- 過去の経験（学術文献、公表論文）
- 医薬品開発研究
- 作用機序
- 構造活性相関
- 技術移転活動
- プロセスバリデーション
- 製造の経験
- 継続的改善・変更マネジメント
- 安定性試験報告書
- 製品品質レビュー／年次製品レビュー
- 苦情、有害事象報告書、逸脱、回収
- CAPA 報告書

これら知識のための情報源は製品ライフサイクルの医薬品開発だけでなく、商業生産等を含むライフサイクル全般を通した活動に関連する。従って、知識管理の体系の整備は、製品ライフサイクル全般に関連する体制を総合的に整備することにある。

製品ライフサイクル	知識管理のための体制整備
医薬品開発	- Q8/Q11 に準じた医薬品開発 - 事前の知識の活用環境の整備 - 開発段階での変更管理・逸脱管理
技術移転	- 技術移転図書の整備 - 生産部門への移転体制 - バリデーション計画への反映 ※参考：医薬品製造技術移転指針（厚生労働科学研究）
商業生産～製品の終結	- GQP、GMP - PQS

5. 製造プロセスの稼働性能及び製品品質のモニタリングシステムと知識管理・継続的改善について

モニタリングシステムは PQS の要素の一つとして定義される。Q10 の中で、Q10 モデルの実施により各極 GMP 要件を補完し、又は向上させるための 3 つの主要目的として、製品実現の達成、管理できた状態の確認、継続的改善の促進が規定されている。これらの目的は相互に関連するため、同じ次元で横並びにするものではない。特に、製品ライフサイクルにおける商業生産段階での管理戦略に着目すると、PQS の目的のうち、管理できた状態の確立及び維持が重要な概念となると考えられる。

Q10 に記載される管理できた状態の確立及び維持には、その要件として製造プロセスの稼働性能及び製品品質に対する実効的なモニタリング及び管理システムを開発、運用

し、それにより継続する適切性及び製造プロセスの能力の保証を提供することとある。医薬品開発段階で実施されるモニタリングシステムは管理戦略の確立に用いられる（Q10 表Ⅰ）。管理戦略は、医薬品開発の最終段階として恒常的に一定の製品品質を得るために用いられる。原薬製造における管理戦略は、原薬の原材料及び構成資材に関連するパラメータ及び特性、設備及び装置の運転条件、工程管理、原薬の規格並びに関連するモニタリング及び管理の方法及び頻度となる。開発された管理戦略は、Ongoing Process Verification の段階で活用されるが、モニタリングシステムはその管理戦略で得られるデータを分析・評価するツールを提供しなければならないとされる（Q10 3.2.1）。また、分析・評価した結果を継続的改善につなげる動きとしなければならない。このように管理戦略から得たデータを評価して継続的改善の方針を定めるためにはデータから知識へとその情報の質を高める必要がある。Q10 3.2.1 の記述から、管理できた状態の維持から継続的改善への流れと管理戦略との関連について PV のライクサイクルを含めて考察する（図 1）。

実効的なモニタリング／管理システムの開発のためには、工程デザイン段階で開発した管理戦略が活用される（Q10 3.2.1 の(a)）。Q10 で定義するモニタリングシステムは、管理戦略の運用時の条件を Q10 3.2.1 の(b)～(d)で規定しており、これが前述のように、管理戦略を運用することにより得たデータを分析し、変動要因を特定するといった知識レベルに質を上げる作業となる。一方、製品品質に関する内部情報及び外部情報（製品品質の照査に係る項目）の情報も分析の対象となり（Q10 3.2.1 (e)）、これら情報源から継続的改善に向けるための知識へと高める活動（知識管理）がモニタリングシステムに求められる（Q10 3.2.1 (f)）。以上の作業により、次の製品品質や製造プロセスの改善、必要に応じて法的手続きの判断が行われるという流れとなる。

