September, 2008

平成20年度度GMP事例研究会

Quality by Design による製剤開発とCTD申請

- FDA Pilot Program による弊社の事例 -

ファイザー株式会社

CMC薬剤科学部

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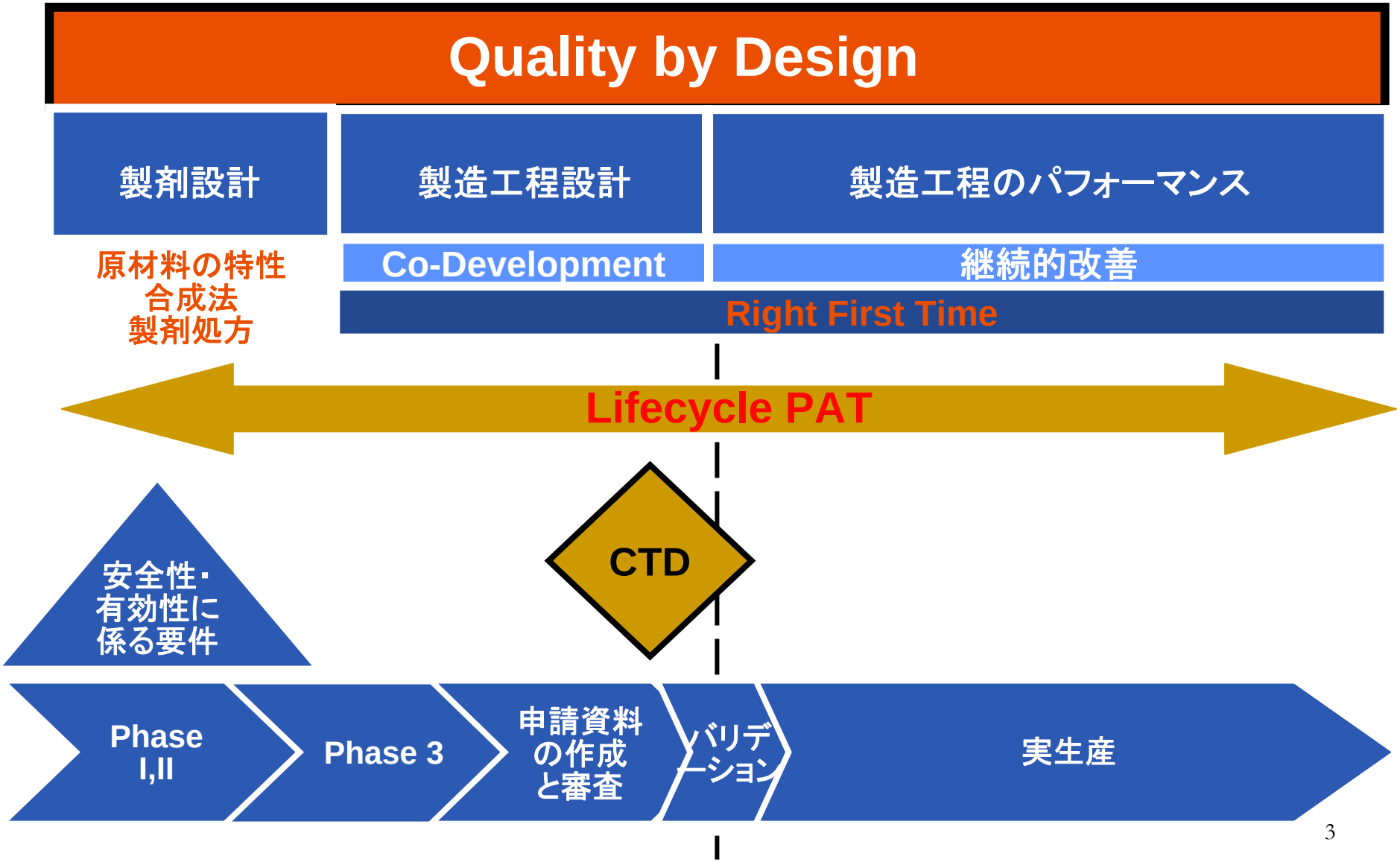
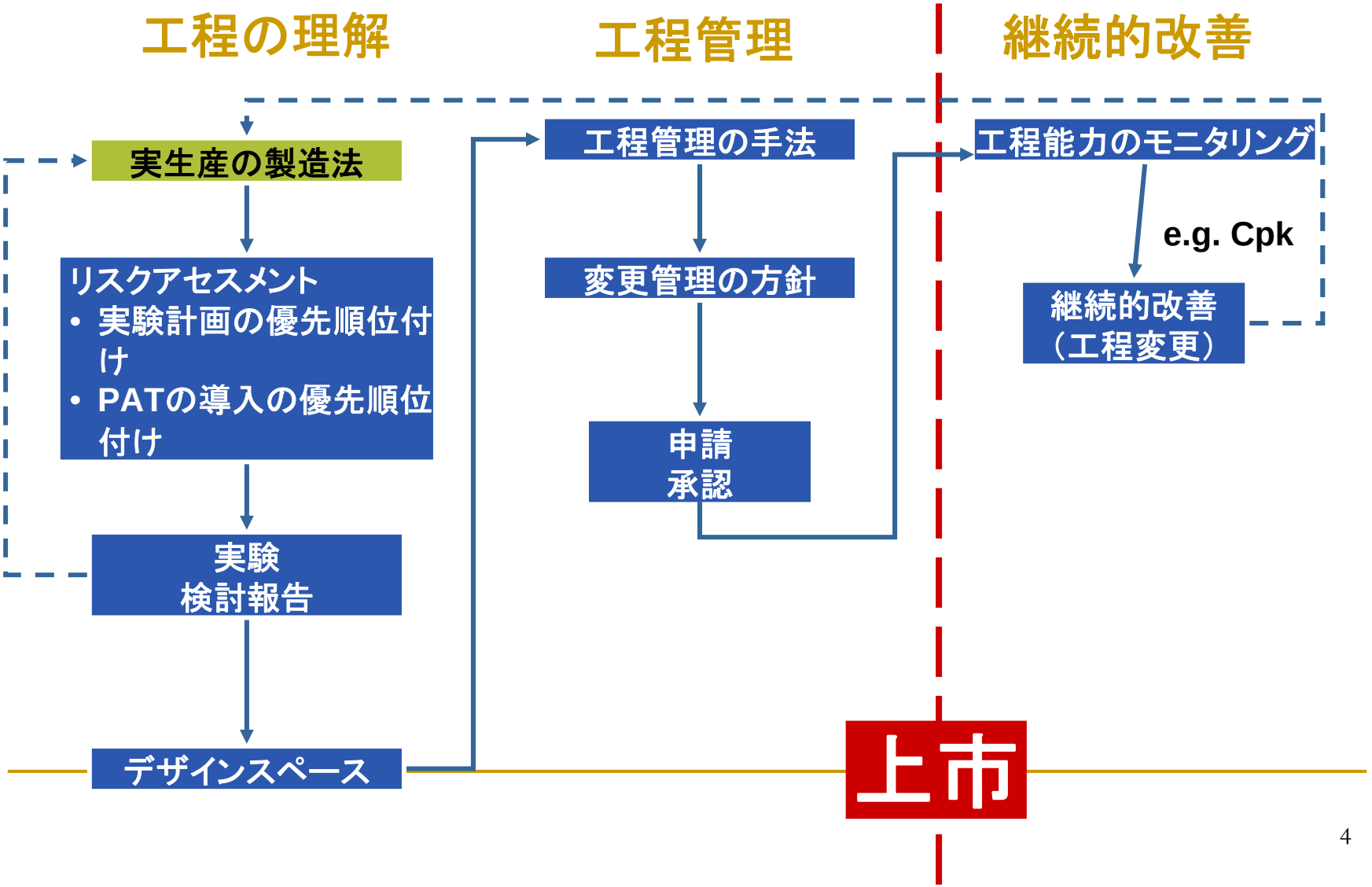
Content

