変更管理システム
に関する提言

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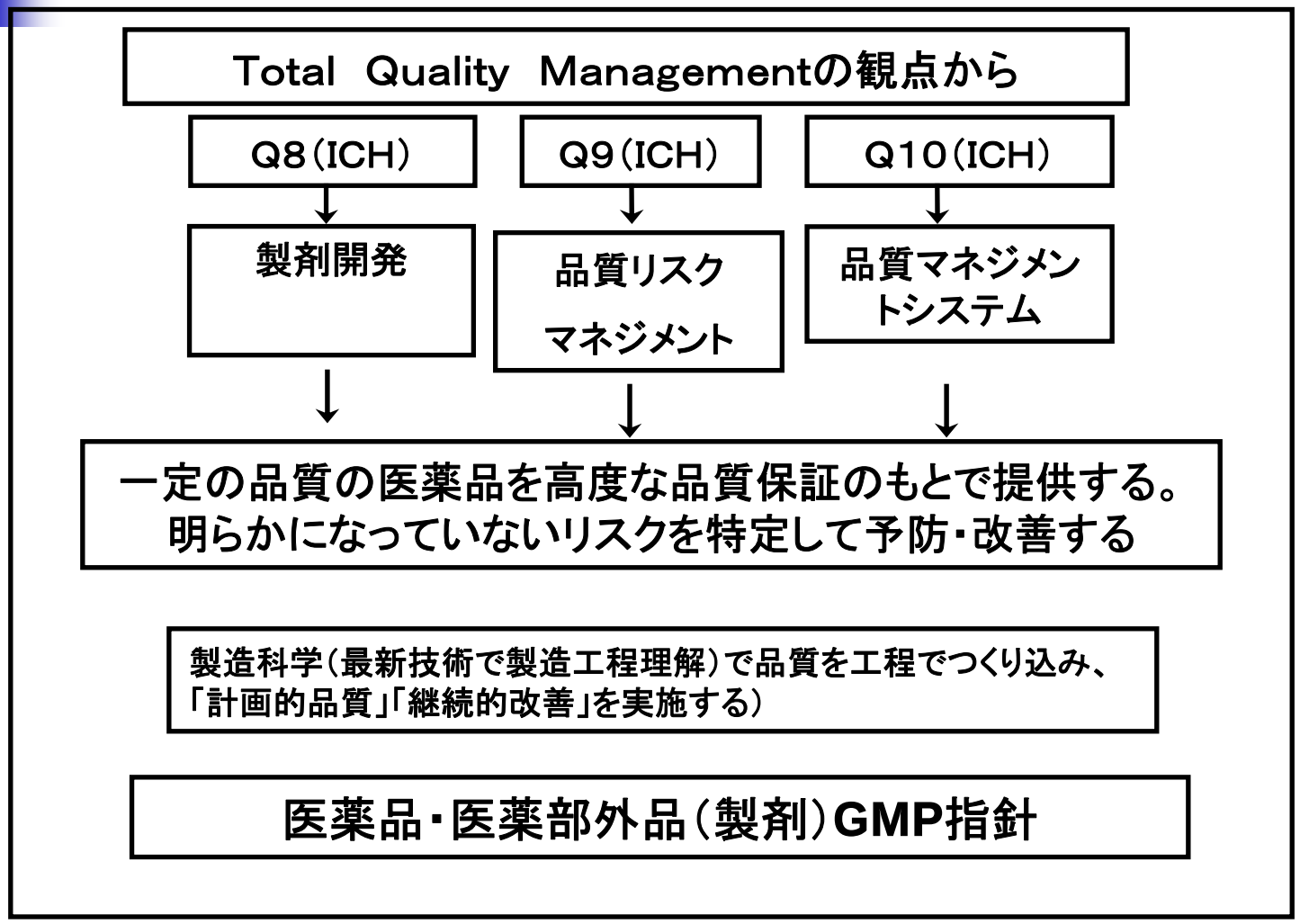
最新の品質保証の動向


Total Quality Managementの観点から
Q8（ICH）
Q9（ICH）
Q10（ICH）
製剤開発
品質リスク
マネジメント
品質マネジメン
トシステム
一定の品質の医薬品を高度な品質保証のもとで提供する。
明らかになっていないリスクを特定して予防・改善する
製造科学（最新技術で製造工程理解）で品質を工程でつくり込み、
「計画的品質」「継続的改善」を実施する）
医薬品・医薬部外品（製剤）GMP指針

議論のポイント

1. 承認取得後の製造の実態として日常の改善等が製品ライフサイクル上で重要。GMPにおける変更管理を実効的にすることが必要。
2. 変更の妥当性は、開発過程の品質解析データや製造経験に基づいて評価・実施可能。
3. 前提として、変更による品質へのリスクアセスメントが必要。その重み付けとして、変更の重要性のクラス分けがあるべき。
4. 変更内容の適格性の判断は、企業の品質システムの基で行われることが必要。

製薬企業の役割

- 患者さんに適正な品質の医薬品を提供し続ける
- 承認書記載事項は社会に対する契約
- 維持すべき医薬品の品質
  - 承認申請書に規定した規格
  - 有効性と安全性が確認されている品質・機能は、原則的には、ピボタル臨床試験で使用された治験薬と同等
- 適正なコスト
- 適正な利益循環により必要とされる医薬品の開発

GMP及びGQPから見た変更管理

製造業者

GMP関係：第14条(変更管理)

- 予め指定したものによる管理業務
- 製造所の構造設備並びに手順、工程その他の製造管理及び品質管理の方法に係る製品の品質に影響を及ぼす恐れのある全ての変更が対象
- 変更後の最初の複数ロットについては、変更に係る実生産規模での確認を含めて、影響の程度を評価
- 変更の実施にあたり、影響を受ける全ての文書が確実に改訂され、関連する職員への教育訓練の徹底

製造販売業者

GQP関係；第7条(取り決め)

- 製造業者における製造管理及び品質管理の適正円滑な実施の確保を目的とした、製品の製造業者との取り決め、品質管理業務手順書等への記載
- 製造方法、試験検査方法等についての変更が当該製品の品質に影響を及ぼすと思われる場合の事前連絡の方法および責任者に係る事項の取り決め、品質管理業務手順書等への記載

GQP関係；第10条（適正な製造管理及び品質管理の確保）

- 品質に影響を与えるおそれのある製造方法、試験検査方法等の変更について製造業者等から連絡を受けたときは、当該内容の評価実施。

製造業者GMPと製造販売業者GQPとの
品質および品質管理に関する適切な取り決め（契約）

製剤GMP指針
「13　変更管理」

1. 変更管理体制の確立（13.10）
2. 変更管理体制が取り扱う変
3. 変更管理手順書（13.12）
   システム、原料・資材、規格、製造工程、
4. 変更管理手順書に含まれる
   ①変更計画書の作成、
   ②再バリデーション、追加試験検査、
   ③変更後の製品品質の評価方法と基準（事前設定）
   ④文書の改訂及び職員の教育訓練の方法と実施
   ⑤「その他所要の措置」の決定
5. 計画と結果の起案・報告・照査、品質部門の承認（13.14）
6. 変更実施後の最初の複数のロットの評価（13.15）

本指針と解説により、GQPとGMPの関係において考慮すべきことが共通の理解となっていくことが期待できる

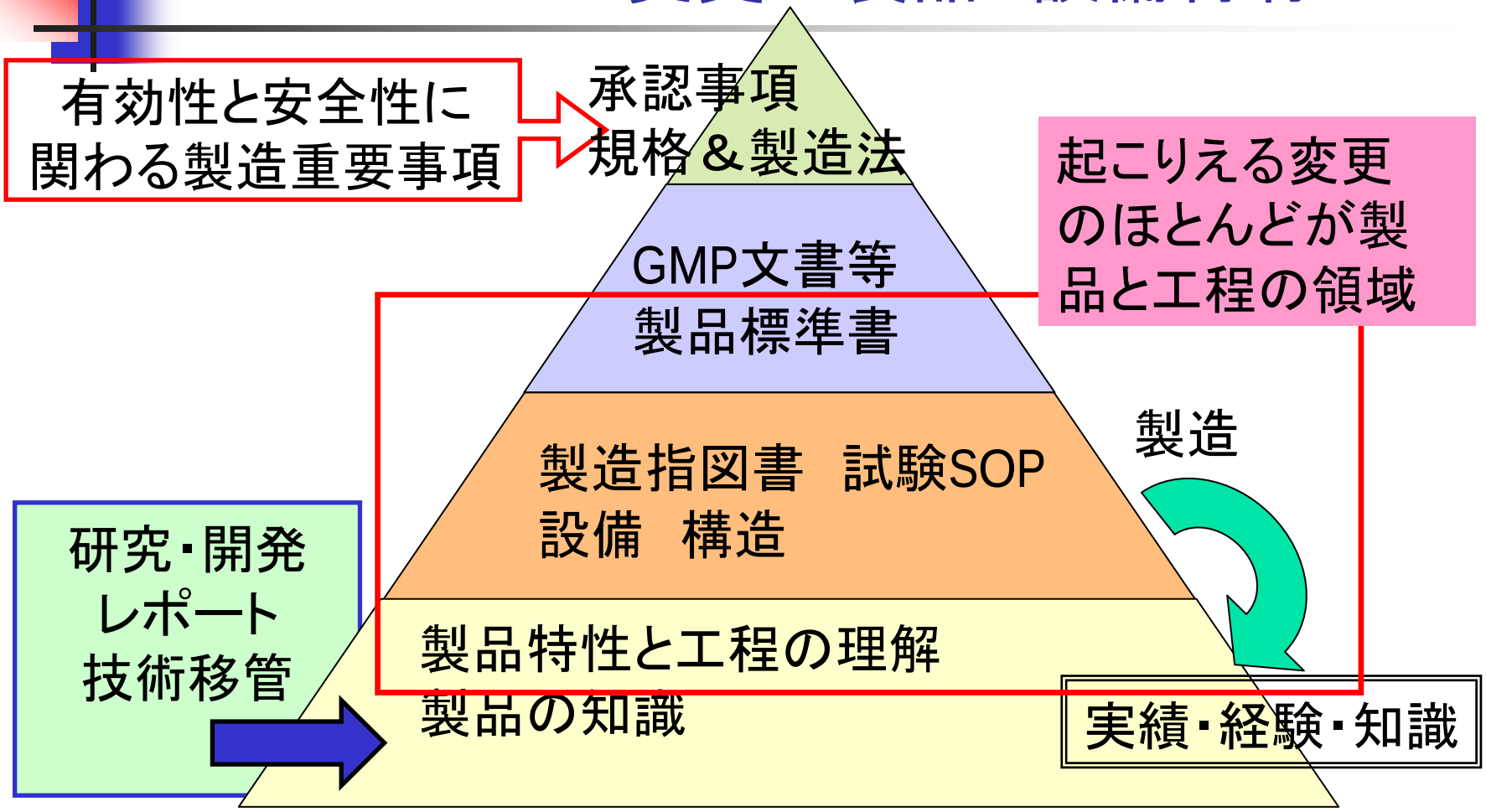
変更の理由

1. 逸脱や不適合の本質的な是正と予防
2. プロセス・試験法の改善や更新
3. コスト削減
4. 技術革新
5. 設備更新
6. 付加価値の向上
7. 管理要件の増減
8. その他

改善と技術革新
→製品ライフサイクルに
関わる要因
①恒常的な生産と供給
②製品寿命とコスト

GMPにおける変更発生の領域

ほとんどの変更は製品&設備特有



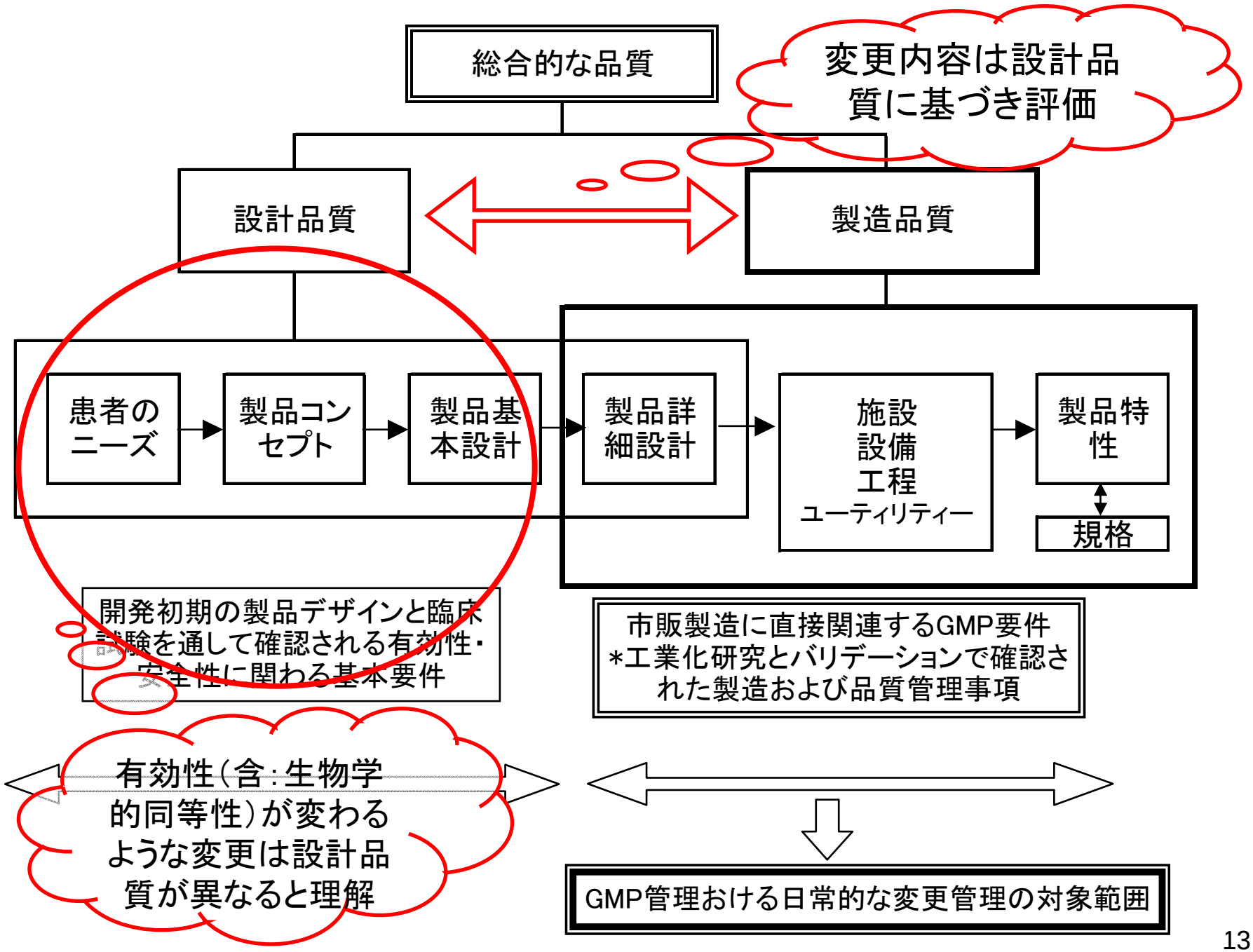
品質の定義

- Q6a 「新医薬品の規格及び試験方法の設定について」(医薬審発第568号　平成13年5月1日)
  - **品質**:「**原薬あるいは製剤の意図した用途への適切さ**のこと。同一性、含量、物質の純度のような特性を指すこともある。」
  - **規格および試験方法**:「試験方法、その試験に用いる分析法の記載、ならびにその方法で試験したときの適否の判定基準からなるリスト。**原薬または製剤が意図した用途に相応しいものであるために適合すべき一組の基準**」
  - 「規格に適合する」:規定の方法で試験するとき、原薬や製剤がリストにあるべき判定基準に適合することを意味する。」

- Q9「品質リスクにマネジメントに関するガイドライン」
（薬食審査発第0901004号　平成18年9月１日）
  - 「**品質**：製品、システム、または工程に係る**本質的性質の組み合わせが要求事項を満たす程度**」

⇒品質は開発過程の実績から成るとの視点から・・

- 総合品質：「ユーザーの満足度をどの程度満たすことができるか」をもって評価する製品の価値。
- **設計品質**：製造の目標としてねらう特性であるが、「患者や治療のニーズをどの程度取り込めているか」との視点の基で、**臨床試験を通して確認された有効性と安全性および安定性を発揮した製品特性の実績範囲**
- **製造品質**：**「目標とした設計品質をどの程度正確に実現・再現できているか」**で判断される


総合的な品質
変更内容は設計品質に基づき評価
設計品質
製造品質
患者のニーズ
製品コンセプト
製品基本設計
製品詳細設計
施設
設備
工程
ユーティリティー
製品特性
規格
開発初期の製品デザインと臨床試験を通して確認される有効性・安全性に関わる基本要件
市販製造に直接関連するGMP要件
*工業化研究とバリデーションで確認された製造および品質管理事項
有効性（含：生物学的同等性）が変わるような変更は設計品質が異なると理解
GMP管理おける日常的な変更管理の対象範囲

変更後の品質の同等性とは？

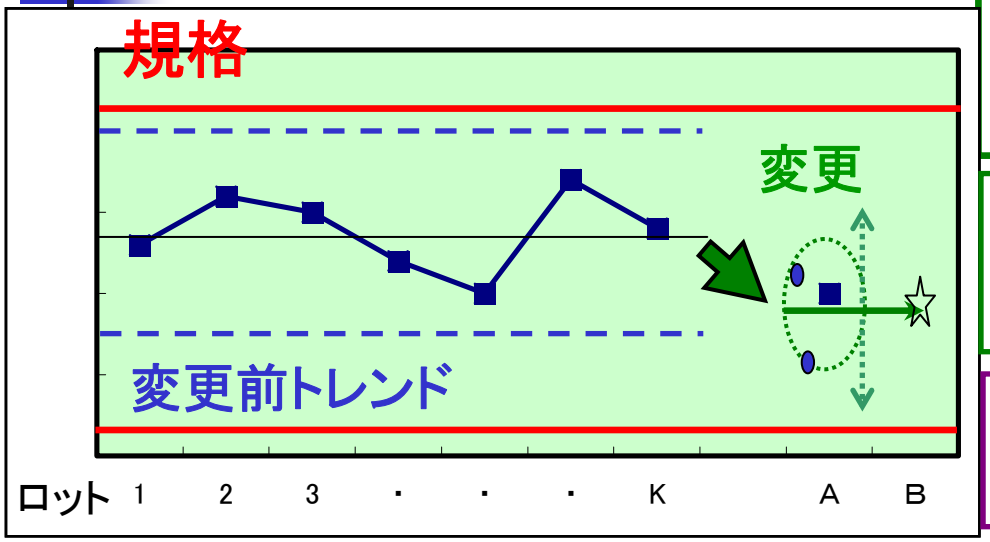
1. 有効性・安全性は維持
2. 理化学的特性は何かしら変化を受ける
   - 「データのアウトプットが一致している」？
   - 「規格内であれば良い」？