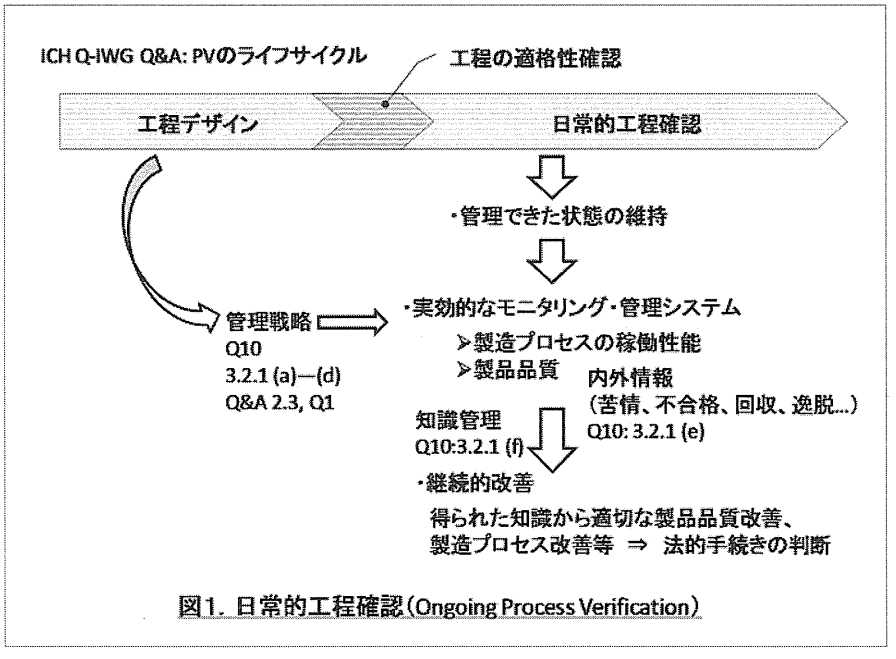


図1. 日常的工程確認(Ongoing Process Verification)

6. 原薬製造工程のライフサイクルマネジメントに係る継続的課題について

Q11では、開発段階で計画されている変更について、CTDに情報提供する機会に関する記述がある（Q11 9.）。そこでは、製造工程の変更内容とともに、原薬及び必要に応じて製剤の品質に及ぼす影響についての評価のための、適切な試験の設定を求めている。一方で、Q11の適用範囲からは、承認後の変更に対する各極要件は除外されており、Q12ガイドライン[5]の議論を踏まえつつ、より弾力性のある規制取組のための研究の継続も重点課題の一つである。

参考資料

1) 「原薬の開発と製造(化学薬品及びバイオテクノロジー応用医薬品/生物起源由来医薬品)ガイドラインについて」，厚生労働省医薬食品局審査管理課長，薬食審査発 0710 第9号 平成26年7月10日

2) 「医薬品品質システムに関するガイドラインについて」，厚生労働省医薬食品局審査管理課長 監視指導・麻薬対策課長，薬食審査発 0219 第1号 薬食監麻発 0219 第1号，平成22年2月19日

3) 「製剤開発に関するガイドライン」、「品質リスクマネジメントに関するガイドライン」及び「医薬品品質システムに関するガイドライン」に関する質疑応答 集(Q&A)について，厚生労働省医薬食品局審査管理課 監視指導・麻薬対策課，事務連絡 平成22年9月17日

4) EudraLex, The Rules Govering Medicinal Products in the European Union, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation, Status of the document: Revision 1, Brussels, 6 February 2014