- Overview of Pfizer's approach to QbD
- Pfizer’s participation in the FDA Pilot Program
  - Learnings from Varenicline
  - Maraviroc case study
  - Describing QbD in a submission
  - PAI experiences
- Future opportunities

Quality by Design



製造工程設計: Right First Time



開発段階でのQbD

- ‘Right First Time’ (RFT) ‘正しいことをより早く’ は，弊社が取り組む一環でありプロセス開発のためのQbDアプローチである
  - 系統化したリスクに基づく製造プロセスのアセスメント
  - 開発段階から開始し，承認後の継続的なプロセス改善のための基礎へと繋げる
- RFT ‘正しいことをより早く’ は，原薬の合成及び製剤の製造に応用される
- RFT ‘正しいことをより早く’ は，系統化したリスクに基づく開発→ 実験計画 → **デザインスペース**から構成される

Right First Time -リスクアセスメント-

- プロセスを適切なフォーカスエリアに分類する
- 各々のフォーカスエリアに適した品質特性を特定する
- 品質特性に影響を与えうるパラメータを特定する
- 原因となり影響を及ぼすマトリックスの構築
  - パラメータ及び品質特性間のリンク付け
- パラメータ及び品質特性が製品の品質（安全性と有効性）に及ぼす影響のランク付け