⇒ 規格適合性の評価は必須。ただし必要なら設計品質を維持できる「より適正な規格」への変更も可能である。

⇒変更後の製品特性を必要に応じ多面評価

3. 変更前後で、「承認書・申請資料記載事項の記述・文言が同等」は本質ではない

品質評価と追加試験



目標値の変化は
意図した通り？

予測変動幅は
変更前と同じ？

工程内での特性変化
ex.固形剤の顆粒など

⇔

製品知識・工程理解

追加試験（必要に応じた設計品質に関連する特性評価）の例示

- 安定性（加速・苛酷・長期）→経時変化挙動・不純物プロファイル
- 不純物プロファイルの変化→毒性試験
- 溶出特性のpH依存性など詳細プロファイル評価　など

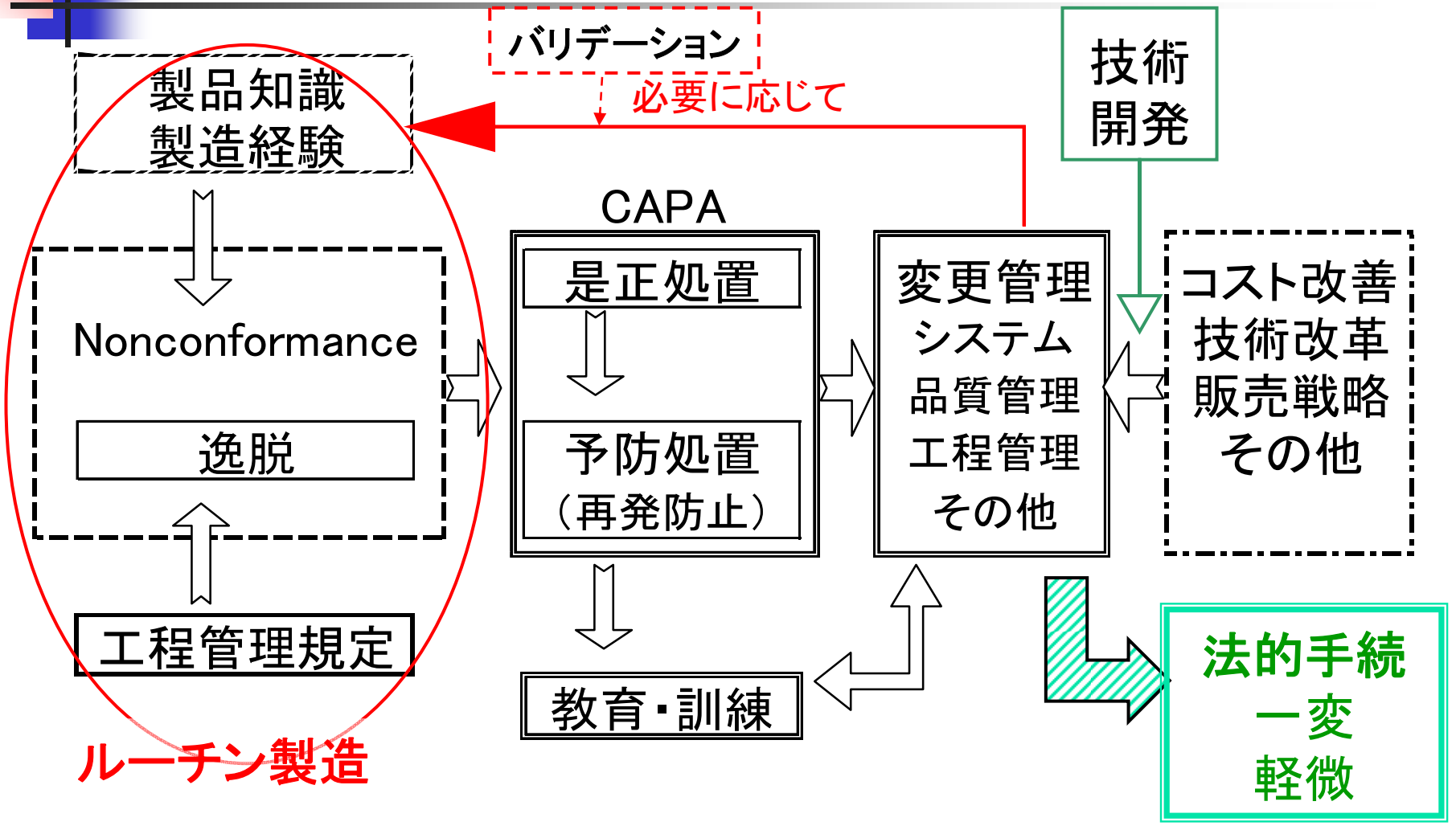
→ **品質の多面評価による規格適合性と同等性の判定**

変更管理の基本

1. GMPとしてすべて記録されること。
2. 製品の品質保証に効果があること。
3. 基本的な設計品質は、変わらないこと。意図している用途、使用方法に合致していること
4. 達成すべき製造品質は、変更前後で同等。
5. 変更後の製品の規格適合性は、設計品質を基に慎重に評価。
6. 総合品質は、変更後でも市場（患者）に受け入れられること（患者へのリスクが増大しないこと）。

品質への影響として確認・考慮すべき事項

変更管理のサイクル

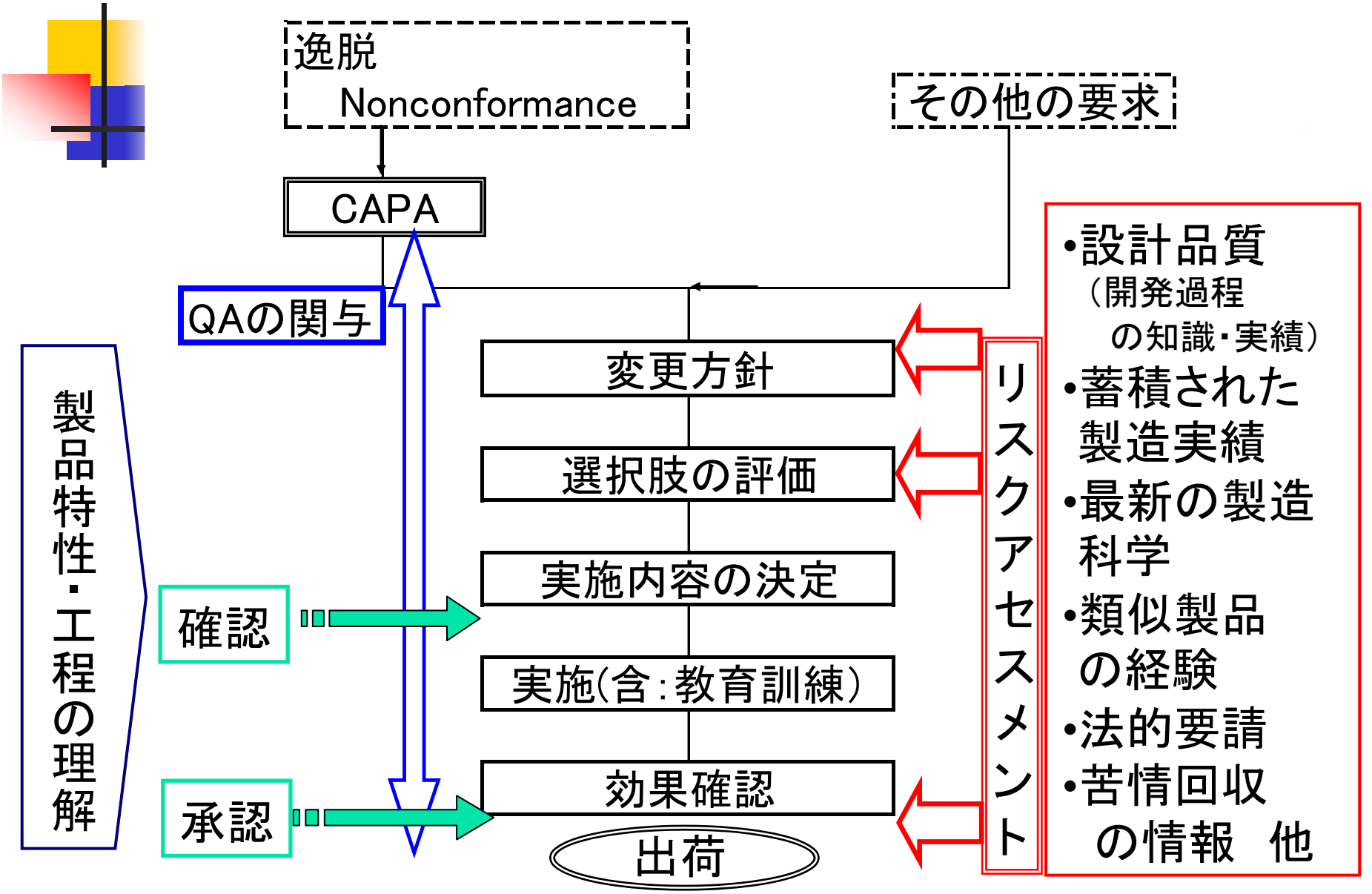

バリデーション
必要に応じて
技術
開発
製品知識
製造経験
CAPA
是正処置
Nonconformance
逸脱
予防処置
（再発防止）
変更管理
システム
品質管理
工程管理
その他
コスト改善
技術改革
販売戦略
その他
工程管理規定
教育・訓練
法的手続
一変
軽微
ルーチン製造

リスクマネジメント

- リスクは個々の医薬品特異的
- リスクは医薬品ライフサイクルを通して変化
  1. リスクアセスメントに基づく品質保証（ICH　Q9）
  2. リスクマネジメントによる製品開発（ICH　Q8）
  3. リスクアセスメント（マネジメント）手法
     - **HACCP**
     - **ISO13485**　「リスクマネジメントの医療機器への適用」規格
     - **ISO14971**　例：FMEA（故障ﾓｰﾄﾞ影響解析）
     - その他

  ICH Q9品質リスクマネジメントブリーフィングパック（教育資料）参照
- チームによるアセスメント／コミュニケーション

変更管理におけるリスクアセスメント

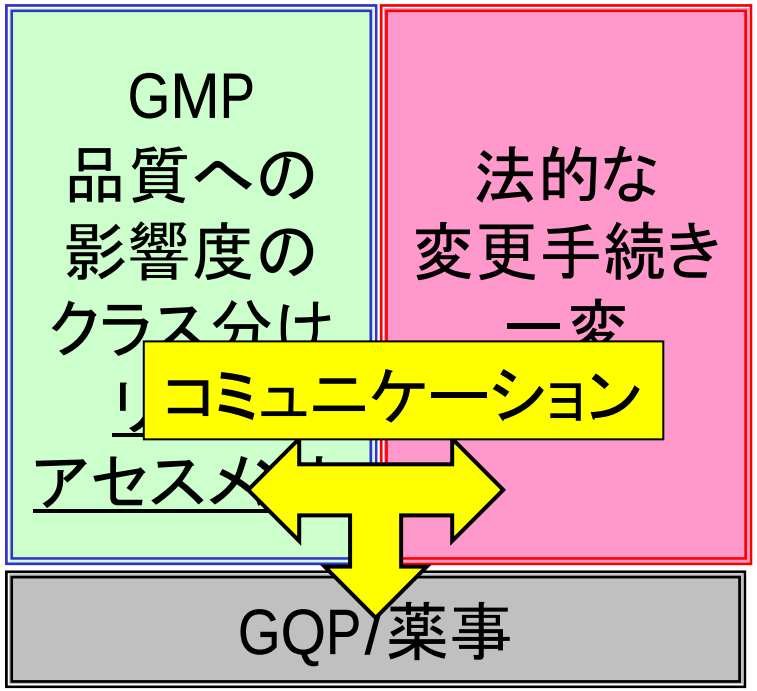


変更のクラス分け

変更の品質への影響

1. リスクは個々の製品特有
2. ライフサイクルを通じて変化
3. 個々のリスクを複眼・多面的にアセスメントする事が必要

1. GMP下の変更は、日常的
2. 変更項目に対する一義的なリスク分類は適切か？
3. 一変、軽微は承認書記載事項の法的手続きの分類
4. 本質への影響は承認書見直し



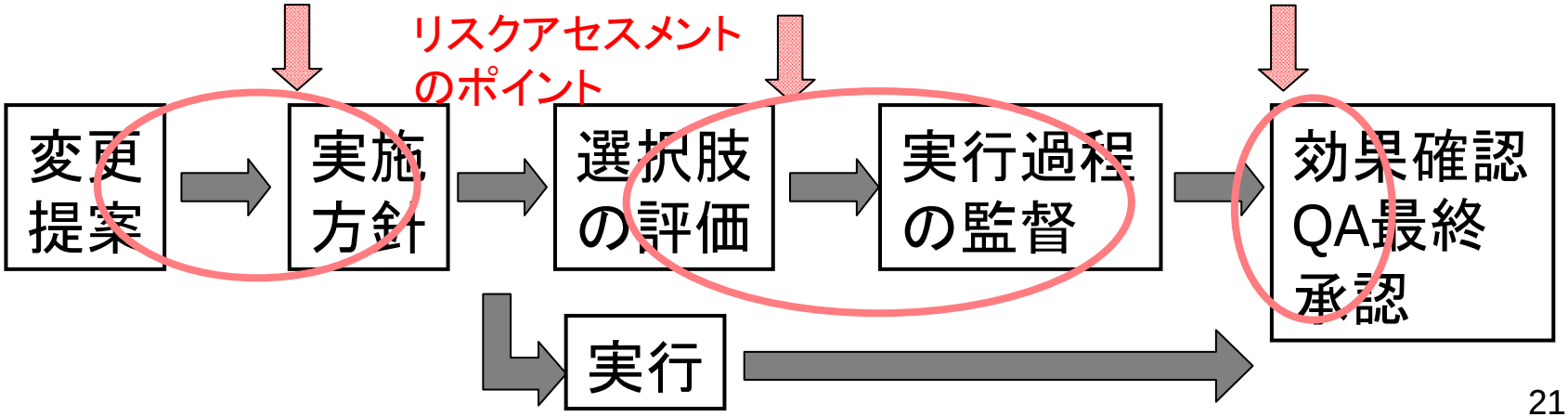
***品質への影響と承認書記載事項へのインパクトの評価の二本立て**

クラス分けとリスクアセスメント

クラス	品質特性の変化
1 品質に影響する	明らかに顕在化
2 品質に影響する可能性	顕在化する可能性
3 品質に影響しない	微々たる変化として顕在化
	特性変化に寄与しない