5) Final Concept Paper, Q12: Technical and Regulatory Consideration for Pharmaceutical Product Lifecycle Management, dated 28 July 2014, Endorsed by the ICH Steering Committee on 9 September 2014

do more feel better live longer

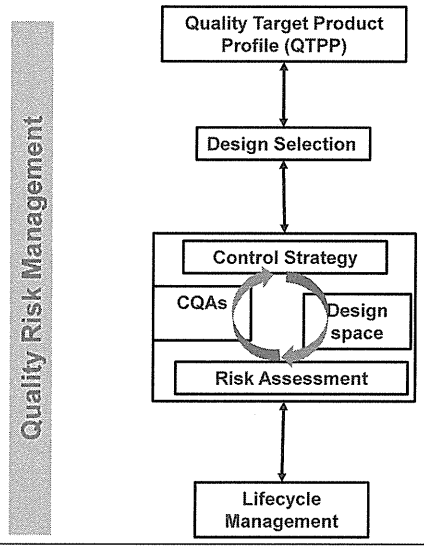
GSK's QbD Implementation Approach - Process Validation

September 2014

Objective

- The objective of this presentation is to:
  - Provide an overview of GSK's Lifecycle Approach to Process Validation and show how it supports and enables implementation of QbD principles

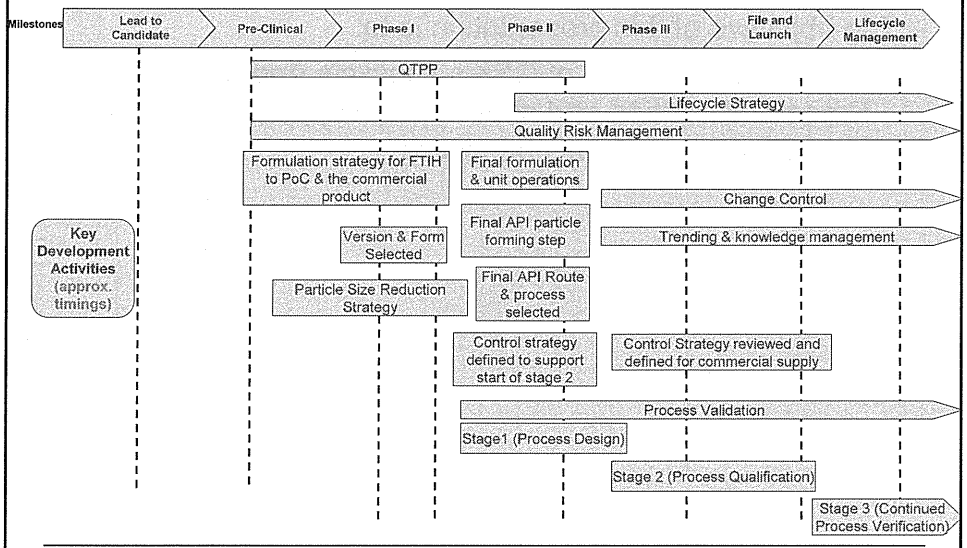
GSK's QbD Approach



- Define the QTPP
- Determine potential drug substance and drug product CQAs
- Risk based selection of route, formulation and manufacturing process
- Perform detailed risk assessment
- Link material attributes and process parameters to CQAs
- Design and implement a control strategy
  - Identify CPPs
  - Develop Design Space
  - In-line controls, PAT, RTRT, analytical methods and specifications etc
- Verification and scale-up
- Manage product lifecycle, including continual improvement
- Ongoing Risk Management