- チーム構成は各分野の専門家から成る
- リサーチ及び製造
- 幅広い経験及び知識に基づく

<u>利用可能なもの</u>

- 科学に基づく合理的根拠
- 開発を通じて得られたプロジェクトの経験
- 類似プロセス・製品に基づく経験

Right First Time -実験-

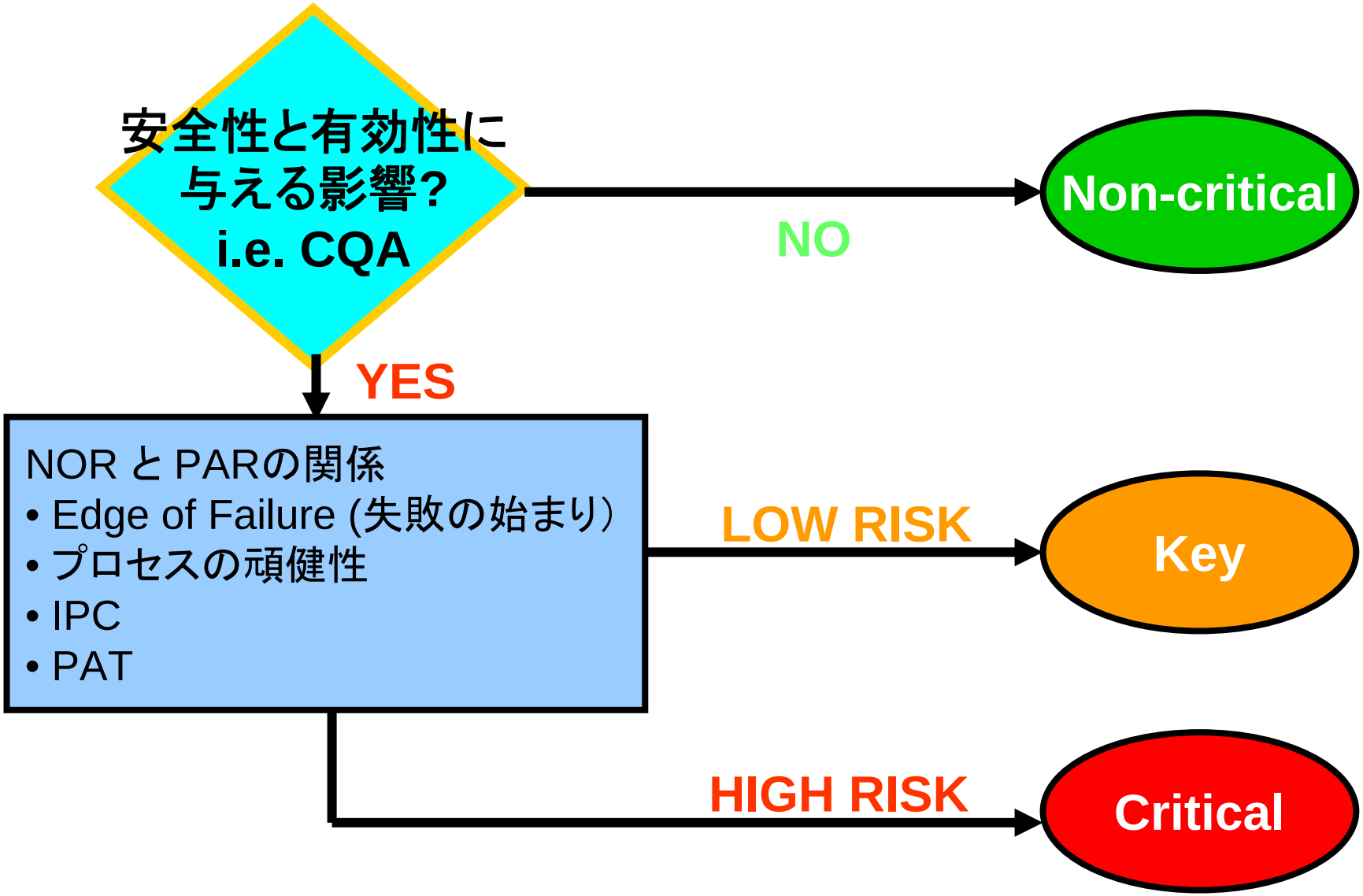
実験計画を工夫し実行する

- 品質に与える影響の重要度に基づいた優先付け
- プロセスパラメータと品質特性のリンク付け
- 品質特性に与えるプロセスパラメータの特定およびデザインスペースの境界決定
  - 多次元的スクリーニング実験計画法を通して
  - 複合的スクリーニング実験計画法を通して

Right First Time -デザインスペース-

- 原薬および製剤のデザインスペースから得られる成果（output）
  - 品質に影響を及ぼす可能性のあるプロセスパラメータおよび品質特性の特定
  - プロセスパラメータの Proven Acceptable Ranges (PARs) を特定
  - Critical, Key or Non-critical の選定
- コントロールストラテジーの確立
  - 適切な管理による品質のリスクマネージメント
  - 入力品質，社内管理および規格を包括的にコントロールする

プロセスパラメータのCritical またはKeyの定義



NOR = Normal Operating Range （通常の稼動範囲）
PAR = Proven Acceptable Range （許容範囲）

品質特性 (QA) とプロセスパラメータ (PP) の分類

- 製品の安全性や有効性に影響を与え得るとみなされる品質特性やプロセスパラメータを分類
- Critical, Key, Non-critical
  - Critical: 製品の品質に影響を与える品質特性及びプロセスパラメータ
  - Key: 潜在的に，製品の品質に影響を与える品質特性及びプロセスパラメータ
  - Non-critical: 製品の品質に影響を与えない品質特性及びプロセスパラメータ

Pfizer's participation in the FDA pilot program

1st Pilot Candidate

Varenicline
NCE (IR tablet)
Smoking Cessation
Submission of the NDA:
Nov 2005
Accelerated Review
Retrospective QbD
application

2nd Pilot Candidate

Maraviroc
NCE (IR tablet)
AIDS
Submission of the NDA:
Dec 2006
Accelerated Review
Prospective QbD
application

Varenicline Pilot: Outcomes

- NDA was approved under 1st cycle accelerated review