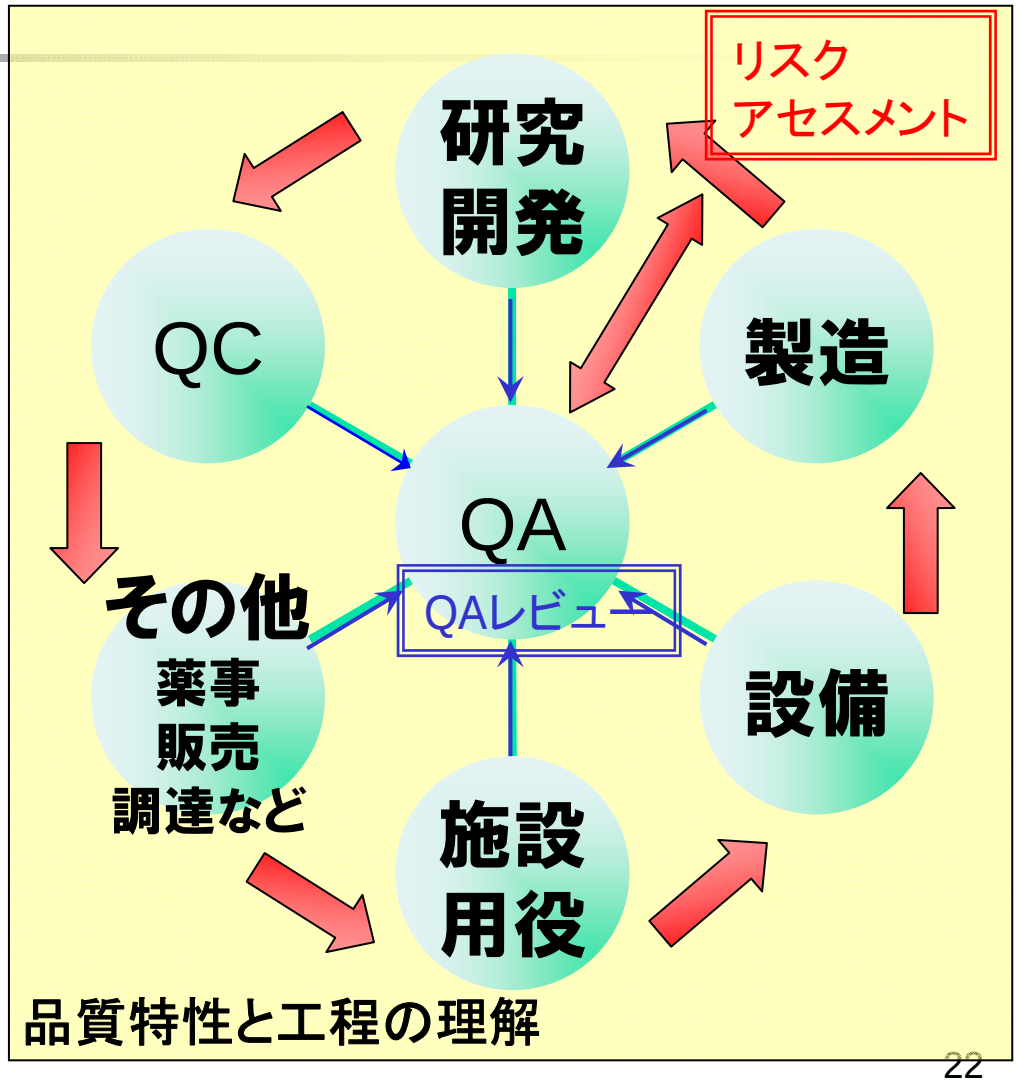
品質評価と効果確認の厳密さと詳細さ

詳細な確認
ex.Validation



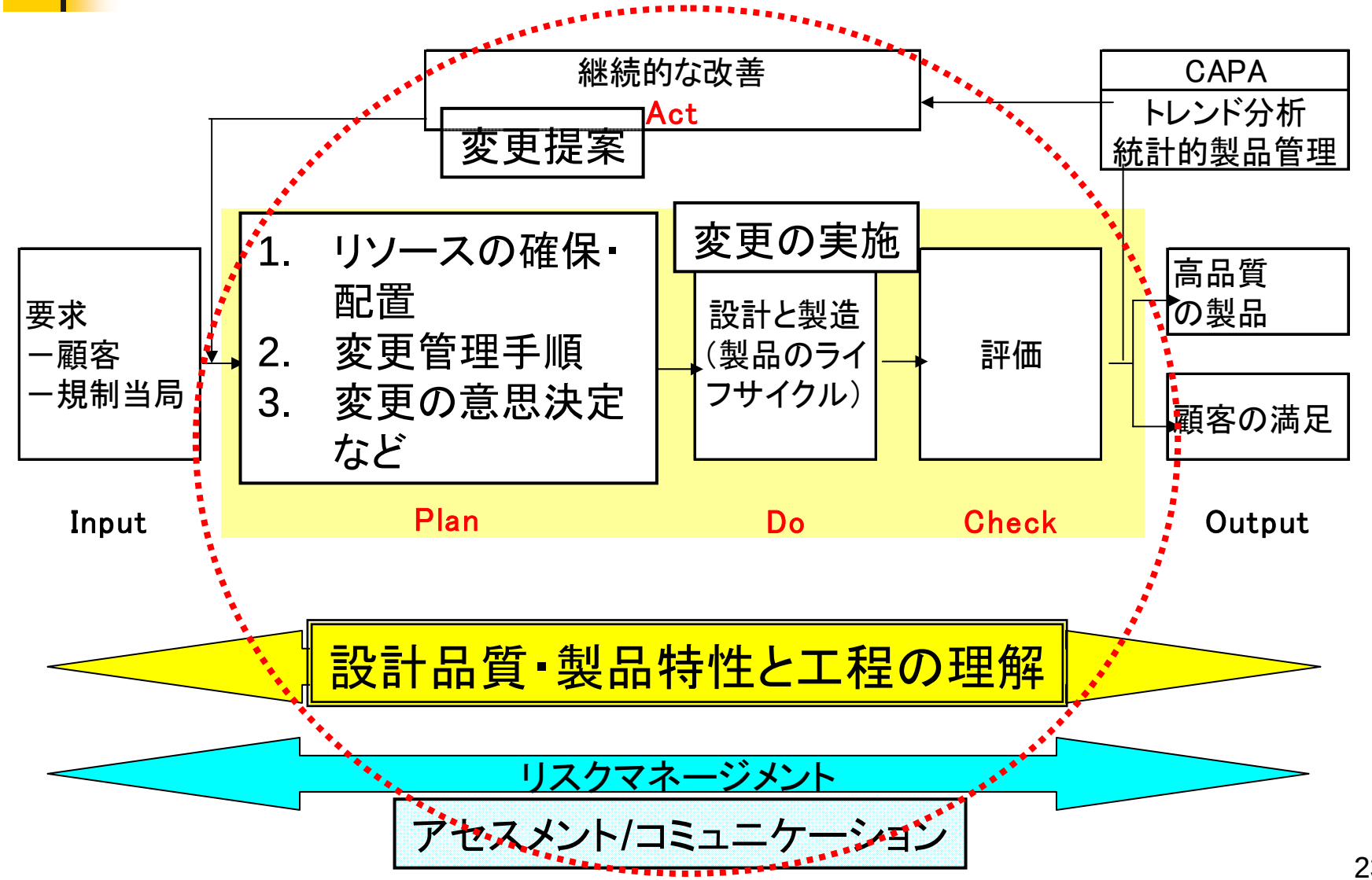
変更のリスクアセスメントとQAレビュー

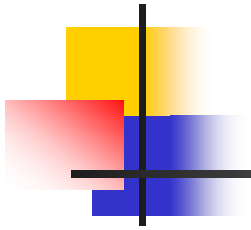
1. リスクは多面的に製品特有の品質特性と工程の理解に基づきアセスメント。
2. 適切な文書システム
3. 必要な各セクション毎にレビュー（必要な確認あるいは承認）
4. QAレビューは各セクションのレビュー集約と最終判断
5. 単一組織だけの単眼的なレビューにならないシステム



最新の品質システム

Chris Joneckis, Ph.D. Senior Advisor CMC Issues, CBER, FDA 発表資料より





（以下予備資料）

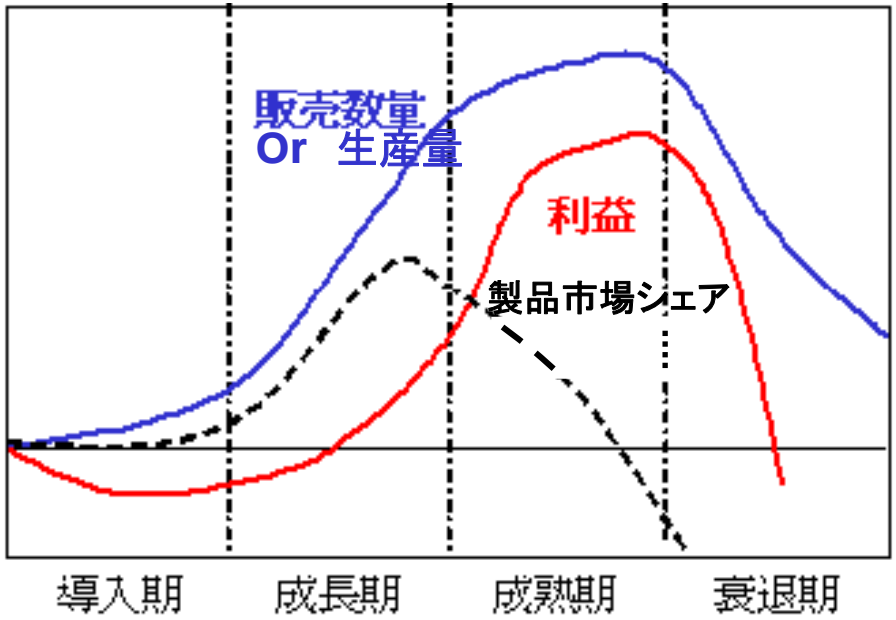
製品ライフサイクルマネジメント

- 工業製品開発の企画段階から設計、生産、さらに出荷後のユーザサポートなどすべての過程において製品を包括的に管理する手法。
- 医薬品の場合、市場への導入は、製造販売承認取得を前提とし、承認は臨床試験を通じて安全性と有効性を示すことが確認された品質と、その品質を製品として形づくる製造法に対するもの。
- 医薬品の品質は、開発段階から情報と知識が集約されて市販製品に至ったと考えると、いかなる変更も製品ライフサイクルマネジメントとして捉えるべきかもしれない

製品ライフサイクル

- 導入期：新製品発売時期がこれに相当。製品を広く認知させる時期。初期宣伝活動とPMS解析が重要。市場での成長規模予測。
- 製造部門の役割

1. プロセスバリデーションからルーチン製造への移行における初期流動管理
2. 製造の再現性データ蓄積
3. 初期逸脱管理と是正。必要に応じ、承認範囲内での手順等の微調整
4. 市場予測規模に応じた追加設備投資準備等の対応

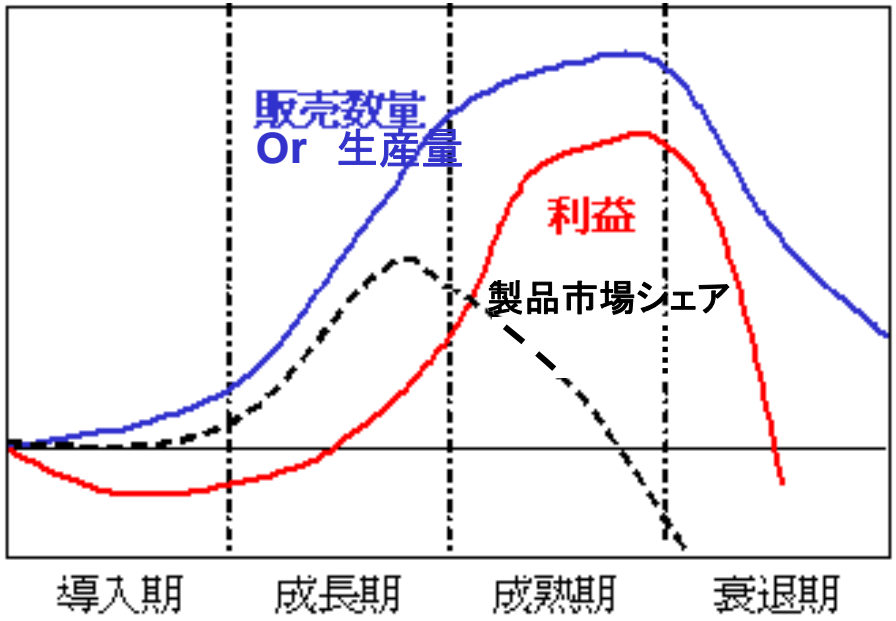


ルーチン製造期のライフサイクルと生産量

製品ライフサイクル

- 成長期：PMS・Vigilanceデータの解析と適正使用情報の継続更新と普及。販売拡大活動。成長期延長の施策。設備投資の必要性判断。
- 製造部門の役割

1. 生産量増大への対応
2. 成熟期対応として生産コスト削減検討
3. 管理トレンドに基づく工程安定化
4. 定期照査
5. 製品苦情対応

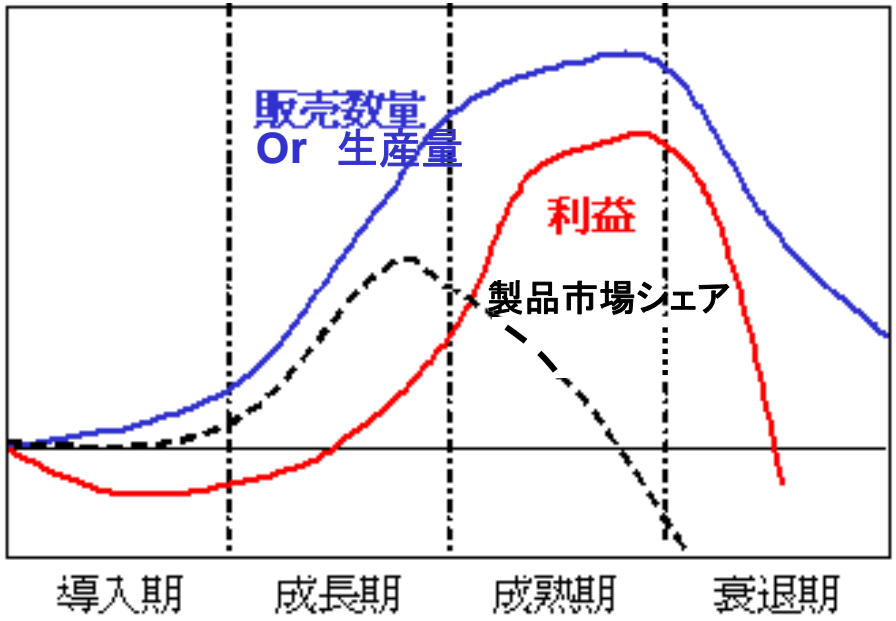


ルーチン製造期のライフサイクルと生産量

製品ライフサイクル

- 成熟期：治療方法の浸透。薬価切り下げ、後発品。製品価値を上げるための適応症拡大や剤形追加。
- 製造部門の役割

1. 利益最大化
2. 衰退期に向けた工程合理化策
3. 技術革新、設備更新あるいはアウトソーシングの検討

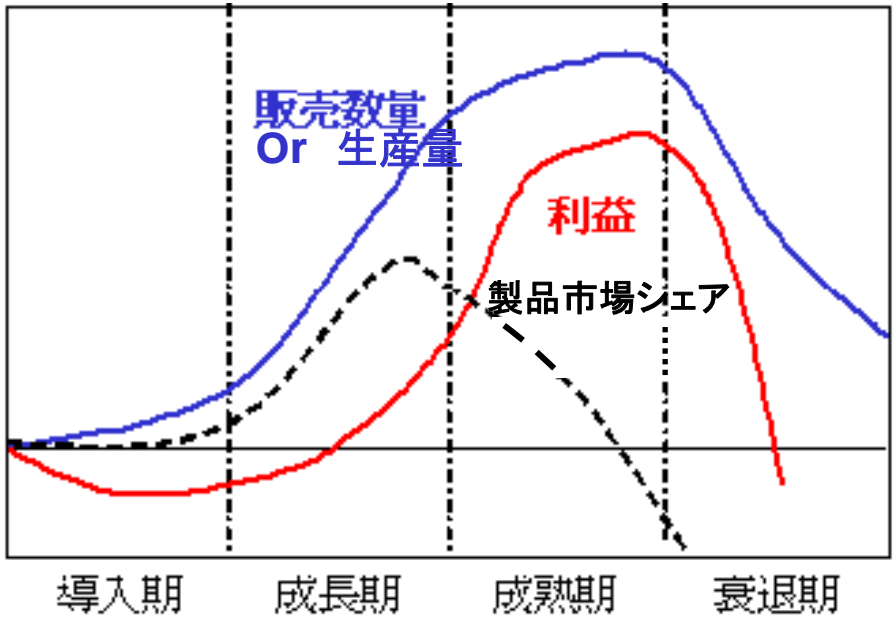


ルーチン製造期のライフサイクルと生産量

製品ライフサイクル

- 衰退期：新しい医薬品・医療技術への移行により供給責任遂行が主となる時期。
- 製造部門の役割

1. 設備投資や更新を抑えた状況での安定生産
2. アウトソーシングの実施
3. 製造ライン統合



ルーチン製造期のライフサイクルと生産量

製品ライフサイクル
承認後変更＆改善（進歩）を考えてみると・・・
変更方針を決める議論

例：凍結乾燥製剤

- 製造者の経験：
  - 製造の一貫性の欠如：逸脱と何バッチかの不合格
    （許容できない品質：外観、水分、含量）

アプローチ１：

既存凍乾サイクルの再バリデーション→進歩なし。

アプローチ２：

凍乾サイクルの再開発→生産性・品質向上（進歩）

アプローチ３：

溶液製剤への剤形変更

→利便性アップ（進歩）vs.安定性向上の困難さによる開発リソース↑

変更におけるリスクアセスメント
FMEA利用例（想定ケーススタディー）

- 現状：

1. プロセス：攪拌造粒・乾燥・混合・打錠
   - 造粒：原薬・バインダー溶液スプレー添加法
   - 乾燥：流動層乾燥
   - 混合：造粒2BT・滑沢剤―V型混合
   - 打錠：打錠圧力変動検出-充填深さ調整
   - 工程能力指数：Cpk　約1.3
2. 品質管理状態における問題
   - 規格不適合発生頻度　含量逸脱：１回／年
   - 含量均一性等の試験結果を勘案。OOSと調査処理が適切に行われ、誤出荷なしと認識

変更起案時のリスク評価

潜在的故障または誤動作	原因	影響	低減策前				低減策（CCPの低減）	低減策後				責任部門	検証方法	インパクト
			重大さ	頻度	検出度	RF		重大さ	頻度	検出度	RF			
1．含量値の分布はずれ（バッチ内・バッチ間の不均一性） 2．打錠機の杵臼きしみによるチョコ停頻発	1．造粒時の粒度別含量分布 2．顆粒充填性	含量OOS 均一性担保 生産性低下	6	4	4	96	スプレー法改善 造粒条件見直し 打錠圧FB制御	2	3	3	18	プロセス技術 QC	Qualification 製造 バッチ内詳細調査分析 傾向分析	一変or軽微 コスト中 所要期間中
							流動層造粒法への変更 粒子制御のリアルタイムモニタ	2	2	2	8	プロセス技術 技術開発 QC	スケールダウン研究／Feasibility バリデーション	一変 コスト大 所要期間長
	3．滑沢剤量・混合時間不足（推定）	生産性低下 錠剤破損	5	4	3	60	滑沢剤量の変更 混合時間延長	3	3	3	27	製造、 QC	Qualification製造 同時的検証	軽微or内部 コスト小 所要時間短

変更発案時のリスク評価

潜在的故障または誤動作	原因	影響	低減策前				低減策（CCPの低減）	低減策後				責任部門	検証方法	インパクト
			重大さ	頻度	検出度	RF		重大さ	頻度	検出度	RF			
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	3．滑沢剤量・混合時間不足（推定）	生産性低下 錠剤破損	5	4	3	60	滑沢剤量の変更 混合時間延長	3	3	3	27	製造、 QC	Qualification製造 同時的検証	軽微or内部 コスト小 所要時間短

リスク中

リスク大

リスク小～中

Japanese Regulatory Workshop

September 26-27, 2007 | Washington, D.C.

AGENDA

Wednesday, September 26, 2007

1:30 p.m. – 2:40 p.m.

Opening Plenary Session

Moderator: Shigeru Hayashi, PhD; Associate Research Fellow, Regulatory CMC Pharmaceuticals, *Pfizer Inc*

1:30 p.m. – 1:40 p.m.
Welcome and Opening Comments
Robert L. Dana, Vice President, Quality and Regulatory Affairs, *PDA*

1:40 p.m. – 2:40 p.m.
Keynote Presentation
Yukio Hiyama, PhD, Chief, Third Section, Division of Drugs, *National Institute of Health Sciences*

2:40 p.m. – 3:00 p.m.
Break

3:00 p.m. – 4:30 p.m.

Plenary Session 2: Marketing Applications – Current and Future Thinking

Moderator: Speaker invited

This session will focus on the current and future state of applications for marketing new products under the Japanese Pharmaceutical Affairs Law, as well as how recent ICH Guidance might impact those submissions.

3:00 p.m. – 3:30 p.m.
Japanese Government Perspective
PDMA Speaker invited

3:30 p.m. – 4:00 p.m.
Industry Perspective – Quality by Design (QbD) Submission
Tom Garcia, Research Fellow, Regulatory CMC PharmSci, *Pfizer Global Reseach*

4:00 p.m. – 4:30 p.m.
Industry Perspective – Traditional Submission
Robert Fike, Vice President Global Regulatory Affairs Japans, *Wyeth Research*

4:30 p.m. – 4:50 p.m.
Panel Discussion and Q&A featuring afternoon speakers

4:50 p.m. – 5:00 p.m.
Closing Remarks
Moderator: Shigeru Hayashi, PhD, Associate Research Fellow, Regulatory CMC Pharmaceuticals, *Pfizer Inc*

Thursday, September 27, 2007

8:30 a.m.
Welcome and PDA Technical Report Briefing
Moderator: Robert Myers, President, *PDA*

8:30 a.m. – 10:00 a.m.
Plenary Session 3: GMP Inspections I
Moderator: Simon Golec, PhD, Senior Director, Women's Health, Global Regulatory Affairs, CMC, *Wyeth*

This session will provide an overview of the Japanese Pharmaceutical and Medical Device Agency's (PMDA) GMP inspection program.

8:30 a.m. – 9:15 a.m.
Overview of the PDMA GMP Inspection Program
Hirokazu Hasegawa, Director for GMP Inspection, Office of Compliance and Standards, *PDMA*

9:15 a.m. – 10:00 a.m.
GMP Inspections – Current trends and Inspectional Findings
Takashi Nagajima, GMP Expert, Office of Compliance and Standards, *PDMA*

10:00 a.m. – 10:15 a.m.
Break

10:15 a.m. – 11:45 a.m.
Plenary Session 4: GMP Inspections II
Moderator: Robert L. Dana, Vice President, Quality and Regulatory Affairs, *PDA*

This session will continue the discussion of GMP inspections by providing the industry perspective on the Japanese PDMA inspection program.