3

Product Development Roadmap



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QbD and Process Validation

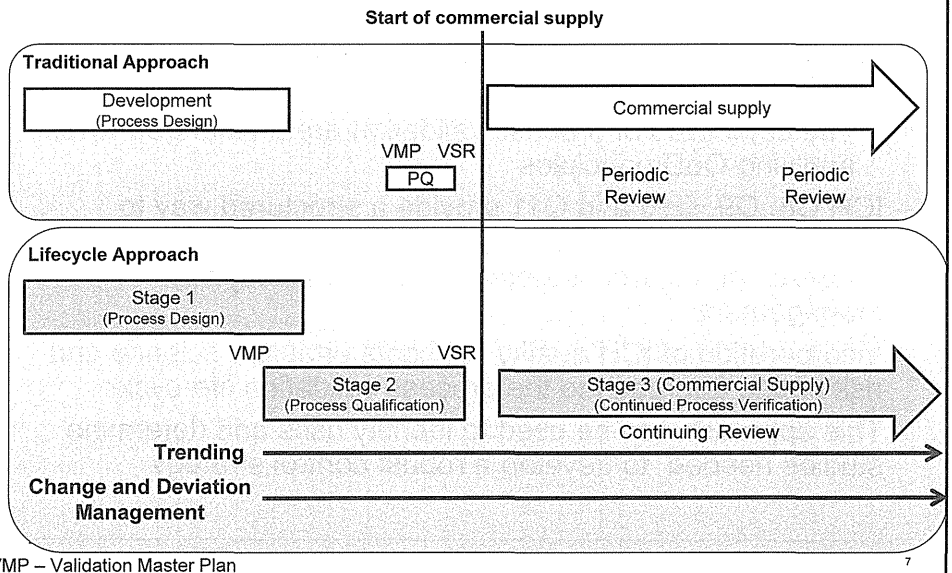
- The main objective of process validation is unchange; a process design yields a product meeting its predefined quality criteria.
  - The objectives of process validation are unchanged when applying QbD principles
- ICH Q8, Q9, Q10 and Q11 provide a structured way to define product critical quality attributes, the manufacturing process, the control strategy and product lifecycle management.
- Incorporation of ICH quality concepts enable a science and risk based approach to the process validation life-cycle
- This approach can be used to identify risks and determine studies needed to develop a robust control strategy

5

GSK's Lifecycle Approach to Process Validation - A key enabler to the implementation of QbD

6

Traditional vs. Lifecycle Approach to Process Validation



VMP – Validation Master Plan
VSR – Validation Summary Report

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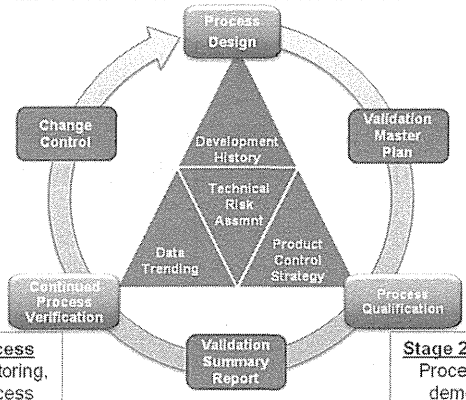
Product Quality Lifecycle Management

Stage 1 - Process Design - Performed to confirm the formulation and process and determine the control strategy, which is used as the basis for PQ.



Stage 3 - Continued Process Verification - Ongoing monitoring, trending and review of process performance to ensure that the control strategy remains capable and product quality is maintained.

Stage 2 - Process Qualification - Process design is evaluated to demonstrate that the control strategy is capable of delivering the desired product quality for commercial launch

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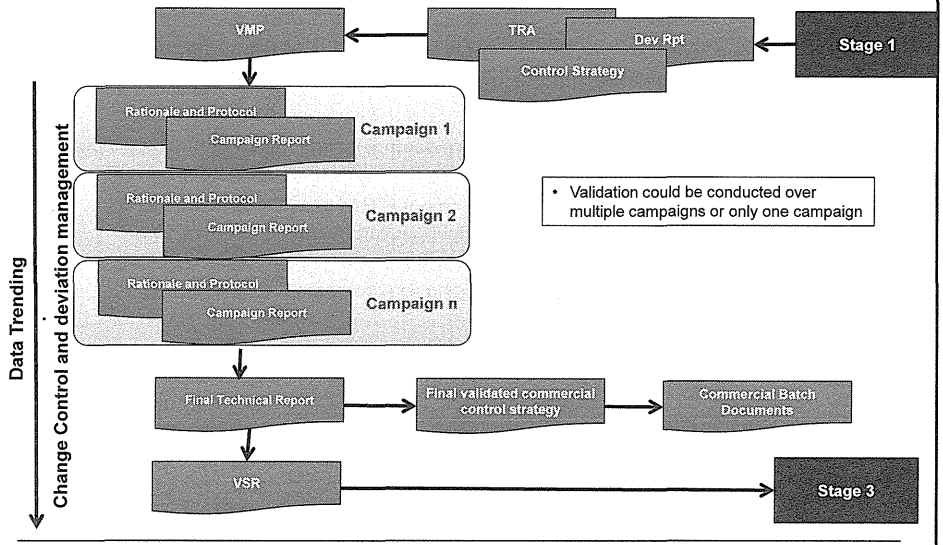
Stage 2 – PQ Overview