- Excellent communication and opportunity to interact
  - Several thought provoking queries,
  - Introduced delineation between commitments & data
  - Opened discussions on CMC Regulatory agreement
- FDA did not understand our risk assessment process
  - Not adequately conveyed in filing
  - FDA requested additional process controls
  - Pfizer did not provide a compelling control strategy

Varenicline Pilot: Outcomes

- Manufacturing process descriptions = design space
  - Include reasonable level of detail (summarize/tabulate)
  - Process parameters link to QA
    - *Identify critical process parameters*
    - *Include range for non-critical process parameters*
- FDA acknowledged value and applicability of prior knowledge
  - Use of precedence should be referenced and justified
  - Effectively demonstrate how prior knowledge is used for risk assessment

Varenicline Pilot: Outcomes

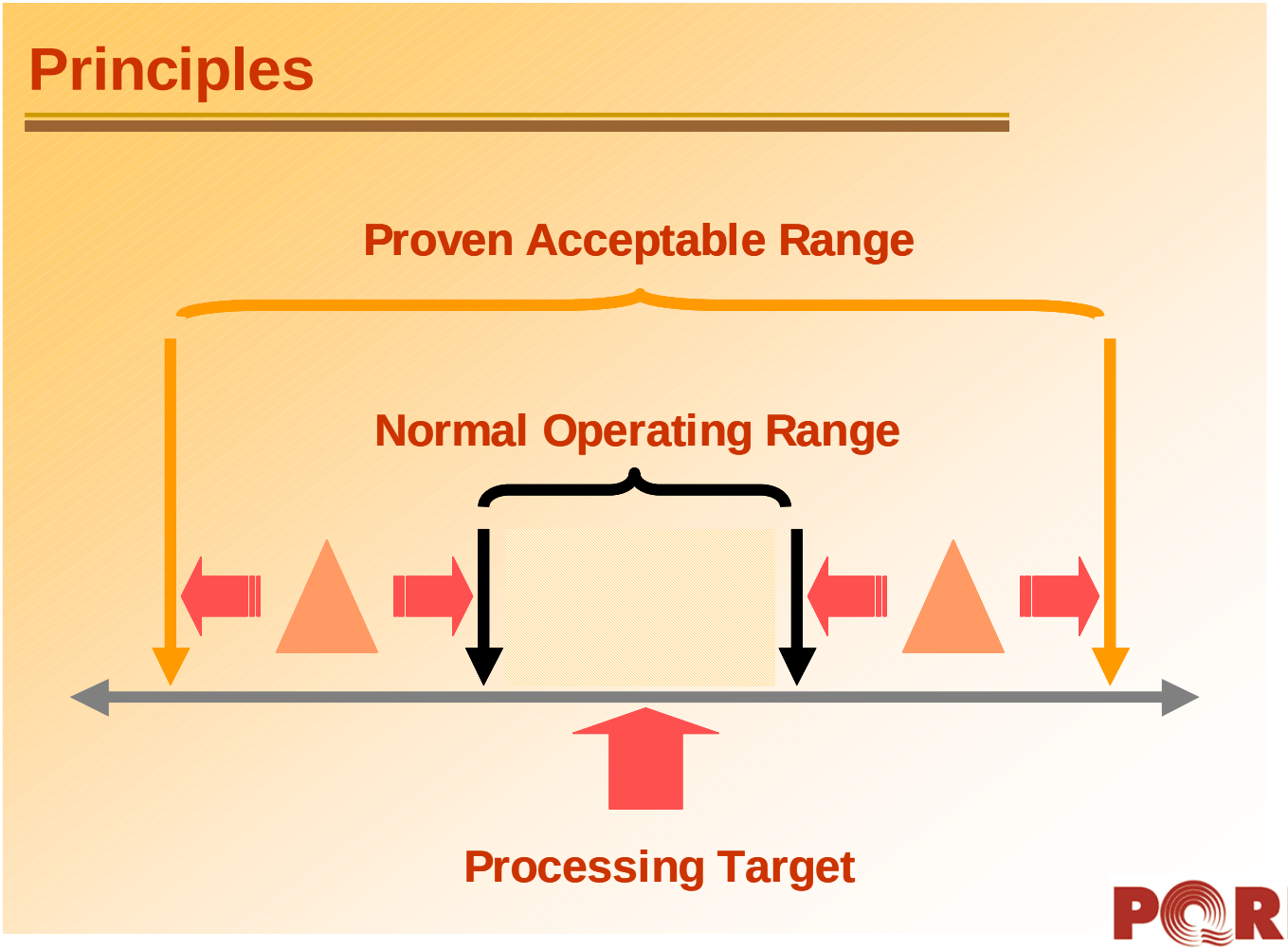
- FDA requested disclosure of ‘Control Space’ (NOR) in NDA
  - Control space for process = normal operating ranges
  - Provides increased understanding of risk (NOR vs PAR)
  - Control space provided as information only
- Both Pfizer and FDA struggled with definitions
  - Functional relationships - quality attribute vs process parameter
  - ‘Critical’ and ‘key’ designations
  - FDA recommended adoption of *’PQRI definitions’*

