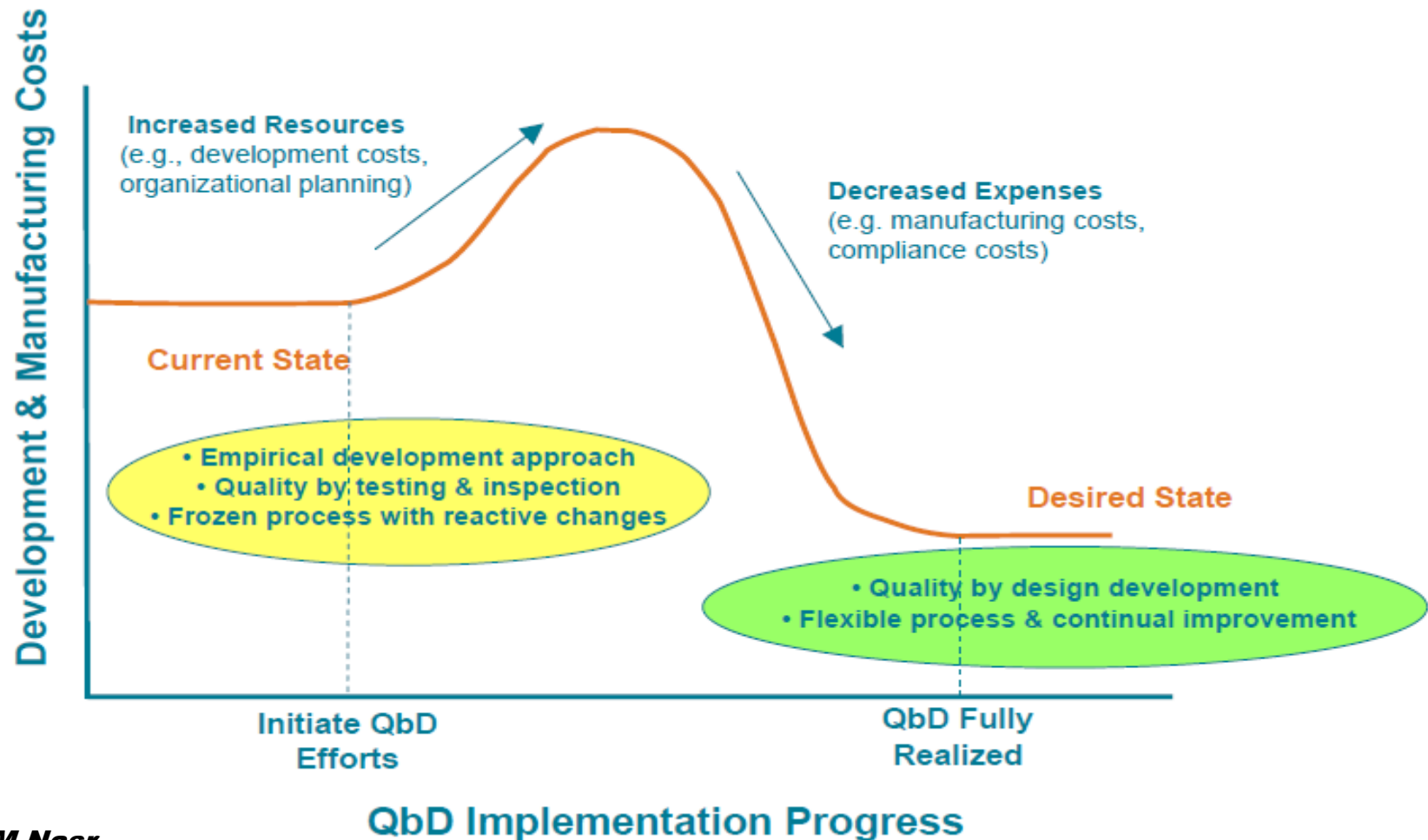
주요 목표 (Main purpose of ICH Q series)

제조업체와 규제 당국간에 상호 신뢰를 더 확고히 다지는데 기여
Main goals of ICH Q8, 9 and 10 is for having better confidence between regulators and industry.

Regulatory compliance에 머물지 않고 과학적 근거 및 리스크의
근거에 의해 확립
Moving from regulatory compliance to science and risk based decision !!!

4. 결론 (Conclusions)

고려사항 (Consideration)



5. References

- 1) WHO “ Quality Risk Management & its application in sterile processing”
Ian R Thrussell, MHRA, UK**
- 2) FDA “ Utilizing RM in a Submission for Developing Critical Process Parameters and
Critical to Quality Attributes**
- 3) FDA “ Implementation of Quality by Design (QbD): Status, Challenges and Next Steps**
- 4) WHO “Quality by design; Training Workshop on Pharmaceutical Development with focus on
Paediatric Formulations Mumbai, India**
- 6)Pharmaceutical Development: ICH Q8/Q(8)R
Moheb M. Nasr, Ph.D..Office of New Drug Quality Assessment Center for Drug Evaluation and
Research (CDER) Food and Drug Administration (FDA)**

Thank you for your attention