11

Stage 3 – Continued Process Verification

- Enhanced monitoring is performed during initial commercial supply to establish statistical process control levels (where a sufficient number of batches are made) and to monitor any low risk variation not assessed during PQ
  - Validation Master Plan / Rationale and Protocol define the approach
  - Report on completion of Stage 3a
- Through the product lifecycle the process is verified through :
  - Ongoing trending and periodic review of trends.
  - Annual Product Performance Reviews
  - Validation Review Reports
- Planned changes are implemented through the site change control system and follow a risk based approach:
  - Risk / Impact Assessment is performed to determine impact on product quality.
  - Level of implementation activities and any additional validation is based upon the impact on the control strategy
  - The level of validation / change activities are commensurate with the risk to product quality

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Stage 1 – Process Design

- Process Design uses development work, product and process understanding and Technical Risk Assessment to confirm the formulation and manufacturing process and determine the control strategy to support the start of stage 2.
- The core elements are:
  - Development History - A summary of development work completed to support the control strategy, process and formulation for the commercial process.
  - Risk Assessment - Technical Risk Assessment (TRA) uses Failure Mode Effect Analysis (FMEA) to identify process risks impacting the drug product CQAs
  - Control Strategy - The control strategy details the CPPs and CQAs and their targets/ranges . The monitoring and trending requirements are established.

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Stage 2- Process Qualification (PQ)

- Prior to starting PQ, the equipment qualification is completed and the process and control strategy is defined
- The acceptance criteria are pre-defined
  - CQAs met
  - CPPs maintained within range (design space) or set points
  - Unit operation end points met (where defined)
  - Manufacture follows the defined process
- Production scale batches to support clinical, registration, stability or commercial may be included as part of PQ
  - A minimum number of batches will be defined as part of the plan/protocol/rationale to enable the control strategy to be demonstrated to be robust
  - Each campaign (where required) is a pre-defined number of consecutive batches
- The pre-defined acceptance criteria must be met for PQ to be considered successful
- At the completion of PQ a final technical report is produced assessing all PQ batches against the final commercial control strategy
- Issue of the VSR enables commencement of commercial supply

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Advantages of Lifecycle Approach

- Collate process knowledge during stage 1 to support stage 2 (PQ)
- During PQ, process performance is determined on an increased number of batches
- Process and product robustness demonstrated across an increased number / variety of input material batches
- Validation is based on knowledge from on-going development and manufacture
- Responsive to enhancements to the control strategy
- Data trending is used to monitor process performance on an on-going basis
- The approach supports implementation of changes throughout the life of the product

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Challenge in practical term: Message to the Study Group

- Application of QbD includes Design Space, RTRT and Lifecycle Approach to Process Validation
  - However, uncertainty regarding acceptability of file and associated flexible regulatory approaches in different regulatory bodies
- Change Management
  - Differences in regulatory expectations governing changes
  - Timing of approval of changes (from 0 to 24 months or more...)
- Uncertainty as to consistency of global acceptance of science and risk based approaches in the dossier
  - Different dossiers
  - Different criteria
  - Different regulatory interpretation of design space, CPV, etc.
  - Need to manage multiple post-approval variations