Critical とは – PQRI* White Paper

- CQA
  - 中間体や最終製品において，製品の意図した純度や有効性，安全性を確立するために重要とみなされる，定量化が可能な特性．すなわち，最終製品の品質を担保するために，事前に定めた範囲内であることが要求される特性.
- CPP
  - ある限定された範囲を超えて変化させたとき，直接的に又は顕著にCQAに影響を与える，工程に係る入力因子．CPPがその限定された範囲を逸脱した場合には，高い確率でCQAも不適となる.
  - Proven Acceptable Range（PAR）とNormal Operating Range（NOR）が近接している，許容差の少ない，十分にrobust でない工程.

*PQRI: The Product Quality Research Institute, 高品質医薬品を製造するために最良の基準を定めることを目的とした FDA CDER，業界，大学共同体

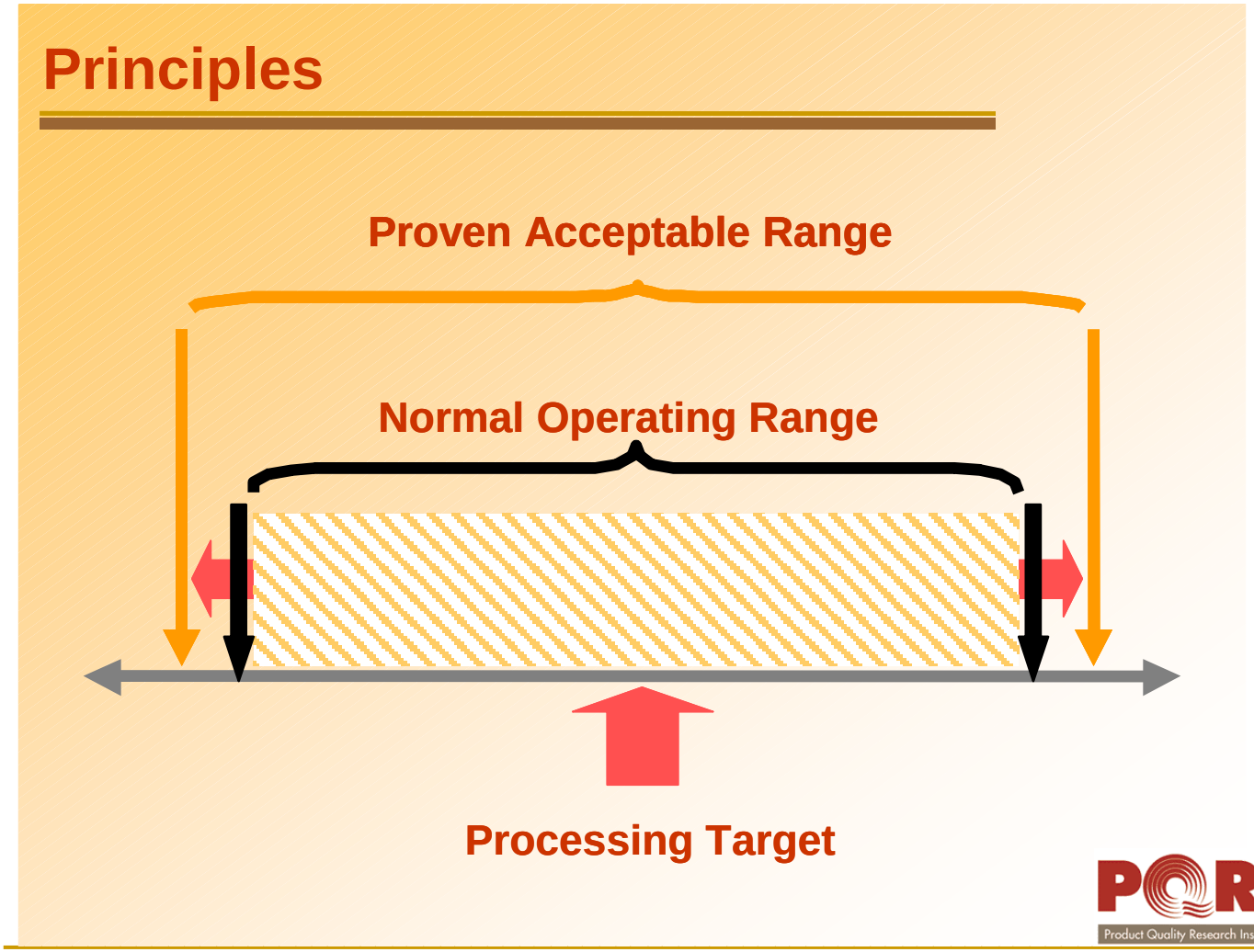
Robust な工程



Cpk > 1.5

PQRI
Product Quality Research Institute

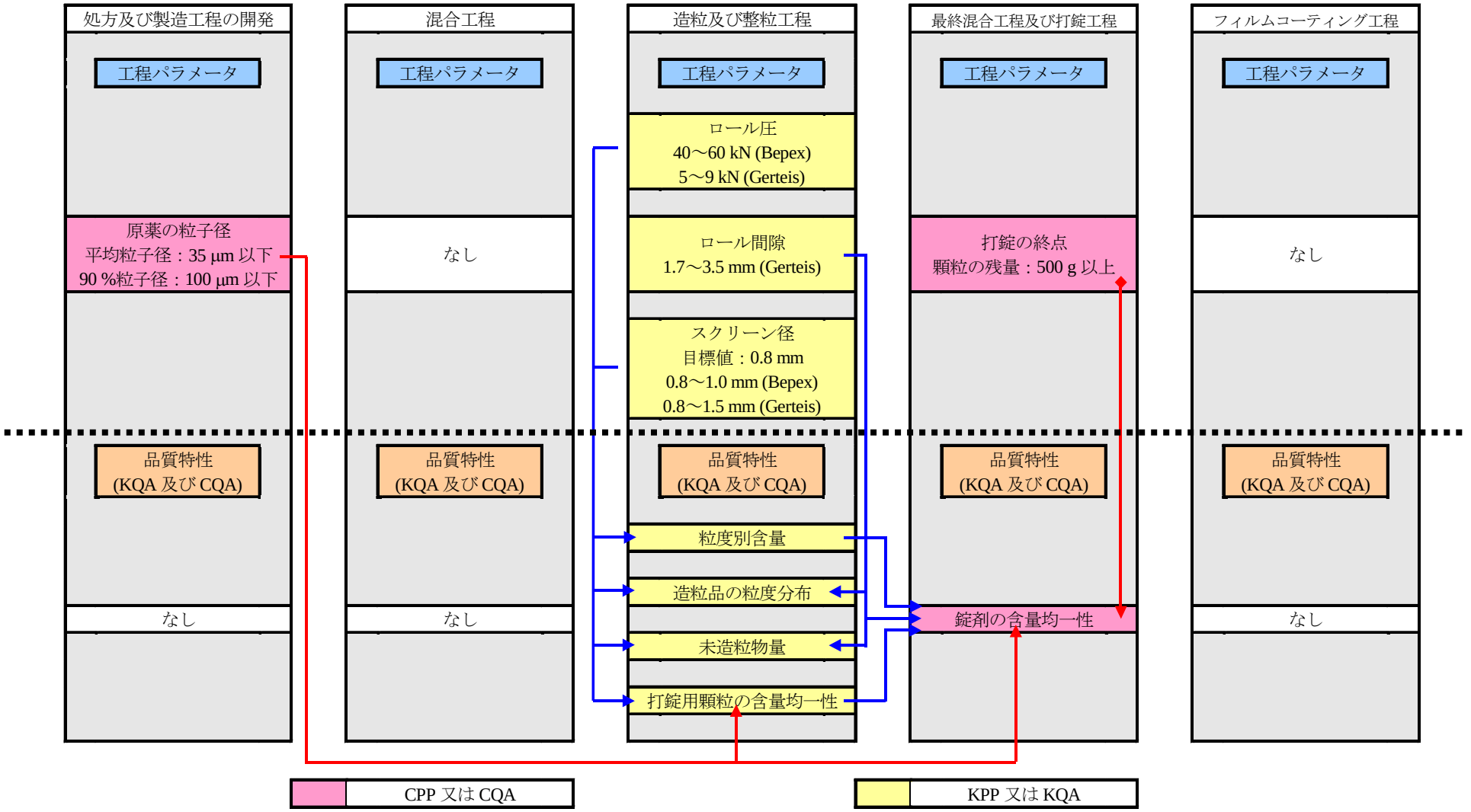
Robust でない工程



Cpk < 1.0

PQRI
Product Quality Research Institute

デザインスペース - Varenicline Pilot-



J-NDA CTD申請における Design Space と製造方法欄への落とし込みの関係

分類	変更管理	承認申請書への記載
CQA及びCPP	一変申請事項	《 》内に記載するか、もしくは記号を付けずに記載する
KQA及びKPP	軽微変更届出事項	『 』もしくは “ ” 内に記載する
非CQA 及び非CPP 非KQA 及び非KPP	社内管理	承認申請書には記載しない

KPP: Key Process Parameter, CPP: Critical Process Parameter
KQA: Key Quality Attribute, CQA: Critical Quality Attribute

Maraviroc case study

QbD at the API/DP Interface

API particle size

API Particle Size

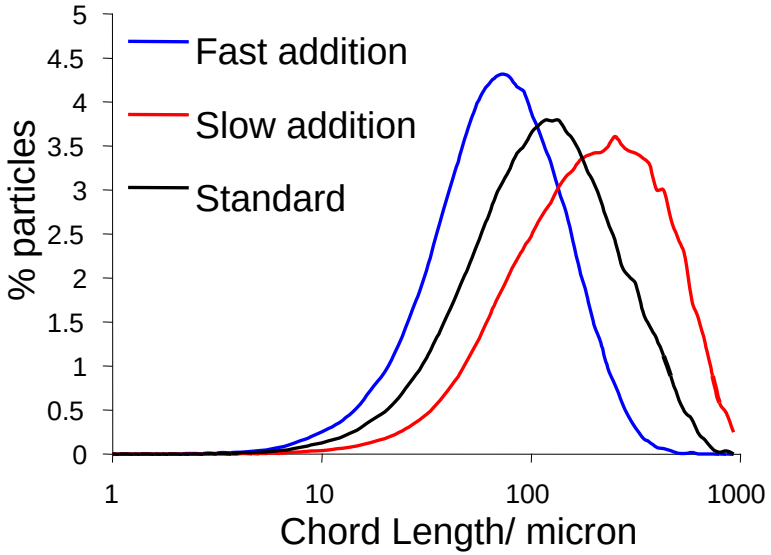
- API particle size has the potential to impact tablet quality i.e. content uniformity and dissolution.
- Conducted studies to investigate the factors that may impact API particle size.
- Impact of changes in particle size distribution on tablet content uniformity and dissolution were assessed.
- Modelling employed to examine the impact of particle size distributions greater than those generated by the drug substance crystallisation process.