10:15 a.m. – 10:45 a.m.
Japanese Industry's Experience of PAI GMP Inspection by PMDA and FDA
Izumi Saito, *Shionogi Pharmaceutical Co Ltd.*

10:45 a.m. – 11:15 a.m.
Case Study-Quality by Design Submission in Japan
Todd M. Smith, Senior Manager, Quality Assurance, Asia-Pacific, *Merck and Co. Inc.*

11:15 a.m. – 11:45 a.m.
Panel Discussion and Q&A featuring morning speakers

11:45 a.m. – 12:30 p.m.
Workshop Wrap-up and Closing Remarks
Moderator: Shigeru Hayashi, PhD, Associate Research Fellow, Regulatory CMC Pharmaceuticals, *Pfizer Inc*

Science and Regulatory Studies at National Institute of Health Sciences

Yukio Hiyama
Chief, 3rd Section, Division of Drugs
NIHS, MHLW
Seminar at US FDA, October 2, 2007

Outline of presentation

- Organization and work relationship within MHLW
- Overview of NIHS
- Health Science Studies

Analytical Methods Development to support product development and manufacturing controls

- Regulatory Sciences Studies

Quality System, GMP guidance, Tech Transfer

GMP inspection policy, guidance

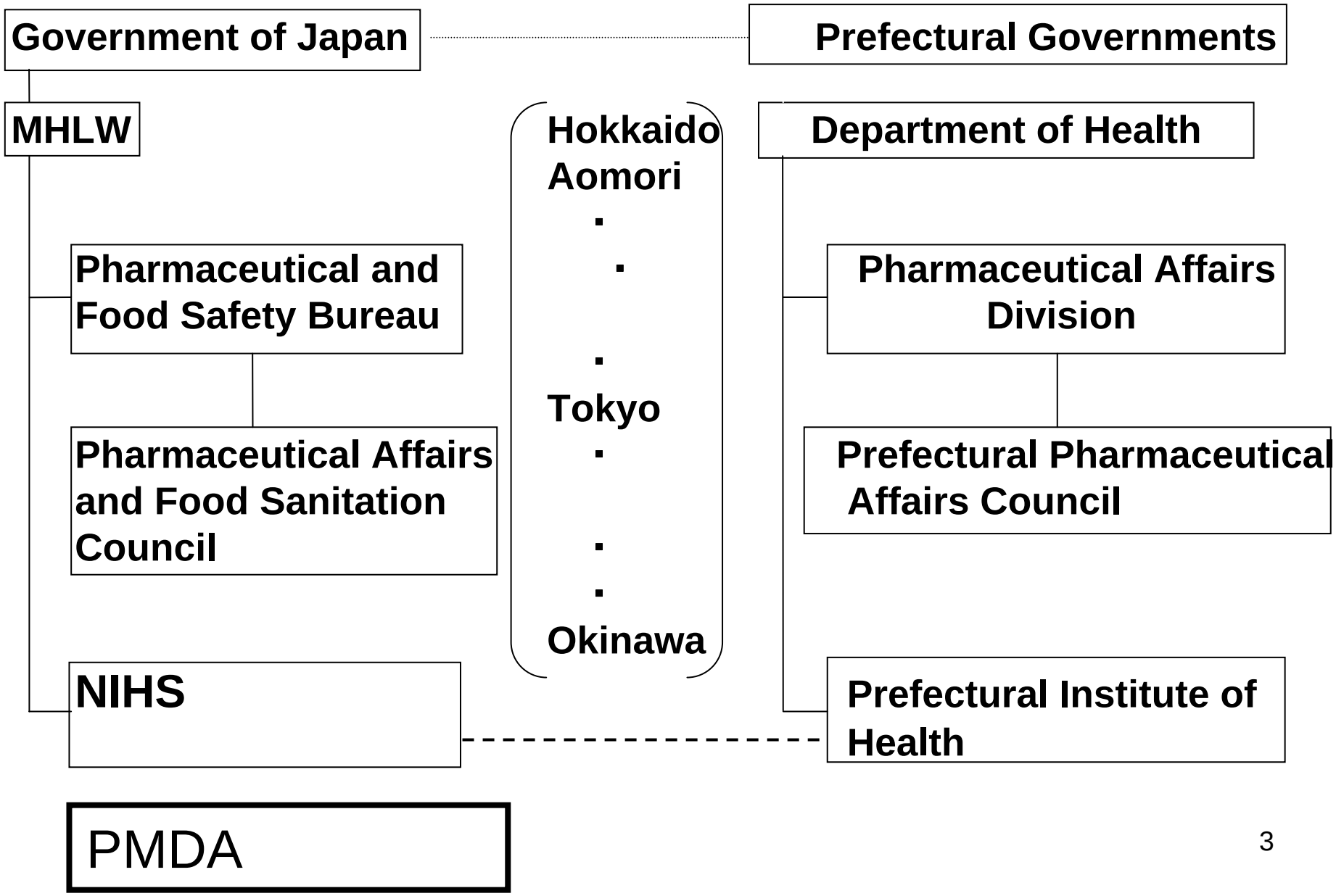
Manufacturing process in Approval- ICH Q8

GMP policy for Clinical Supplies-Exploratory clinical trials

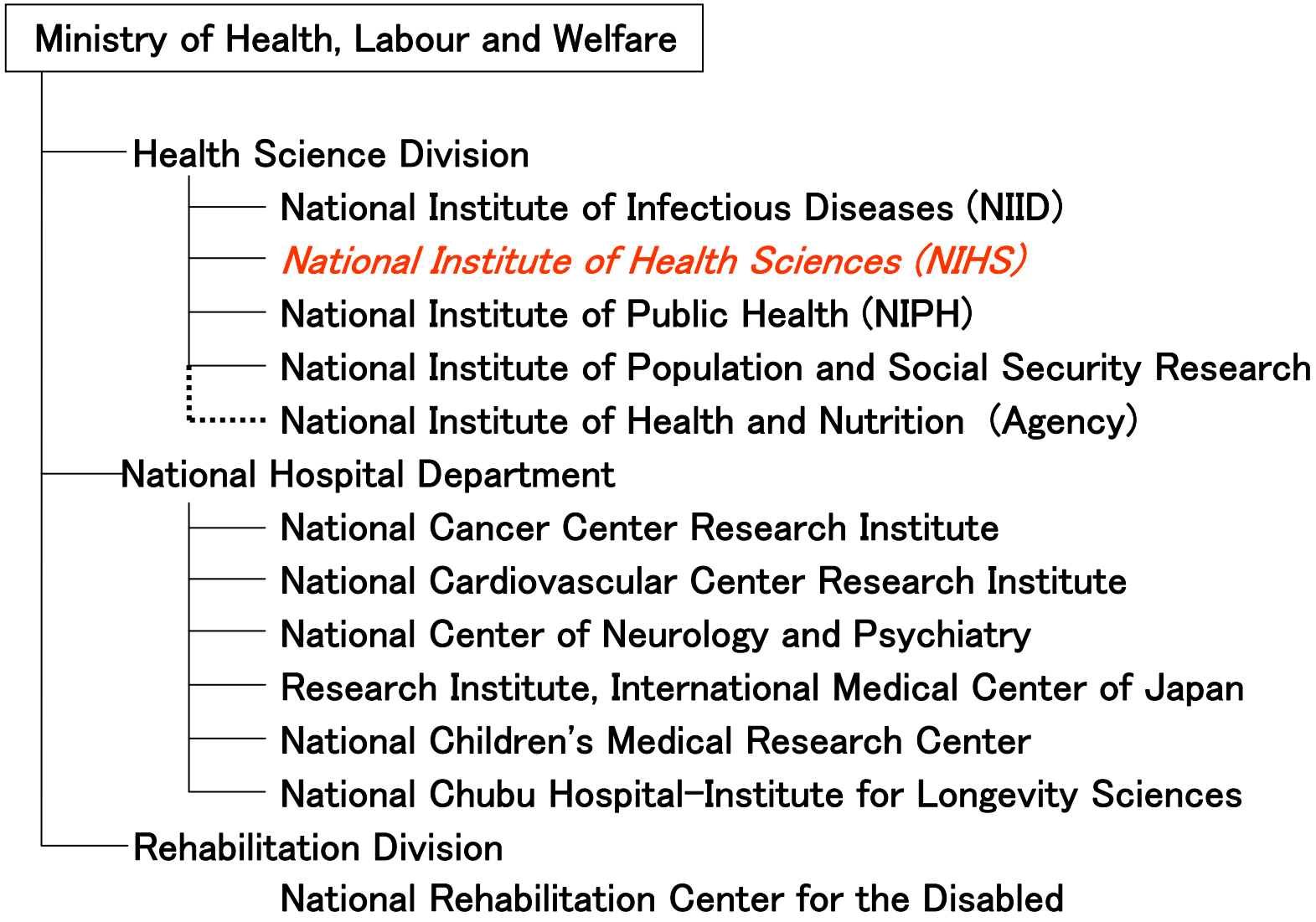
- Pharmaceutical Regulations, Review Process, JP
- Training program for GMP/QMS inspectors

Annual 5 week training course at N I Public Health

Relation of Central and Prefectural Pharmaceutical Administration



National Research Institutes of the MHLW



National Institute of Health Sciences (NIHS)

- Established in 1874 as the Tokyo Drug Control Laboratory / Rearranged on 2002.4.1/Updated on 2004/4/1
- Number of staff :
- Budget
- Major functions and responsibilities of this institute are:

1. to conduct wide range of research works and tests to ensure quality, efficacy and safety of drugs, foods and other goods.
2. (to evaluate drugs and medical devices applied for approval. Moved to PMDA)
3. to gather information and develop databases on the safety of chemicals in drugs, foods, etc.

Organization of PMDA **(est 2004)**

-Review:

New Drugs, Medical Devices, Biologics, Generics and OTC

-Audits: GLP, GCP

-Audits: GMP and QMS

-Standards: JP Secretariat

-Adverse Health Effect Relief Services

-Reviews and Related Operations / Postmarketing Safety

MHLW Grant (Health Science) study on Evaluation Methods for Pharmaceutical and Process Development (2004-2007)

- The needs-quality assurance based on science and risk management, gap between desired state and current status, rPAL and ICH
- The group structure- Industry, Academia and Government (NIHS) Joint

(Industry: Eisai, Fujisawa, Pfizer, Powrex, Shionogi, Santen and Tanabe 2004-2005 member)

List of topics in the Health Science Program (2006)

Characterization of granulated powders by NIR (NIHS)

Characterization of freeze dried formulation by NIR (NIHS)

Water activity and microbiological preservative capability in non aqueous ophthalmic formulation (Santen)

Crystal morphology and dissolution characteristics (Toho University)

Potential application of Ultra Performance Liquid Chromatography for PAT (NIHS)

Rapid microbiological detection for solid dosage manufacturing controls (Pfizer)

Granulation mechanism by NIR imaging technique (NIHS)

Investigational methods for manufacturing deviations (Eisai)

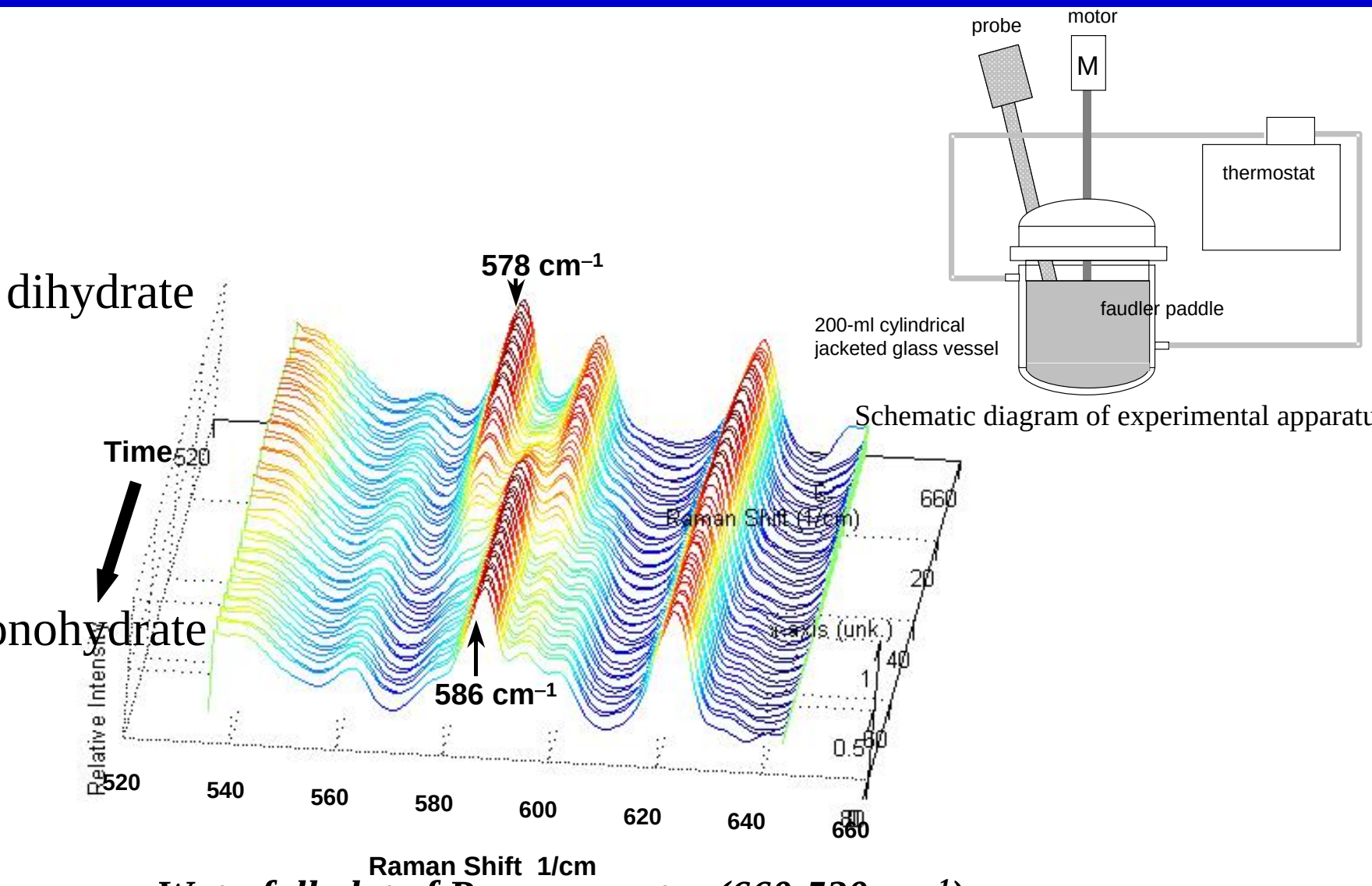
Raman spectrometric application in API crystallization process (Tanabe)

Rapid content determination at tableting process (Astellas)

Identification of packaged clinical formulations by NIR (Shionogi)

Real time process control of coating process (Powrex)

Application of Raman to Process Chemistry - Crystallization -



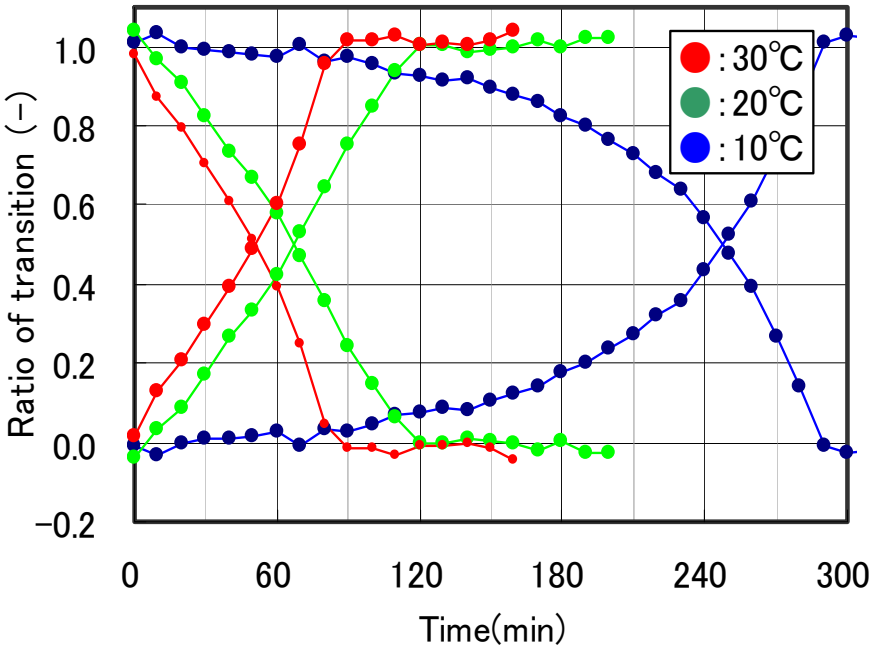
Schematic diagram of experimental apparatus

Waterfall plot of Raman spectra (660-520 cm^{-1}).

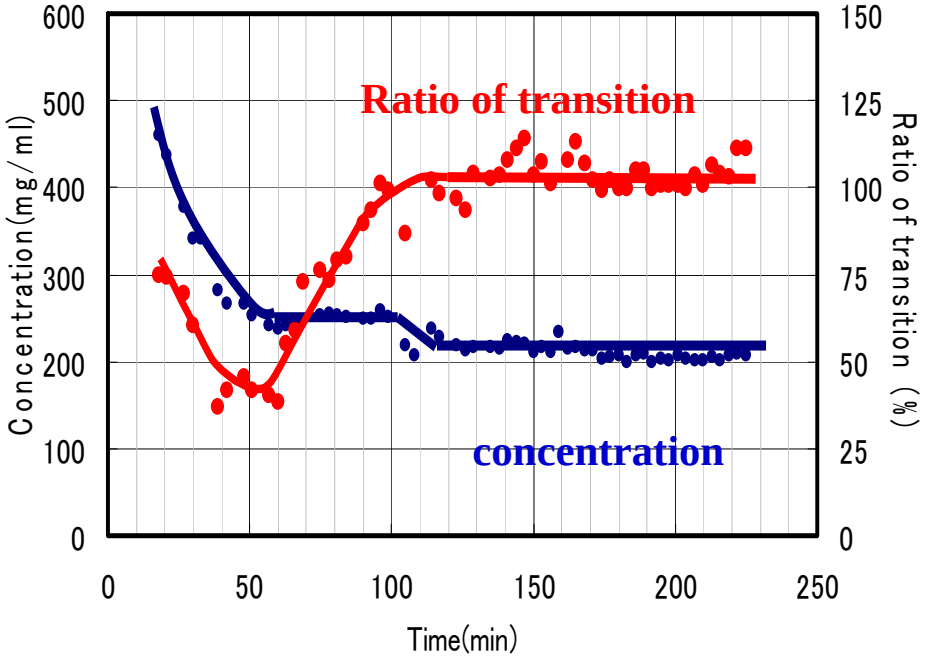
in situ monitoring of polymorphic transition was possible!

TANABE SEIYAKU CO.,LTD.