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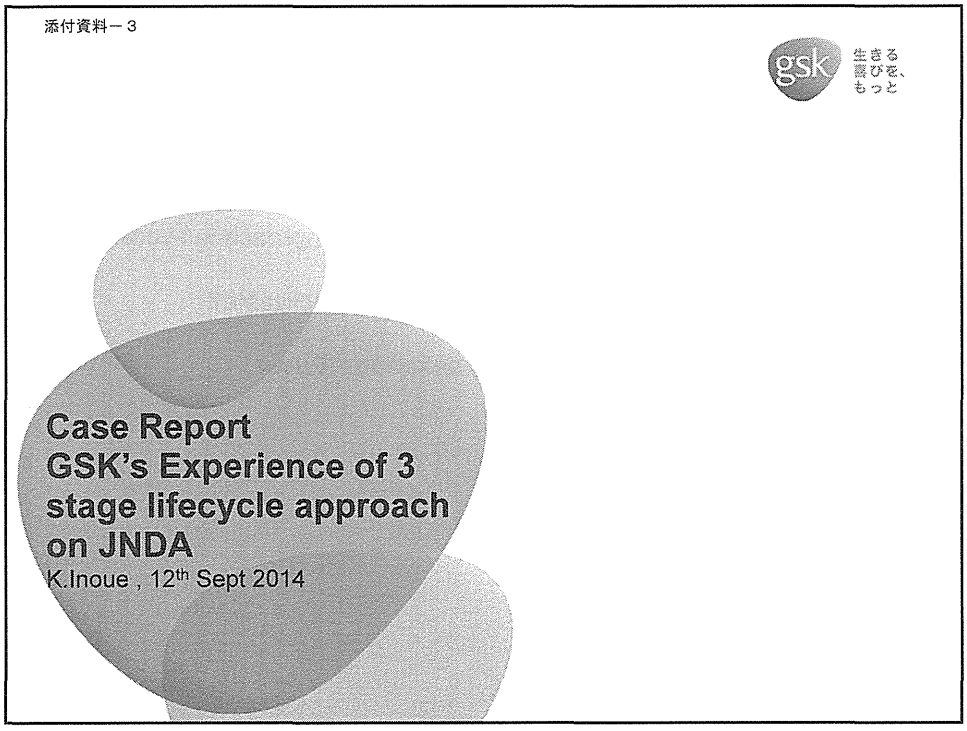
QUESTIONS?

添付資料－3



PMDA Consultations

Actual performance to date

- 2011 4Q:
  Non-minuted and Simplified Consultation with Office of Compliance and Standards
  *Confirmation of acceptability to adopt the 3-Stage Lifecycle Approach** to Process Validation for Drug Product (Product A)*

- 2012 4Q:
  Non-minuted and Simplified Consultation with Office of Compliance and Standards PMDA
  Confirmation of acceptability to adopt the 3-Stage Lifecycle Approach to Process Validation for both API and DP (Product B)

** : At the time of consultation, the approach was called "Continuous Process Verification" (CPV).

Case: Product B

【Purpose of Consultaion

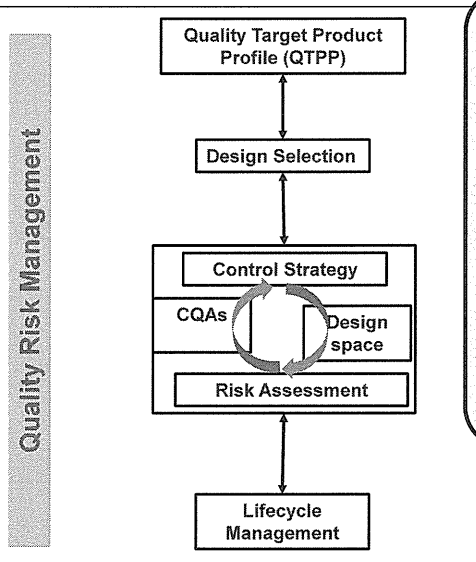
- At the pre-approval GMP inspection for the submitted Product B which has been developed by QbD approach,
  does PMDA accept adoption of 3-stage lifecycle approach to Process validation?
  Also, what type of information will be required if applicable?
- **See next slide for actual questions asked for Relvar**