Final API Process Step

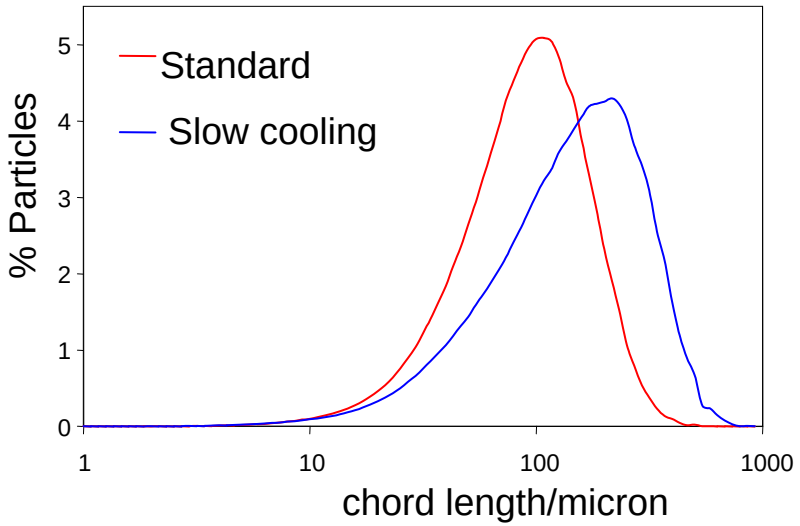
- Potential parameters that could impact particle size include:
  - Concentration of maraviroc
  - Addition rate of solvent during distillation
  - Cooling rate following distillation
  - Duration of stirring after cooling (granulation)
  - Stirring temperature after cooling
  - Extent/degree of agitation

On line Focused Beam Reflectance Measurement (FBRM) used to generate information on size ‘chord length’ and number of particles

Solvent Addition Rate



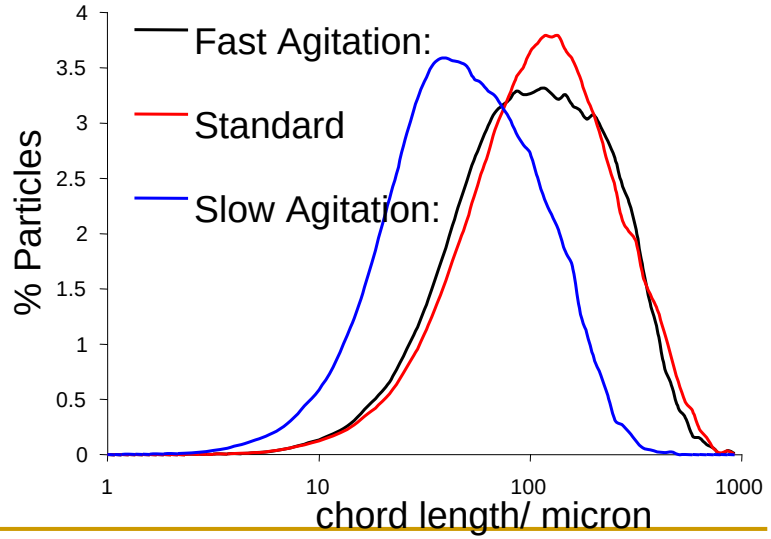
Cooling Rate



Process parameters investigated at laboratory scale mimic extremes of operating capabilities at commercial scale.

Solvent addition rate, cooling rate and degree of agitation have a small affect on chord length.