Application of Raman to Process Chemistry - Crystallization -



temperature vs transition rate



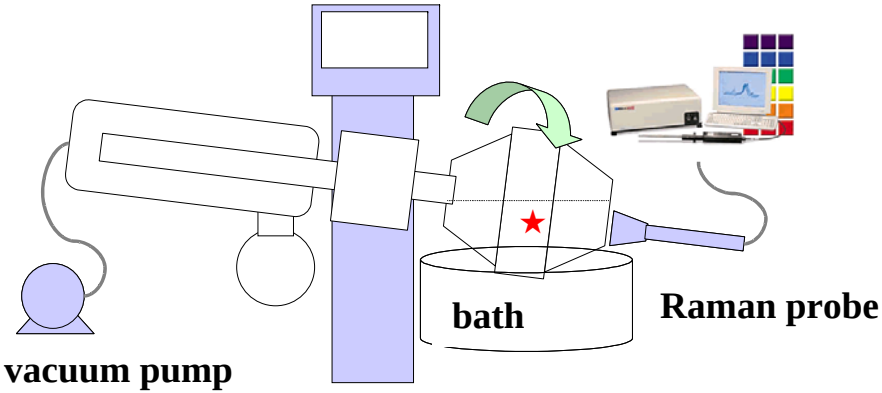
Ratio of transition and concentration in crystallization

The kinetics and endpoint of polymorphic transition can be monitored easily!!

Both the ratio of polymorphic forms and concentration can be determined by PLS!!

Raman is effective as a process analytical technology tool

Application of Raman to Process Chemistry - drying -

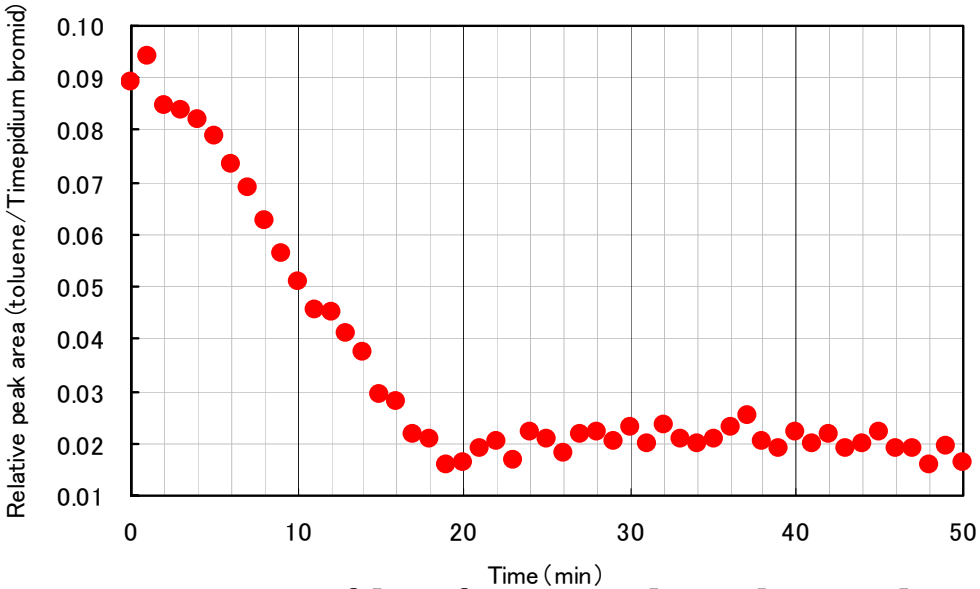


Schematic diagram of experimental apparatus

Solvent Wet cake
toluene(18.2%w/w) in Timepidium bromide

Drying Condition
in vacuum, the bath temperature of 40degrees

Raman probe
Non-contact Optics with working distances of 3 inches



Drying profile of Timepidium bromide

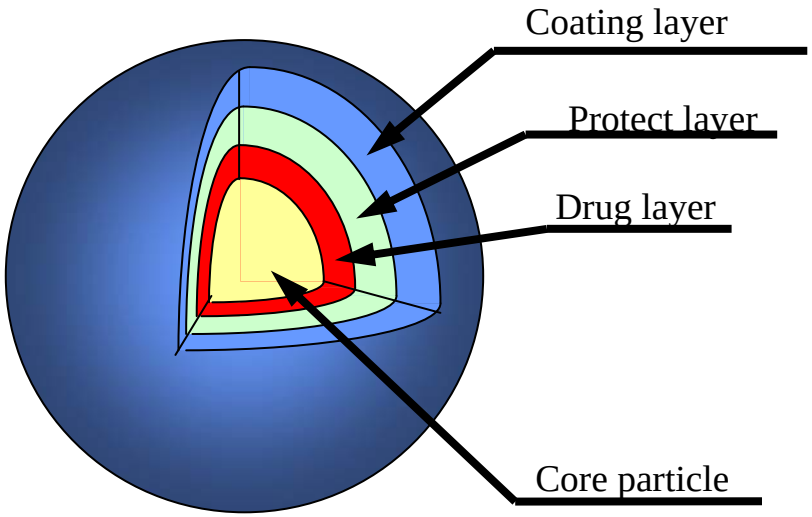
in situ monitoring through glass of drying was possible!

this method do not need braking vacuum for sampling

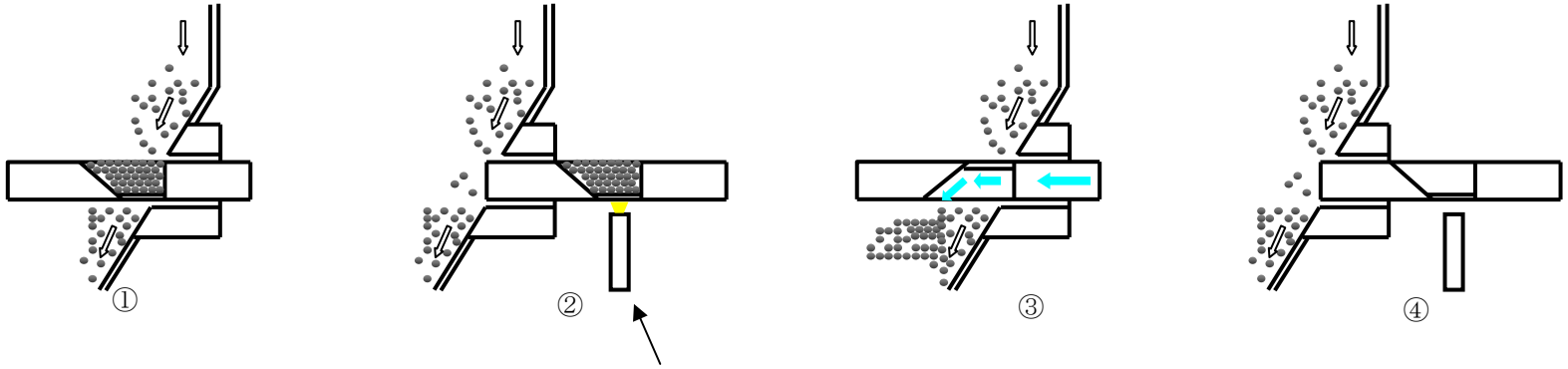
Raman is effective as a process analytical technology tool

TANABE SEIYAKU CO.,LTD.

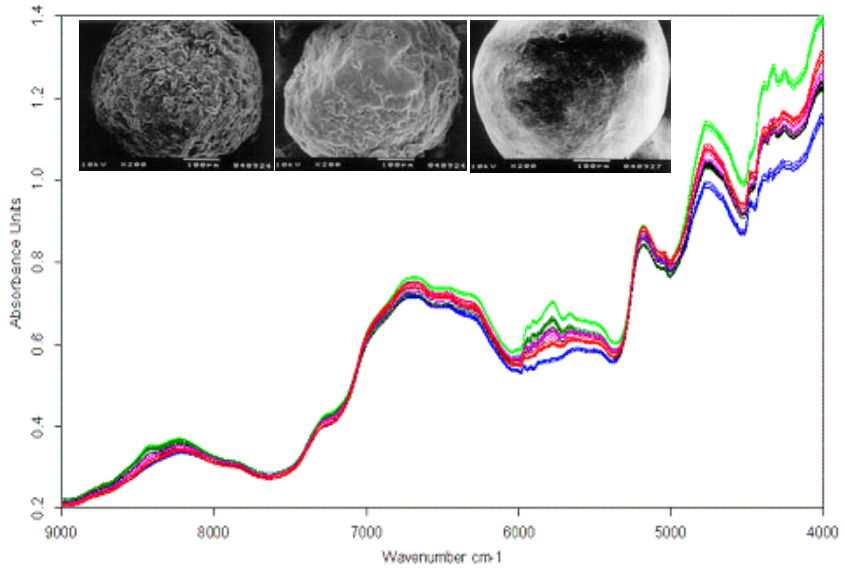
Real-time monitoring of coating performance by NIR (POWREX)

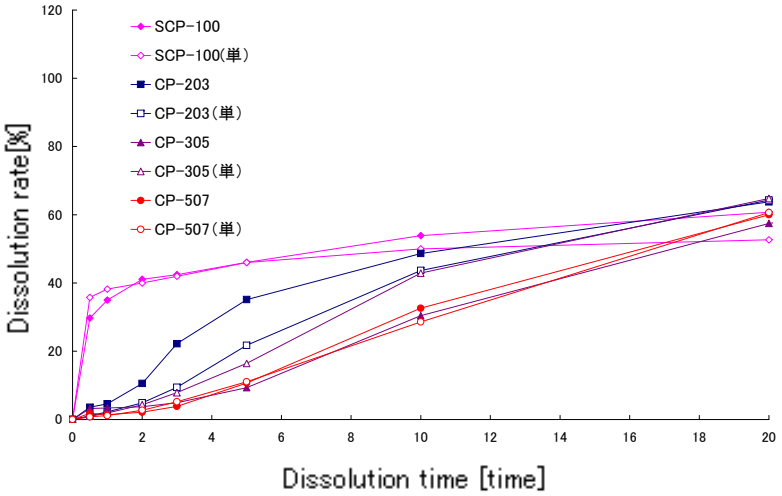


Particle coating

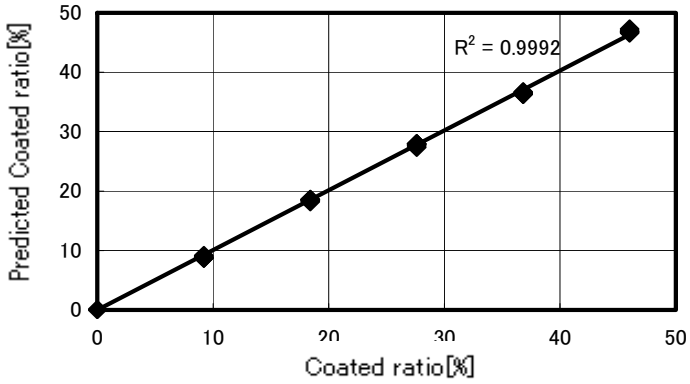


Prediction vs True by NIR (off-line)

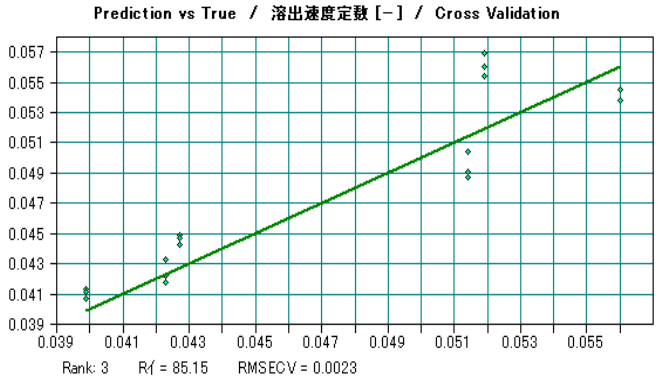




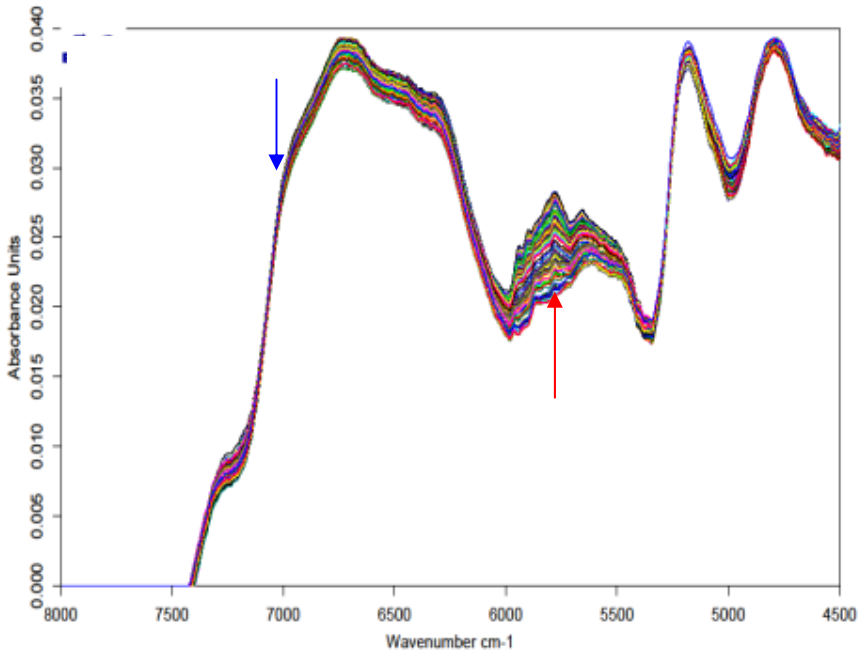
←Real coated ratio

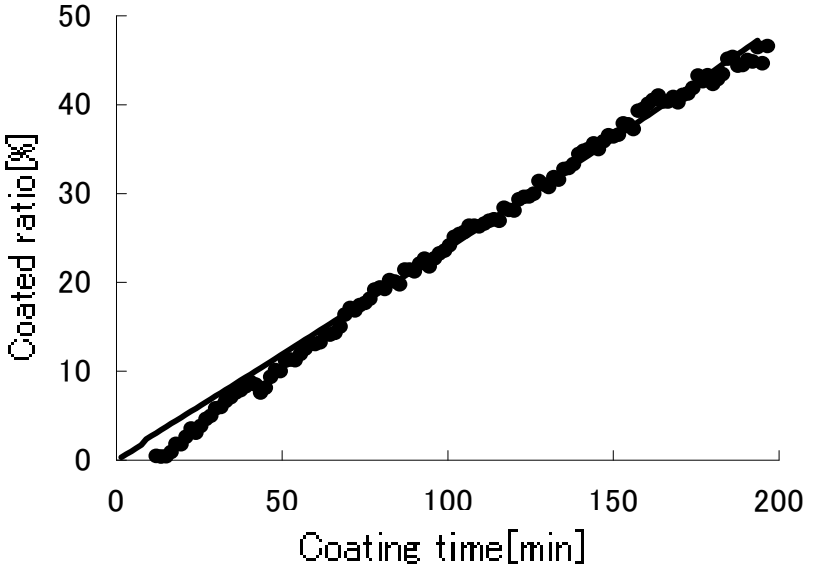


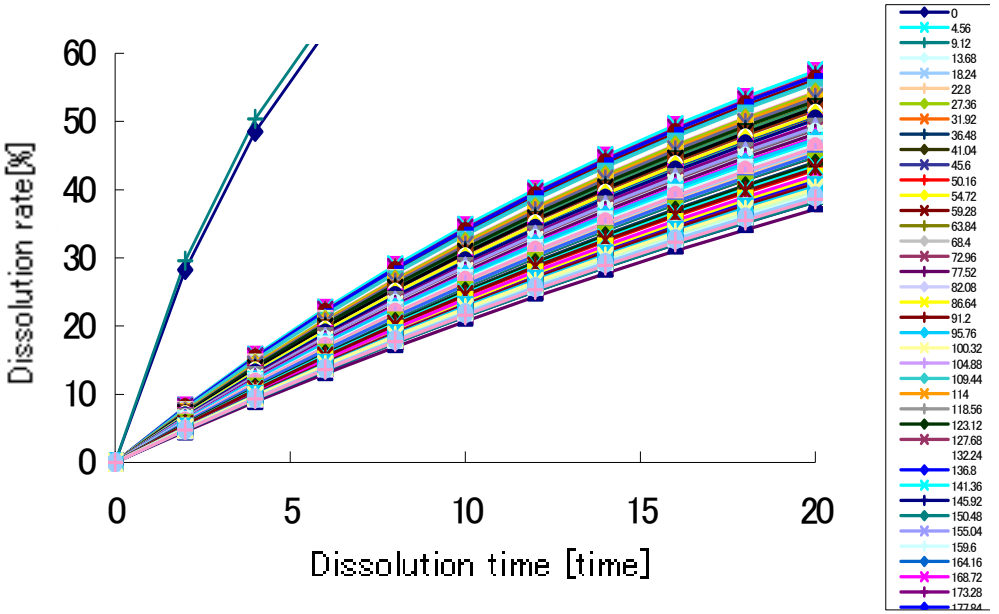
←Coating performance *k*



Coated ratio/Coating performance (Real-time monitoring)







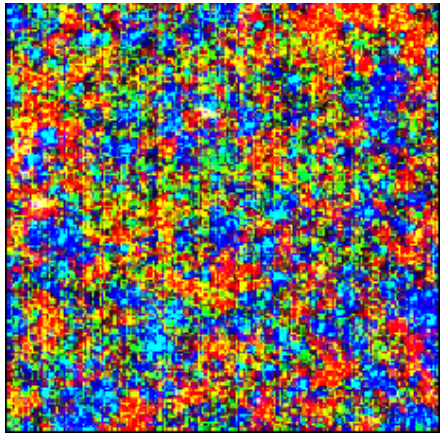
Granulation mechanism by NIR imaging (T.Koide, NIHS)

The wet granulation is commonly employed in Japan.