Case: Product B

【Questions】

- Does PMDA consider that the 3-Stage Lifecycle Approach to Process Validation adopted for API of Product B is acceptable for Japan?
- GSK considers that Stage 2 of process validation for API of product B is complete. Does PMDA agree that, subject to regulatory approval, the batches produced support the point of commercialisation?

Content of Submitted CTD for Product B



Explained in CTD

- Define the QTPP
- Determine potential drug substance and drug product CQAs
- Risk based selection of route, formulation and manufacturing process
- Perform detailed risk assessment
- Link material attributes and process parameters to CQAs
- Design and implement a control strategy
  - Identify CPPs
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  - In-line controls, PAT, RTRT, analytical methods and specifications etc
- Verification and scale-up
- Manage product lifecycle, including continual improvement
- Ongoing Risk Management

Stage 1 – Process Design

- Process Design uses development work, product and process understanding and Technical Risk Assessment to confirm the formulation and manufacturing process and determine the control strategy to support the start of stage 2.
- The core elements are:
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  - Risk Assessment - Technical Risk Assessment (TRA) uses Failure Mode Effect Analysis (FMEA) to identify process risks impacting the drug product CQAs
  - Control Strategy - The control strategy details the CPPs and CQAs and their targets/ranges . The monitoring and trending requirements are established.

All the components listed above for API are discussed and are explained in CTD, S.2.6 section

Contents in CTD S.2.6 Manufacturing Process Development

- Quality by Design Approach
  - Outline of QbD approach taken in GSK
  - Quality Target Product Profile (QTPP) is defined in DP se
- Design Requirements for API
  - Requirements for API to meet the DP QTPP, were defined as DS CQA
- Design Selection for API
  - Development of Manufacturing Process with historical changes

Contents in CTD S.2.6 Manufacturing Process Development

- Development of Control Strategy for API
  - manufacturing process risks addressed during development
  - spiking and purging data that was used to develop the specification limits for impurities in starting materials, reagents and intermediates
  - Control of potential genotoxic impurities from the manufacturing process
  - Impurity-fate map showing the origin and fate of all drug-related impurity
  - Identification of the CPPs and their corresponding PARs for each step
  - Control strategy for API, highlighting the controls for each step
  - Experiments which verify the performance of the control strategy
  - Experiments and batch data which demonstrate how the manufacturing process is impacted by scale of operation
  - Control strategies for residual solvents and heavy metals

Contents in CTD S.2.6 Manufacturing Process Development

- Control strategy established based on Stage 1 activities is clearly defined in the CTD and the elements which make up the control strategy are spread into the following sections
  - S.2.2 Manufacturing Process with CPPs and non-CPPs
  - S.2.3 Control of Materials
  - S.2.4 Control of Critical Steps
  - S.4.1 and S.4.2 Specifications and Test Methods

Stage 2- Process Qualification (PQ)

- Prior to starting PQ, the equipment qualification is completed and the process and control strategy is defined
- The acceptance criteria are pre-defined
  - CQAs met
  - CPPs maintained within range (design space) or set points
  - Unit operation end points met (where defined)
  - Manufacture follows the defined process
- Production scale batches to support clinical, registration, stability or commercial may be included as part of PQ
  - A minimum number of batches will be defined as part of the plan/protocol/rationale to enable the control strategy to be demonstrated to be robust
  - Each campaign (where required) is a pre-defined number of consecutive batches
- The pre-defined acceptance criteria must be met for PQ to be considered successful
- At the completion of PQ a final technical report is produced assessing all PQ batches against the final commercial control strategy
- Issue of the VSR enables commencement of commercial supply