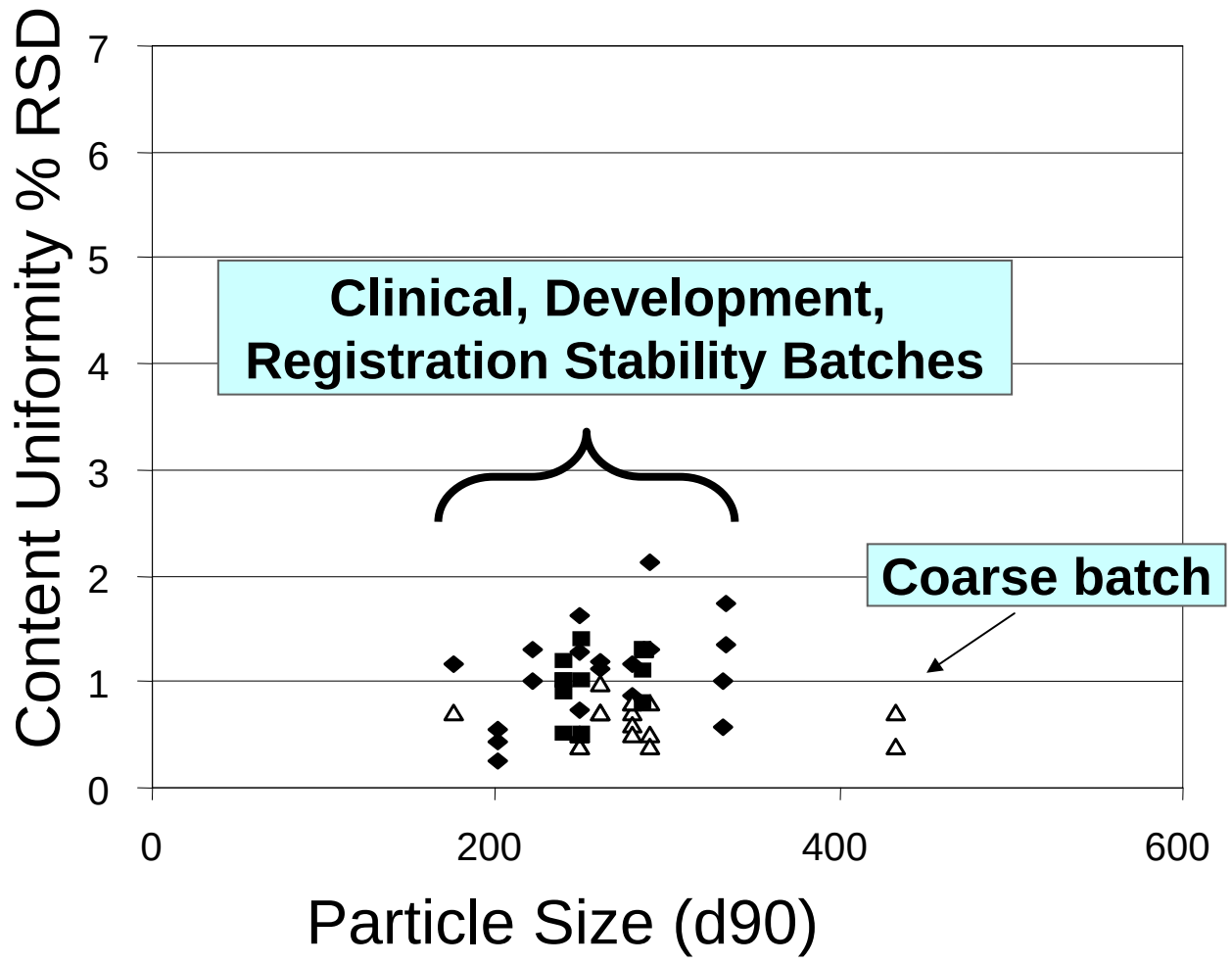
Degree Of Agitation



Impact Of API Particle Size on Drug Product Processing

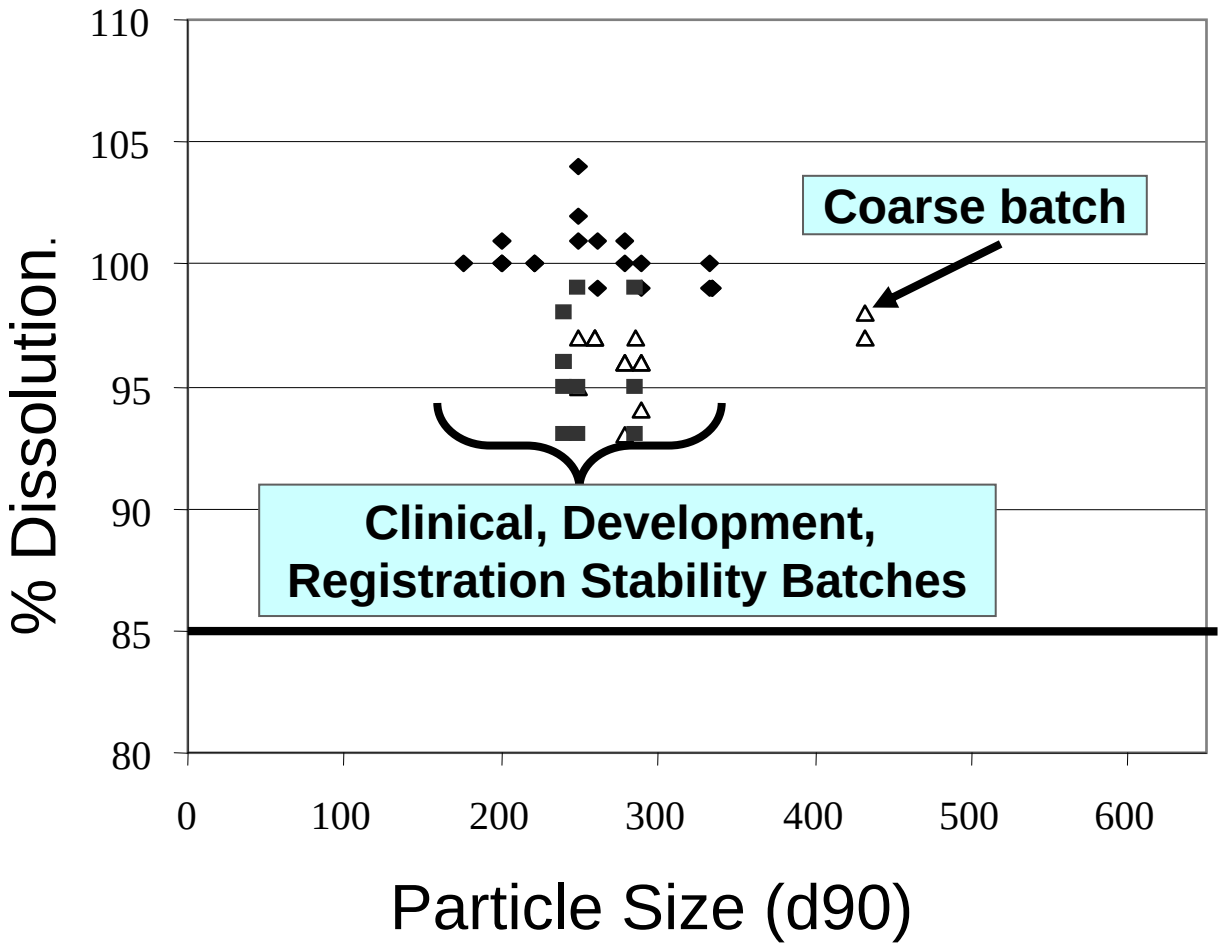
- Using extreme slow solvent addition and cooling engineered a ‘coarse batch’ of maraviroc
- Particle size with d90 of 433 μm cf development batches*164-382 μm*
- Impact of API particle size on content uniformity and dissolution were examined.
- All batches including the coarse batch were processed through to maraviroc tablets