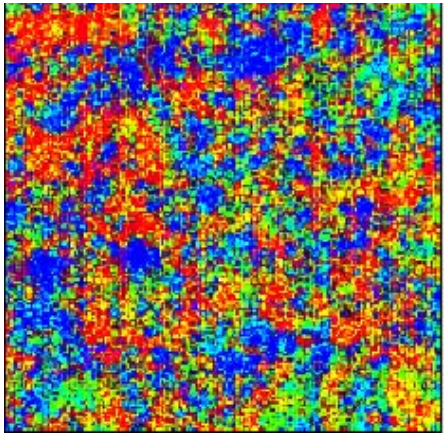
The purpose of this investigation:
To understand granulation mechanisms
To apply its results to pharmaceutical development and manufacturing process control

In this study, we analyzed high shear granulation by NIR imaging system where chemical information at micron level is available

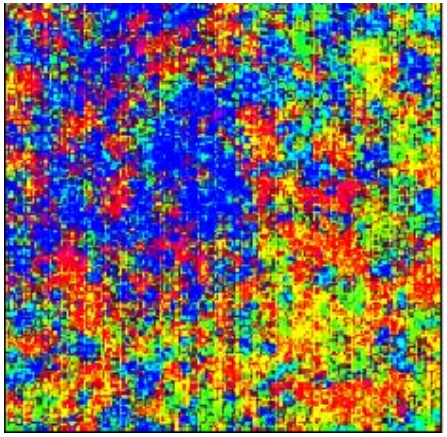
RBG Image by PLS2 (5 min granulation, hand pressed tablet)



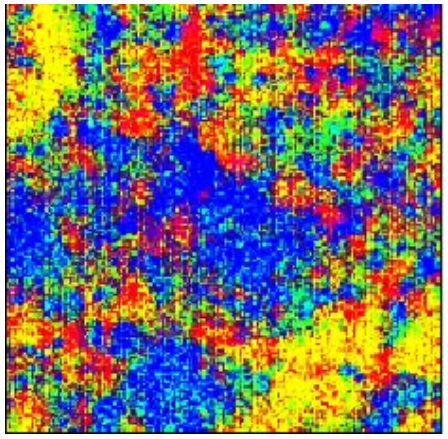
Pre granulation



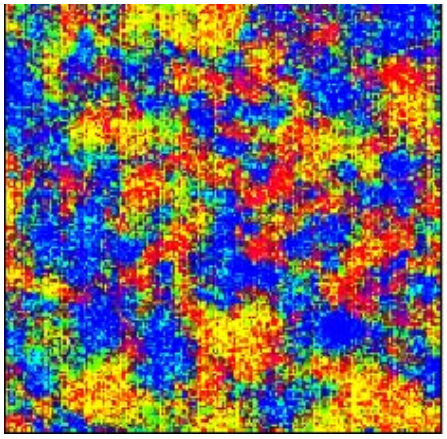
40rpm



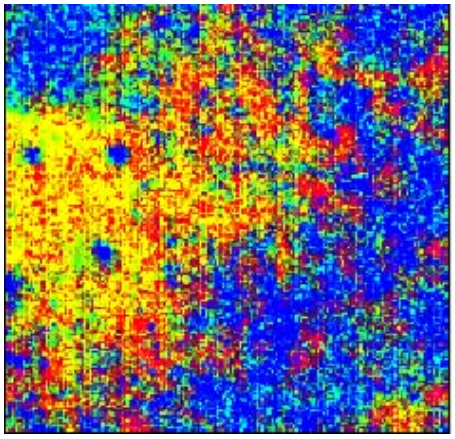
80rpm



120rpm



200rpm



240rpm

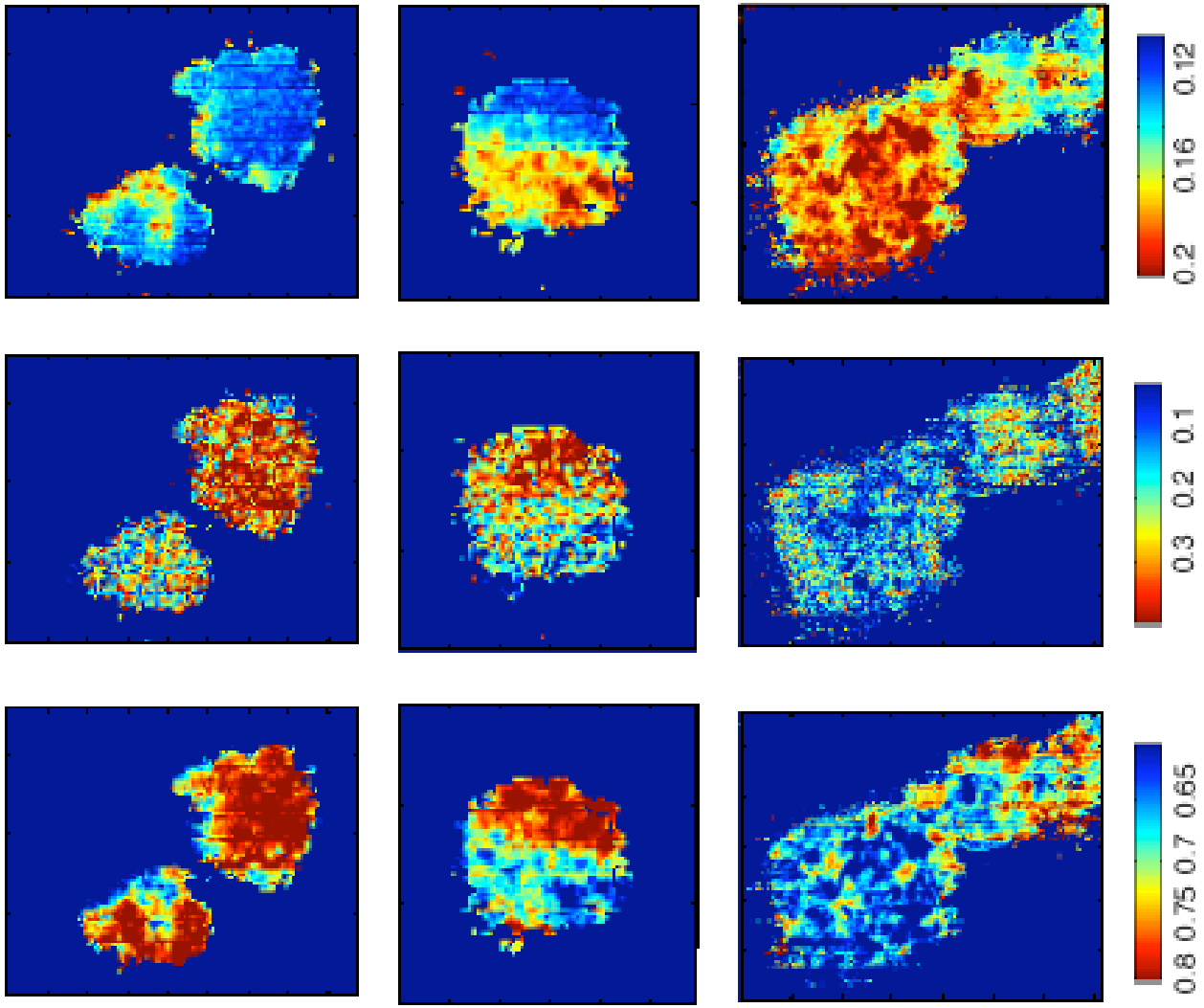
RED: Ethenzamide, GREEN: Cornstarch, BLUE:Lactose
YELLOW: Ethenzamide+ Cornstarch

NIR Image of Granules by PLS2 (160rpm, 10 min granulation):

Lactose

Cornstarch

Ethenzamide



Regulatory Science Studies

- Quality System, GMP guidance (2002-2004, 2005-2007)

QS, Regulations, Product GMP, Information Flow/Tech Transfer, Lab Control, Change Management

- GMP Inspection Policy, Manual(2003-2005, 2006-2008)

Policy, System Base, Inspection Check (Reference) list, Inspection Scenario (Key Questions)

- Manufacturing Process Commitment in Approval Letter

Survey, Technical Elements, Policy, Mock for AL and P2

- Clinical Supply GMP Policy

- Sterile Manufacturing GMP guidance

Pharmaceutical Affairs Law(PAL), ICH Q8/Q9/Q10 and MHLW Grant **Regulatory Science** Studies

PAL regulation changes	ICH discussion	Regulatory science groups
2002	**2002**	**2002**
Revised PAL published	CTD Q&A	QS/GMP guidance
	2003	**2003** CTD mock
2004	GMP workshop in Brussels	Approval matters
PMDA established	Q8 and Q9 started	Inspection Policy
New GMP standards	**2004**	**2004**
2005	Q8 reached step 2	Approval matters
Approval matters policy	**2005**	GMP guideline
Revised PAL enforced	Q9 reached step 2	**2005** Inspection Policy
Inspection policy published	Q8 and Q9 reached step4	Skip Test guideline
2006	Q10 started	Inspection Checklist
Product GMP guidance	**2007**	**2006-** Sterile process guideline
Sterile process guidance	Q10 reached step 2	**2008**
		P2 /application mock
		Change management system

Revision of the Pharmaceutical Affairs Regulation (effective April 2005)

- ***Revision of the Approval and Licensing System***

  = From Manufacturing (or Importation) Approval/License to Marketing Authorization

- ***Enhancement of Post-marketing Measures***

  = To clarify the Market Authorization Holder's (MAH) responsibility of the safety measures as well as quality management (GVP, GQP)

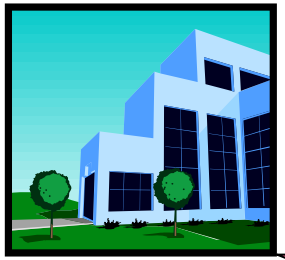
Revision of the Quality Regulation

1. **MAH's＊ responsibility for the Quality management**
   ＊Marketing Authorization Holder
2. Requirement Changes in Approval Matters
3. Drug Master File system to support CTD based application
4. Consolidation of the Legal Positioning of GMP
5. Revision and Consolidation of GMP standards

1. MAH’s responsibility for quality management (GQP)

- Supervise and manage the manufacturer, and ensure the compliance with GMP of all manufacturing sites
- Ensure proper product release to the market
- Respond quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information, etc.

Marketing and Manufacturing



Marketing Approval Holder
in M prefecture

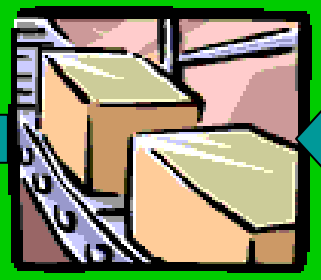
- **Supervise and manage the manufacture**
- **Ensure proper release to market**

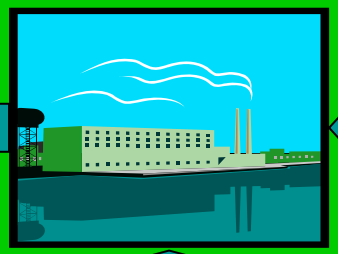
GQP

Manufacturer C
(packaging, label)
In C prefecture

Manufacture B
(bulk product)
In B prefecture

Manufacturer A
(API)
In country X





Market Release

Manufacturers

External
Testing laboratory

Revision of the Quality Regulation

1. **MAH's＊ responsibility for the Quality management**
   ＊Marketing Authorization Holder
2. **Requirement Changes in Approval Matters**
3. Drug Master File system to support CTD based application
4. Consolidation of the Legal Positioning of GMP
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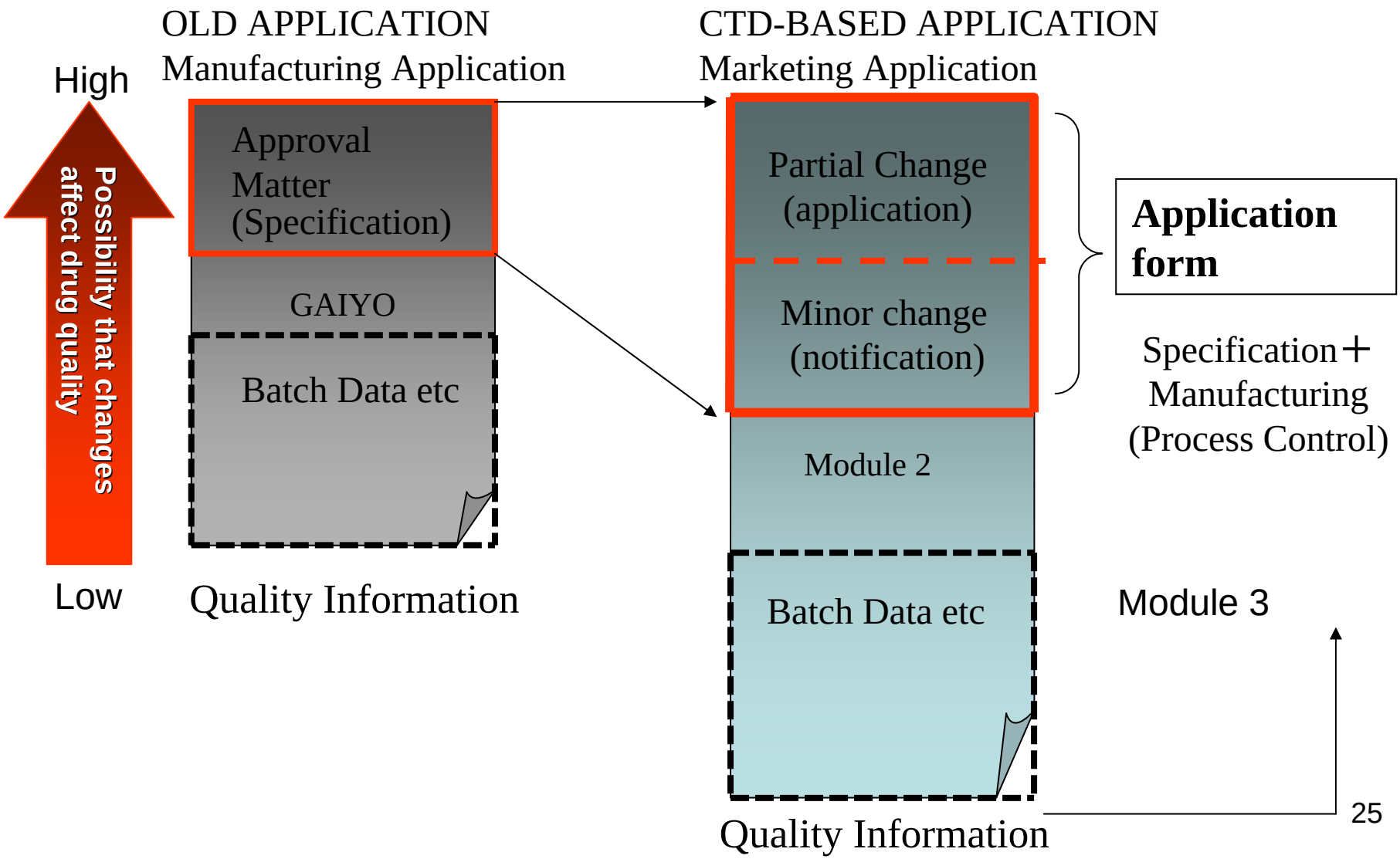
Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



Approval Matters

- General name (for drug substance)
- Brand name
- Composition
- Manufacturing process, including control of materials←NEW under rPAL
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures

Approval Letter

- **No change:**
  - **Approval letter system**
- **Changes:**
  - **From manufacturing approval to marketing approval**
  - **Requirement of detailed description in application form regarding manufacturing process and control**

    Encourage industry to better control quality of products

    Link review/assessment and INSPECTION
  - **Introduction of a notification system pertaining to minor change**

    Effective regulatory system

Approval Matters Policy

Notification from Director of Review Management, 0210001 February 10, 2005

- Manufacturing Process: Principles and end points of the critical manufacturing steps with key operational parameters of commercial scale will become approval matters. Principle and quality end point for each manufacturing step will be subject to pre-approval review.
- In-process procedure is pre-approval matter if it replaces final specification test.

Approval Matters Policy (continued)

- A pilot scale manufacturing processes may be submitted at Application.
- The commercial scale processes will be subject to Pre-approval GMP inspection and the commercial scale must be described in the approval.
- Pre-approval vs. notification classification may be determined through the review process

Matter Subject to Approval under Revised Pharmaceutical Affairs Law

(Chemical drug substance and drug product)

- Manufacturing site
- Manufacturing method

  Detailed information about:

  - Manufacturing process and process control
  - Control of material
  - Container-closure system

Matter to Be Described in Application Form
-Drug Products-

- **All processes from raw material(s) to packaging process**
  - **A flow diagram of manufacturing process including:**
    - **Raw materials**
    - **Charge-in amount**
    - **Yield**
    - **Solvent**
    - **Intermediate materials**
    - **Process parameter (e.g. Target Value and Set Value)**
  - **A narrative description of manufacturing process**

Narrative Description of Manufacturing Process

- Matters needed for assuring the quality consistency should be selected

- Quantities of raw materials, critical processes, process control, equipment, process parameter (speed, time, temp., pressure, pH, etc)
- Test and acceptance criteria of critical step and intermediate
- Identity and specification of primary packaging material (or manufacturer and type number of the packaging material)

Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - the evaluation methods which was approved at the time of previous submission might be invalid.
- Change in materials of primary packaging component
- Change in matters for aseptic manufacturing
- Change in specification of intermediate product in case that the test is performed instead of release test of final drug product

Distinctions between Partial Change Approval Application and Minor Change Notification

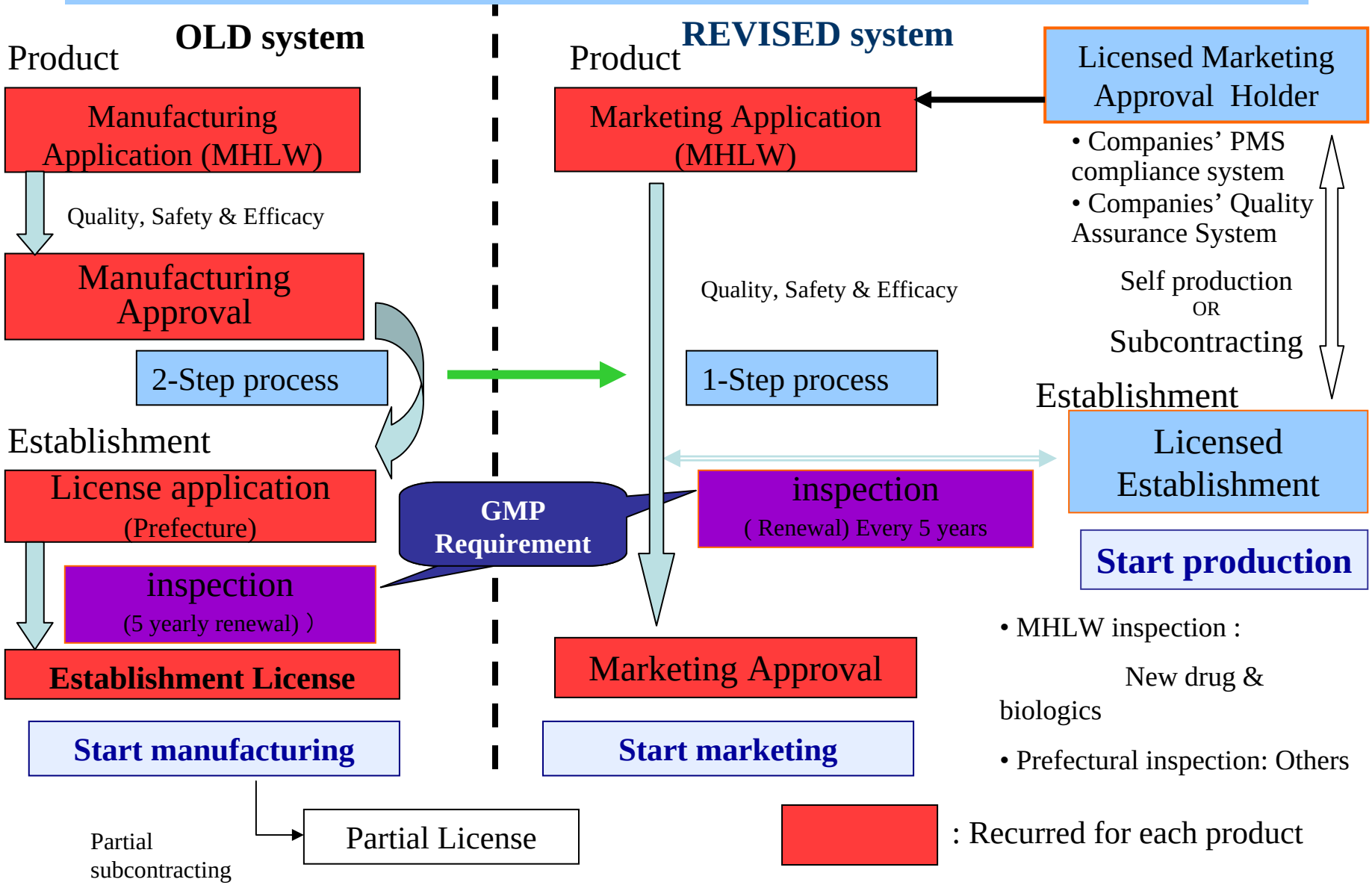
Partial Change Approval Application	Minor Partial Change Notification
Change in the principle of unit operation of critical process	Process parameter to control the quality endpoint criteria
Change in process control criteria as quality endpoint criteria	

4. Consolidation of the Legal Positioning of GMP

- **Became a requirement for product approval**
- GMP inspection **prior to approval**, and periodical GMP inspection in post-marketing phase
- GMP inspection **at the time of application for partial change(pre-approval required) of the approval matters**
- GMP inspection **at foreign sites**

Comparison Flowcharts of Approval and License

Points: (1) MAH's requirements for PMS system, (2) Allow complete subcontract manufacturing, (3) Introduce marketing approval system



GMP/QMS Inspection for Foreign Sites

- GMP/QMS* inspection for foreign manufacturing facilities started in April, 2005.
  - MRA*: Document check only for pharmaceuticals except sterile products and biologics
  - MOU*: Document check only for Pharmaceuticals
- Number of facilities inspected (~July. 2007)
  - Pharmaceuticals: 75
  - Medical devices: 24

QMS*: Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents; MRA* Japan-EU Mutual Recognition Agreement (API: out of scope); MOU* Memorandum of Understanding between Japan and Australia, Germany, Sweden, Switzerland)

Number of Foreign Facilities inspected by PMDA (~July.2007)

	Europe	North America	Central/ South America	Asia	Others	Total
Sterile products/ Biologics	17	21	0	2	0	40
Oral solid etc	1	7	0	0	0	8
API (Chemical)	10	6	1	3	1	21
Packaging, Labelling, Storage and Laboratory	0	6	0	0	0	6
Total	28	40	1	5	1	75

Change by notification and Q8 Design space

	Minor Changes by Notification	Design Space
Scope	**Changes of approval matters do not require reviewer's assessment**	**Space by input/process variables demonstrated to provide assurance of quality**
Areas not applicable	**Excipient range** **Principle of "critical" unit operations**	**No limitation(?)**
Regulatory procedures	**Notification within 30days from the change (market release date)**	**Region dependent** **Regulator will not evaluate changes within DS for pre-approval purpose**
If/when deviation happens	**(Target/set value)** **May be usable if deviation investigation supports**	**Discard the batch**

Basis for Quality Review

- ICH Guidelines are the basis for NDA review.
  - ICH Q8 and Notification #0210001 form basis for product design and manufacturing
- There are some domestic guides for those not covered by ICH Guidelines.

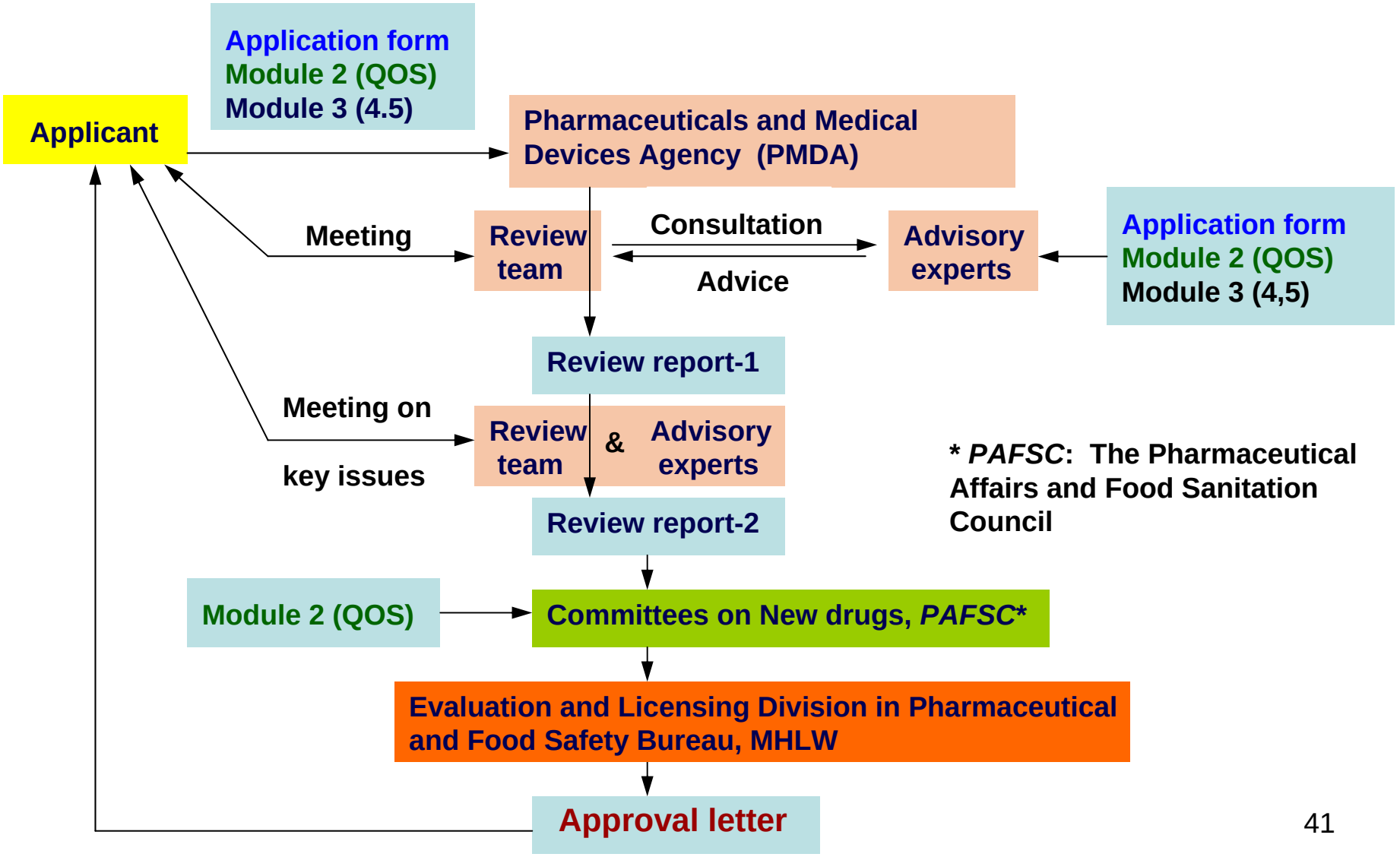
Seizouhou Sisin

- The Japanese Pharmacopoeia (JP) is also the basis for setting specifications and acceptance criteria of drug substances and drug products.

Guideline for preparation of JP16 Draft, *March 2007*

- "General methods described in the JP, and internationally harmonized methods are considered to be validated."

Flowchart of Reviewing Process



* *PAFSC*: The Pharmaceutical Affairs and Food Sanitation Council

Role of Module 2

- Module 2 bridges NDA Application Form (approval matters) and Module 3
- Module 2 is one of the key review documents
  - Reviewers evaluate Module 2 and then narrow down into Module 3, 4, or 5 when they need more detailed information.
  - Module 1 and 2 together with reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.

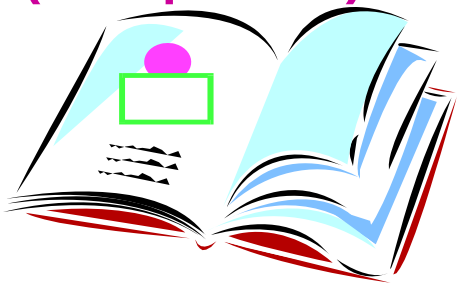
Relationship between Application Form and CTD Documents

Application form (in Japanese)

Analytical procedures (JP style) & acceptance criteria

Manufacturing process

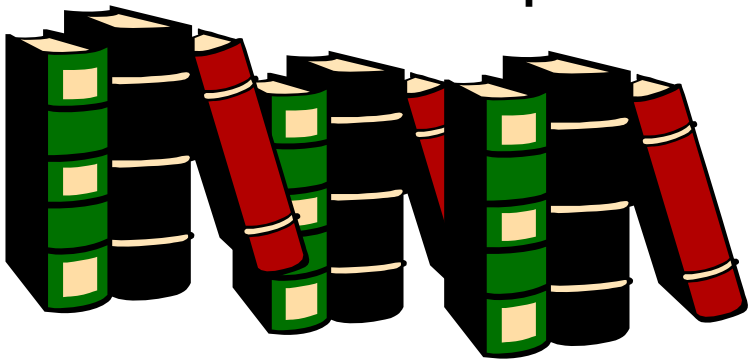
Module 2 (QOS) (in Japanese)



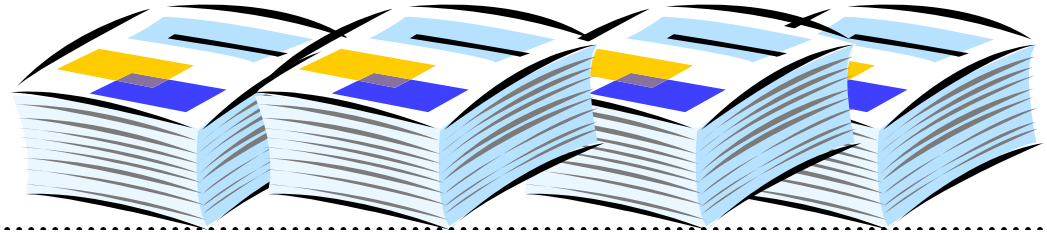
- Specifications
- Analytical procedures
- Pharmaceutical Development
- Manufacturing Process
- batch analyses
- Justification etc.

Module 3 (in Japanese or English)

3.2.S4.1 Specification
3.2.S4.2 Analytical procedures
3.2.S4.3 Validation of analytical procedures
3.2.S4.4 Batch analyses
3.2.S4.5 Justification of specification



Raw data



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- Not covers all information required for each NDA, nor shows acceptance criteria for each categories.
- **NEED more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8 and the revised PAL.←2006-2008 MHLW "Approval matters" study group**

History＆Legal Status of JP

- JP is published by the Japanese Government

  The Ministry of Health, Labour and Welfare
  Ministerial Notification
- First published on June 25, 1886 and implemented on July 1, 1887
- In accordance with the provisions of Article 41-1 of the Pharmaceutical Affairs Law (PAL) of Japan

  *To standardize and control the properties and quality of drugs, **the Minister** shall establish and publish JP, after hearing the opinion of the Pharmaceutical Affairs Food Sanitation Council (PAFSC)*

Various Roles and Characteristics of JP (1)

Official, Public and Transparent Standards for ensuring Quality of Pharmaceuticals

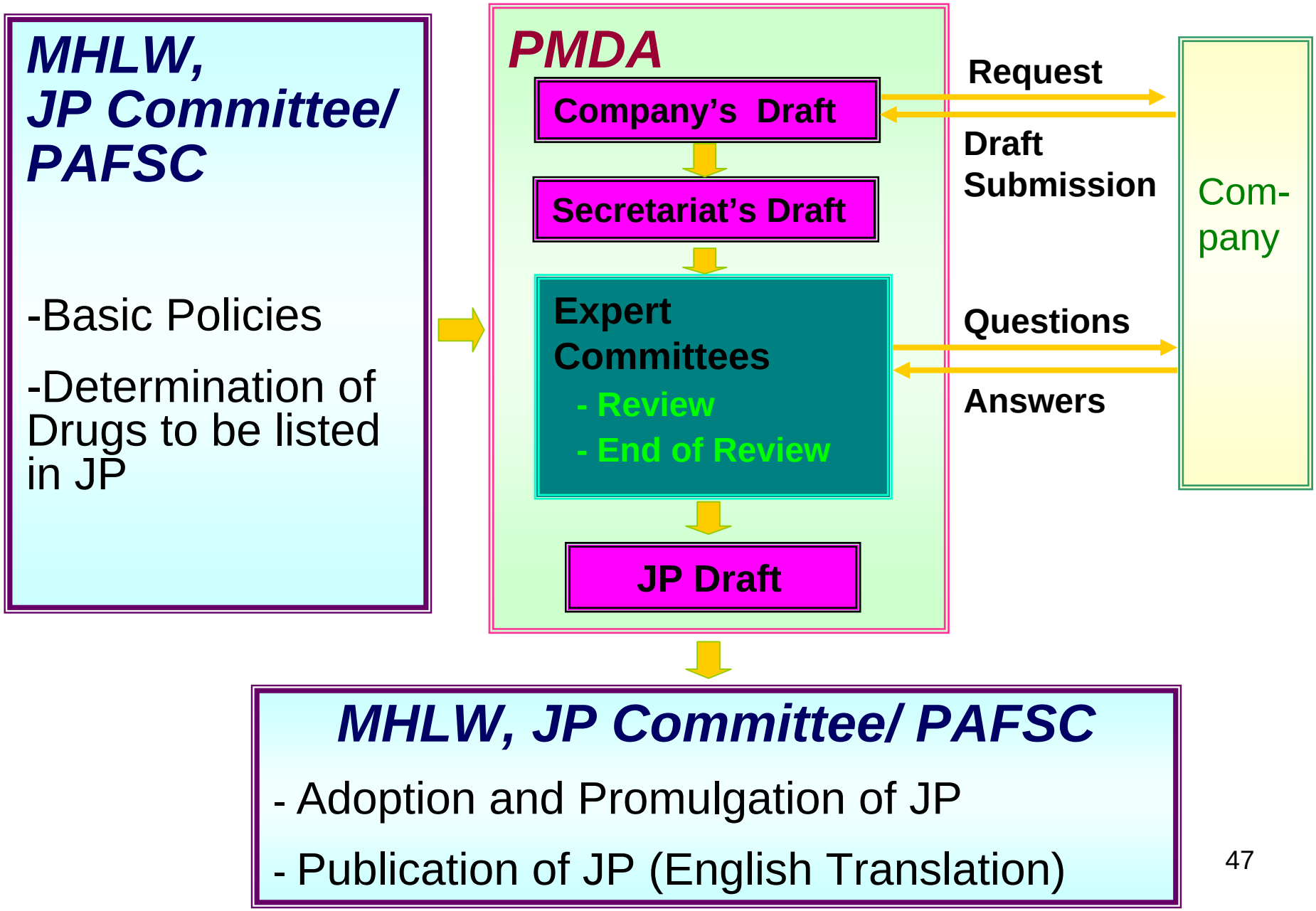
For Pharmaceutical Administration

- Standards of Quality Assessment of the Approval of New Entities and Quality Assurance for Pharmaceutical Vigilances

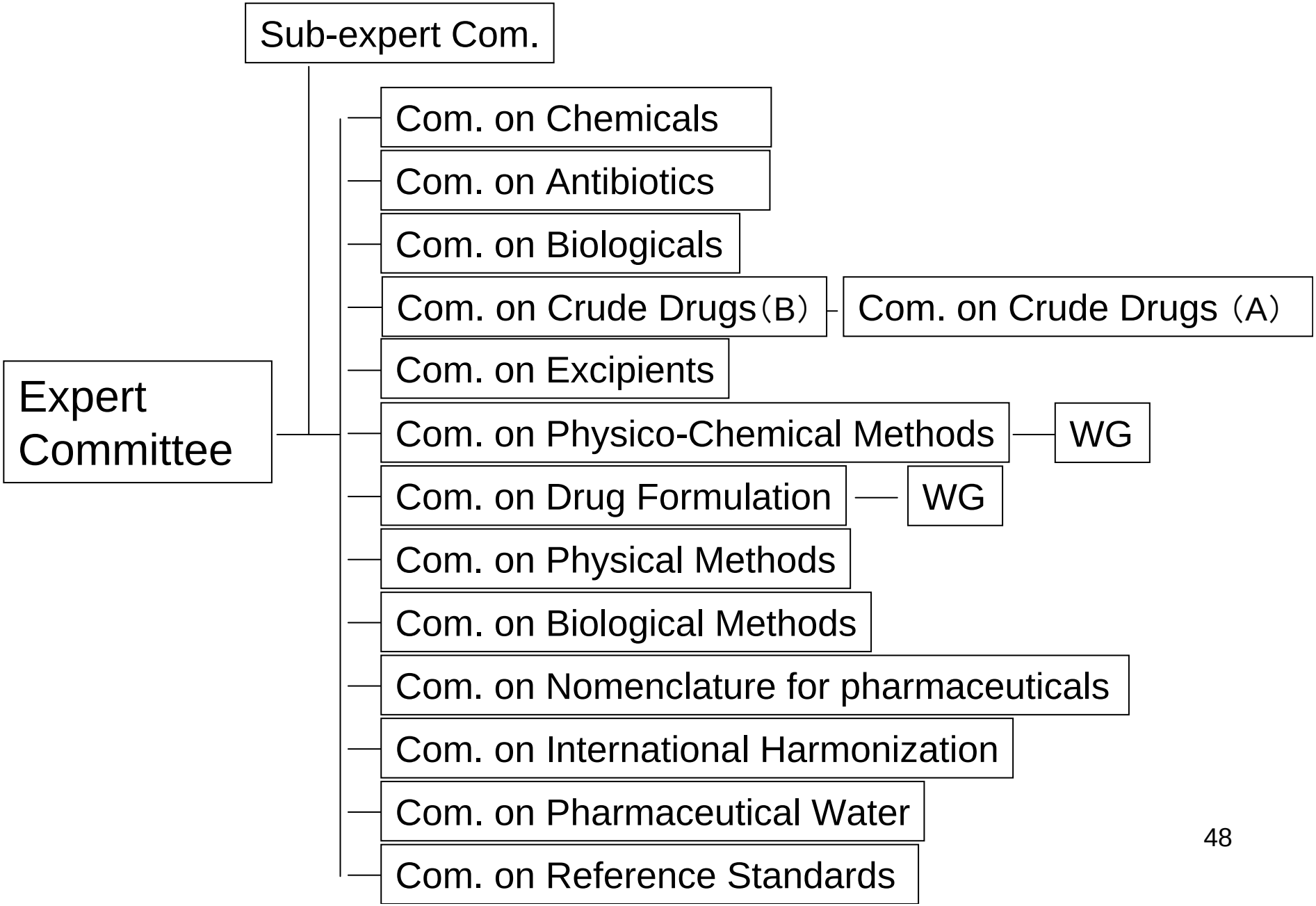
For Pharmaceutical Industry

- Scientific and Technical Standards that are to be Referenced in Drug Development

System of Establishing JP



Organization of JP Expert Committees



Schedule of JP Publication

The Japanese Pharmacopoeia Fourteenth Edition (JP14)

Published on March 2001

Supplement I to JP14

Published on December 2002

Supplement Ⅱ to JP14

Published on December 2004

Main Policies on the Preparation of JP15

November 2001 and December 2002

Guidelines for preparation of JP15 Draft

December 2002

The Japanese Pharmacopoeia Fifteenth Edition (JP15)

Published on March 2006

Supplement I to JP15

To be Published on September 2007

Supplement Ⅱ to JP15

To be published on March 2009

Main Policies on the Preparation of JP16

August 2006

Guidelines for preparation of JP16 Draft

March 2007

The Japanese Pharmacopoeia Sixteenth Edition (JP16)

To be published on March 2011

GMP/QMS training for Inspectors at National Institute of Public Health

- Annual 5 week course for Prefectural and PMDA inspectors and their technical support staff in Wako, Saitama-30 students, several trainees from Review Div of PMDA
- Program

1st week, Regulations, Overview of Development, Analytical Validation, Sterile Product Development /Manufacture

2nd week, Filter/Air, API Development/Manufacture, Medical Devices, 2 day Plant Tour

3rd week, Medical Devices, Solid Dosage Development/Manufacture, Manufacturing Equipment

4th week, Biologics, Drug Information, Inspection Methods, Day Inspection (four sites)

5th week, Report writing, Presentation

- Faculty and Lecturers

8 faculty members to establish program and conduct inspection exercise (NIPH-1, NIHS-3, NIID-1,PMDA-3)

MHLW, NIHS, PMDA, Industry

Current Japanese Regulations and Implementation of ICH Q8-Q10

Shintaro TOBIISHI
Office of Compliance
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare (MHLW)

Yukio HIYAMA
Chief, 3rd Section, Division of Drugs
National Institute of Health Sciences,
MHLW
JAPAN

Presentation Outline

- Pharmaceutical Affairs Law (PAL)
- Approval and Licensing system under PAL
- Review and Inspection
- Relationship between MHLW and PMDA
- MHLW's expectations and ICH vision
- Commitment of Manufacturing Process as Approval Matters
- Roles of ICH guideline

Pharmaceutical Affairs Law (PAL)

Points on 2002 revision of the PAL

- **Fortification of post-marketing safety measures**

→ **Concept of Marketing Approval Holder(MAH)**

- **Revision of the approval and licensing system**

→ **Focus to "Marketing Approval" rather than "Manufacturing Approval"**

Responsibility of MAH under PAL - as prerequisites for license of MAH -

- MAH must comply with GQP for its License.