Content Uniformity



API PS
has no impact
on tablet CU

Dissolution



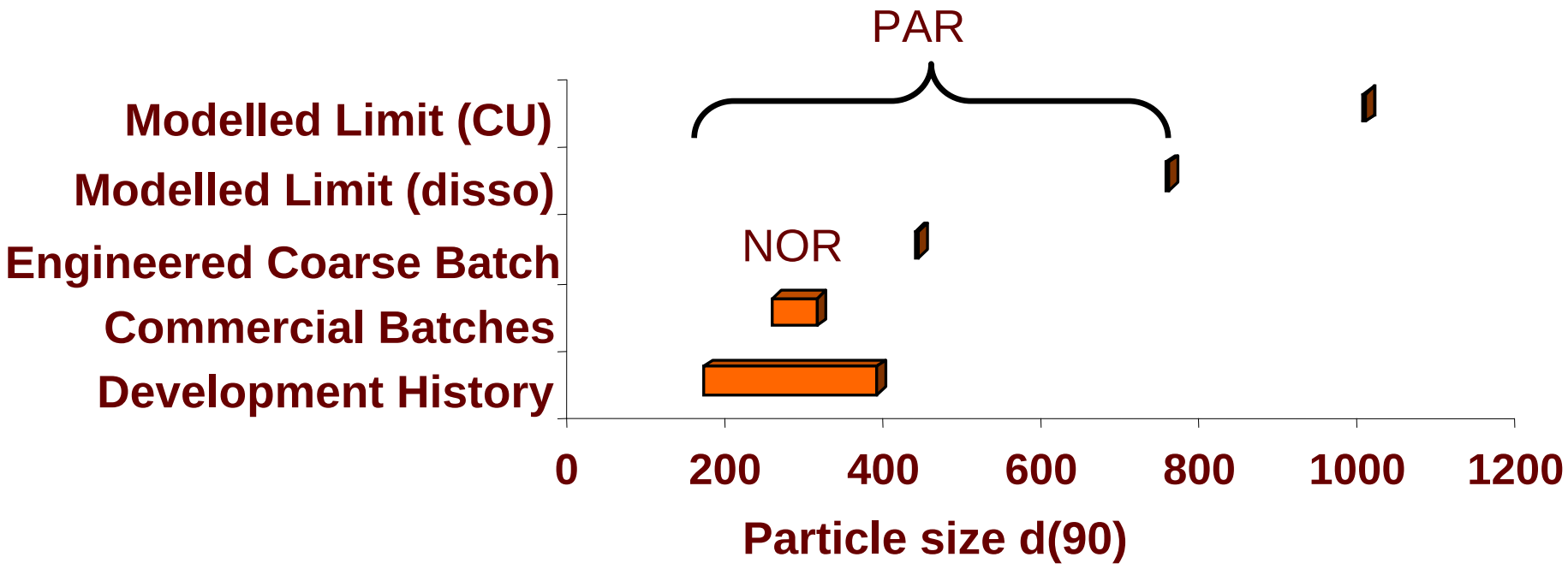
API PS
has no impact
on tablet
dissolution

Modelling the 'Design Space' for API Particle Size

- Modelling used to investigate 'edge of failure' for API particle size
- Employed published models to examine the impact of particle size (>433um) on dissolution and content uniformity
- Modelling shows little impact on these quality attributes until a particle size distribution beyond 750 and 1000 μ m for dissolution and content uniformity respectively
- Hintz and Johnson, 1989. Int J. Pharm 51, 9-17.
- Johnson M.C.R. 1972 Particle size distribution of the active ingredient for solid dosage forms of low dosage. Pharmactica Acta Helvetiae 47. 546 – 559

API Particle Size Conclusion

- Commercial API particle size << PAR.
- Particle size is a non-critical attribute of the API



Describing QbD in the submission

- QbD approach to the development of API and DP processes described in sections 3.2.S.2.6 and 3.2.P.2
  - Risk assessment → design of experiments →design space
  - Focus on quality attributes that may impact product safety or efficacy
  - Parameters identified as critical, key or non-critical
  - Normal operating ranges included ‘for information’
- Design space aligned with the manufacturing description and control strategy presented in module 3.
- Commitments contained within process description aligned with ‘criticality’ i.e. impact to safety and efficacy parameters.

Maraviroc Pilot – *outcomes…*

- Focus on QbD aspects of the filing
  - A *few* challenges to assignment of ‘criticality’
  - Non-routine monitoring of some non-critical QA’s
    - Acceptability of process changes
    - Verification of design space/process capability
  - Greater information requested for some areas
    - Modelling
    - Risk assessment – rationale for eliminating low risk parameters

Maraviroc Pilot – PAI

- Inspection of the API (3 days) and DP (4 days) manufacturing sites
- Inspection conducted by 3 inspectors + 1 reviewer
- Also a GMP inspection of both sites
- Majority of questions handled by manufacturing site
  - Preparation prior to PAI included pharmaceutical research team & Regulatory CMC/GMC
  - Sites had a good understanding of QbD and design space and how their quality systems supported manufacture of QbD product

Maraviroc Pilot – PAI

- Traditional Quality Systems Inspection
- Relatively few review questions
  - A hard copy NDA and query responses were requested to be in the room
  - No specific questions
- No questions on the Risk Assessment Process
- Focus on change control, monitoring, trending of Non-Critical Process Parameters and NORs of CPPs/KPPs

Opportunities: Regulatory Agreement

- Current status: *Some* regulatory flexibility through internal management to changes within the design space.
- Regulatory agreement required to achieve further regulatory flexibility
- Pfizer proposed agreement is based on consideration of design space, justified flexibility, potential post-approval continuous improvement.

  Key aspects:
  - Changes outside of the design space (expansion)
  - Changes to the design space
  - Includes proposals for specific areas of regulatory flexibility

Opportunities: Pilot Extension – Next Steps

- Extension of Pilot to evaluate post approval changes relative to a CMC Regulatory Agreement
- FDA/Industry incorporate learnings from Pilot - determine how to best incorporate QbD information in the dossier.
- Take bold steps in looking to the future. Follow the value!
  - Greatest value to FDA & industry: reduction of post-approval supplements.
  - As more science and knowledge gets built into the application, emphasis on applicants' internal Quality System to manage post-approval changes which are monitored by GMP oversight.

Acknowledgement

- GMP事例研究会関係者の皆様
- Pfizer Global CMC & PGM Groups
- 本日ご来場の皆様

ご清聴ありがとうございました.