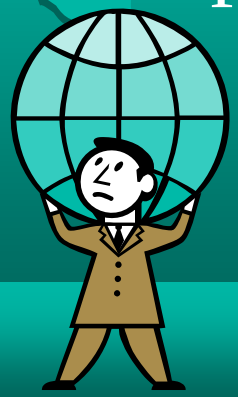
*GQP: Good Quality Practice

Rules for quality assurance operations

- MAH must comply with GVP for its License.

*GVP: Good Vigilance Practice

Rules for post-marketing safety management



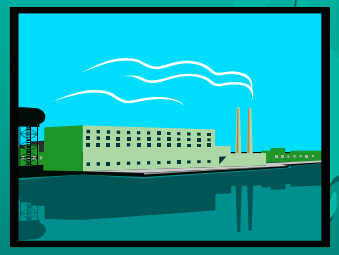
Responsibility of MAH based on GQP

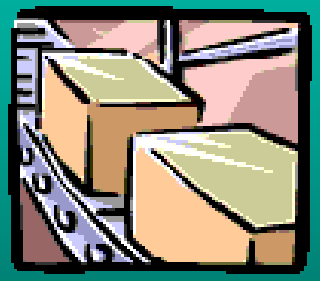
Total responsibility!

MAH

- **Supervise and manage the manufacturers**
- **Ensure proper release to market**

Manufacturer A (API) → **Manufacturer B (bulk product)** → **Manufacturer C (packaging, label)** → **Market Release**





External Testing laboratory

Approval and Licensing System

Product Approval

Prerequisites for marketing approval
***Quality, Efficacy & Safety of Product (including GCP)**
***Licensed Stakeholders**
***GMP-Compliant Manufacturing Sites**

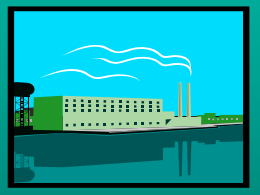
Marketing Approval Application

Review
Inspection

Marketing Approval

Licenses

Licensed MAH



Licensed Manufacturers

Prerequisites for license of MAH
* Human Resources
* GQP/GVP-Compliant

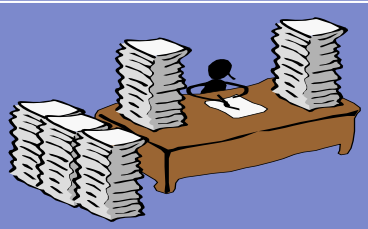
Prerequisites for license of manufacturer
* Human Resources
* Building & Facility

Review & Inspection Flow

2007 Annual Meeting of ISPE in Las Vegas

Application of New Drug

Application of Partial Change (PC) of Approval



Review

Review

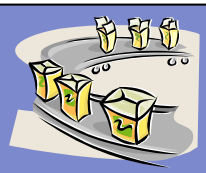
Application

Application form

Submission

Pilot scale Data

Re-submission



Production scale Data

Approval

Approval letter

Submission based on PC

Approval

Approval letter after PC

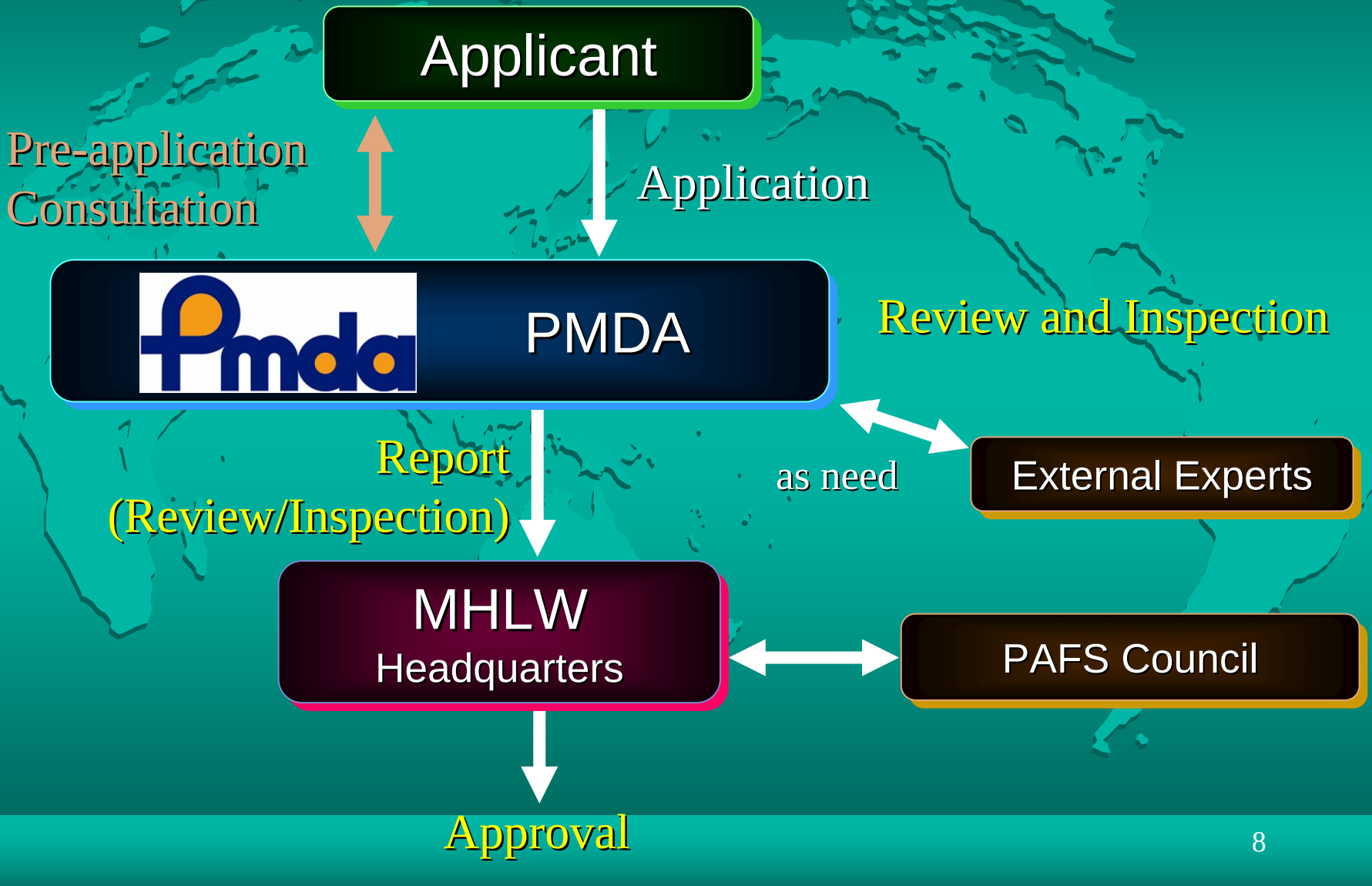
Pre-approval GMP inspection

Pre-approval GMP inspection

Market release based on approval letter

Routine GMP inspection (5-yearly at least)

Relationship between MHLW and PMDA



The 2003 ICH Quality Vision

Industry parties and regulatory authorities of the ICH Quality met in Brussels in July 2003 and agreed on the ICH Quality vision "A harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science".

In order to develop a modern pharmaceutical quality system, discussions on two topics, 1) Pharmaceutical Development (Q8) and 2) Quality Risk Management (Q9) started. The guidelines on the two topics were published in 2006 in the three ICH regions.

(Pharmaceutical Quality System (Q10) and Q8R reached step 2 .)

Expected Outcome

For Industry

- Establishment of quality management system from development to post-marketing

For regulatory authority

- Improvement of the approval review system by integration of the review and the GMP inspection
- To concentrate on higher risk products
- The establishment of effective, efficient, and streamlined quality regulation

Pharmaceutical Affairs Law(PAL), ICH Q8/Q9/Q10 and MHLW Grant Regulatory Science Studies

PAL regulation changes	ICH discussion	Regulatory science groups
2002	**2002**	**2002**
Revised PAL published	CTD Q&A	QS/GMP guidance
	2003	**2003**
2004	GMP workshop in Brussels	CTD mock
PMDA established	Q8 and Q9 started	Approval matters
New GMP standards	**2004**	Inspection Policy
2005	Q8 reached step 2	**2004**
Approval matters policy	**2005**	Approval matters
Revised PAL enforced	Q9 reached step 2	GMP guidelines
Inspection policy published	Q8 and Q9 reached step4	**2005**
2006	Q10 started	Inspection Policy
Product GMP guidance	**2007**	Skip Test guidance
	Q10 reached step 2	Inspection Checklist
	Q8R reached step 2	**2006-2008**
		P2 /application mock
		Change management system

Approval Matters

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- Brand name
- Composition
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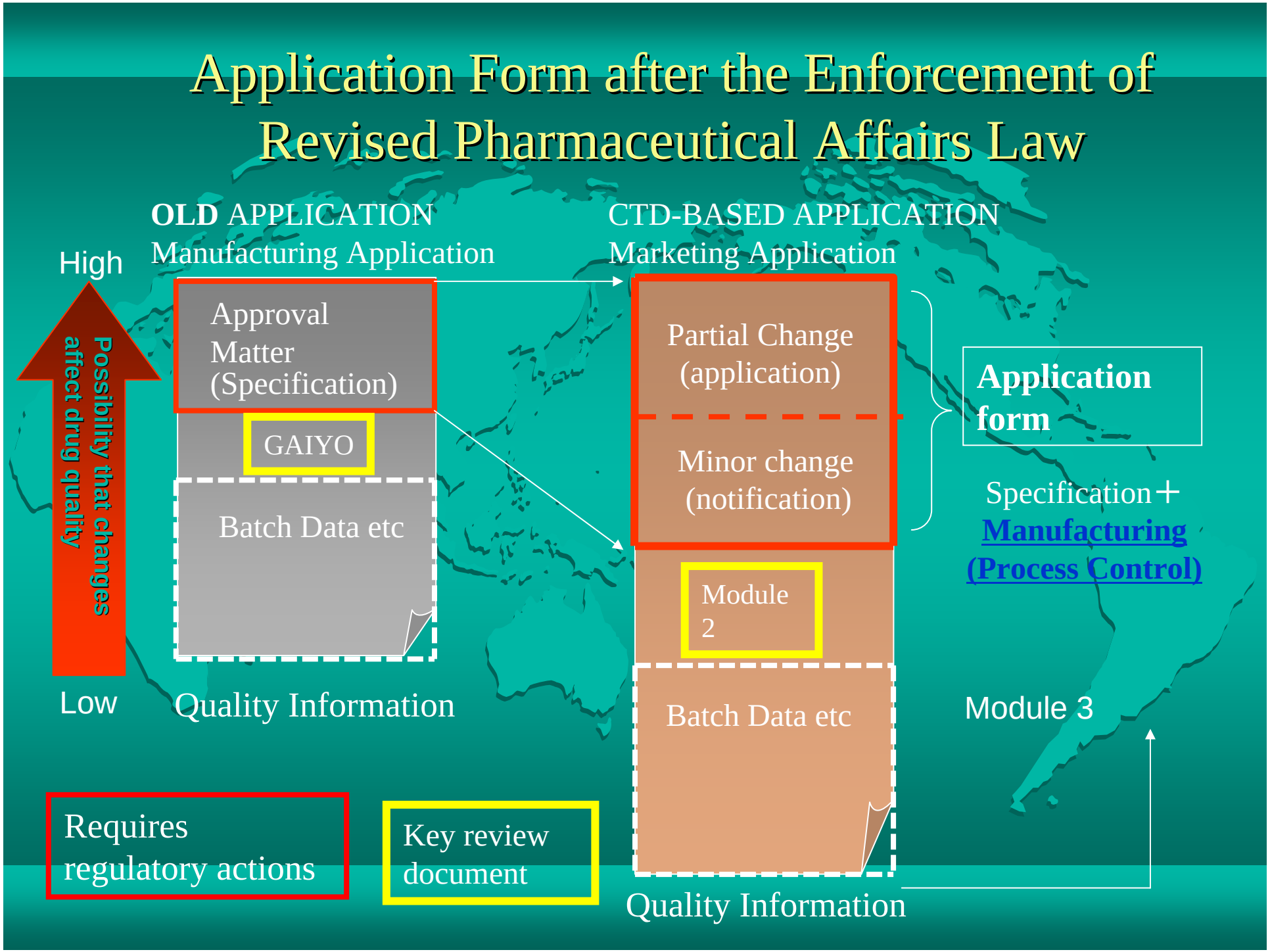

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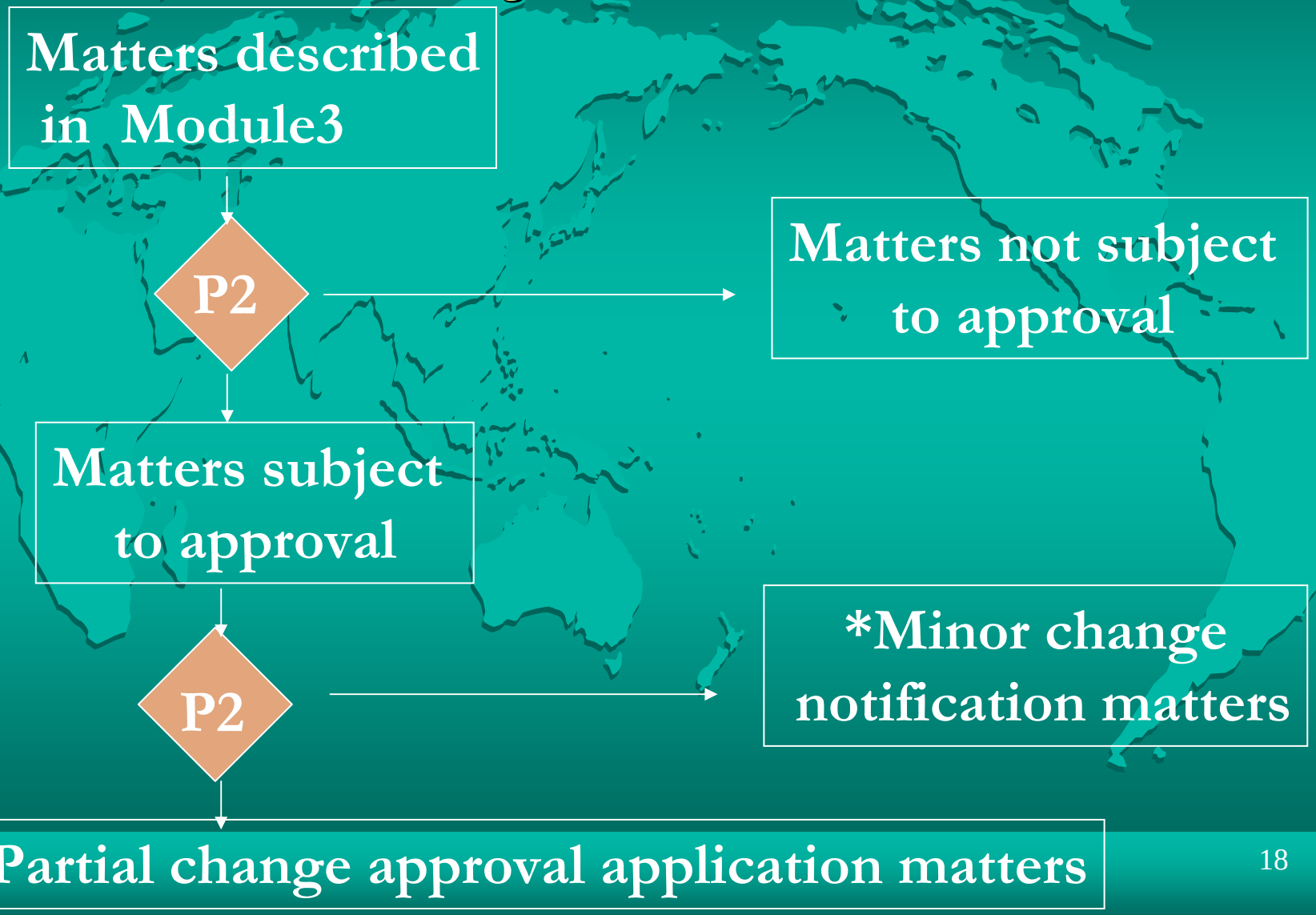
The Role of Pharmaceutical Development(P2) section
-Science and Risk based-
in reviewing NDA under revised PAL



Challenges when implementing rPAL regulations with ICH Q8(-Q10)

- Baseline expectations for P.2 need to be clarified

"At minimum(identify risks and risks controlled)" expectations do not seem to be traditionally submitted in Japanese NDA. With "traditionally" submitted contents, it is difficult to sort out pre-approval matters, minor change matters.←Q8(R) reached step2

- Range for excipients as a design space: scientific basis, description in approval letter←under consideration with "approval matters" study group
- Design spaces with interacting multi-variables and with interacting unit operations:description in approval letter←see industry's creativity. Q8R helps.
- Real time release:process and facility dependence ←Need final scale data to justify. A good Quality system(Q10?) expected. Specification with test method would not go away because of need for later evaluations including generics

Role of Module 2(QoS)

- Module 2 bridges NDA Application Form (approval matters) and Module 3
- Module 2 is one of the key review documents
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Thank you for your kind attention.