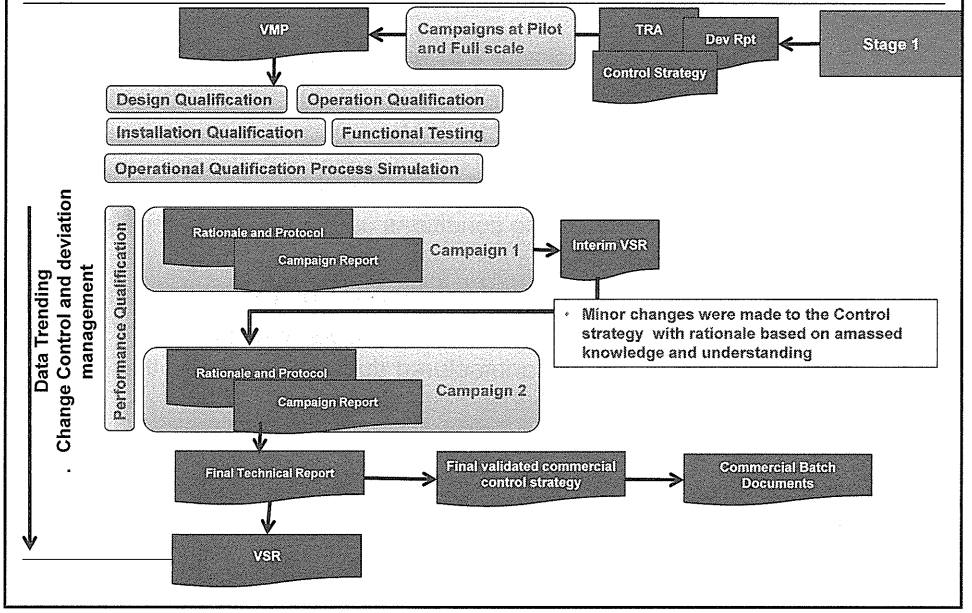
Preparation for Stage 2 at the Site

- Prior to start Stage2 activities, commercial manufacturing site had the 2 full scale manufacturing campaigns and this campaigns provided additional manufacturing understanding. (a part of Stage 1 activities)-
- Validation Master Plan (VMP) that identified CQAs, CPPs and control strategy effective at that time as a part of the Process Performance Criteria was issued.

Performance of Stage 2 at the Site

- Campaign 1 (3 batches at full scale) was carried out under a Validation Master Plan (VMP) based on the latest understanding of the process at that time and the outcome was documented in an interim Validation Summary Report (VSR)
- An updated VMP was issued to govern Campaign 2 (2 batches at Full scale) following the increased process understanding and knowledge gained from Campaign 1. The outcome was documented in a VSR.
- The changes to the control strategy between Campaign 1 and Campaign 2 were evaluated as part of a risk based approach
  - A Risk Assessment was undertaken to ensure that risks were adequately mitigated
  - The changes are documented in the PQ protocols
  - The changes to the control strategy achieved the expected outcomes and had no impact on product quality
- Process deviations have been adequately assessed with respect to impact on the control strategy and product quality; all corrective/preventative actions have been completed
- Campaign 2 to support stage 2 of process validation was successful, the facility is appropriately designed, the control strategy has been shown to be effective and all process performance criteria have been met.
  - The control strategy has been successfully demonstrated to deliver the drug substance CQAs and the quality attributes (specifications) of the intermediates

Stage 2 – PQ Overview for Product B API



Outcome from Consultation

Principle to make judgement for acceptability

There is a premise that the validation approach should be proven to be equal to or greater than the prospective validation (based on 3 batches as a rule) at commercial scale in compliance with Japanese validation standards. Based on this, the answers to your questions are as follows:

- **Q1 Does PMDA consider that the concept of the 3-Stage Lifecycle Approach to Process Validation adopted for Product B and it's API is acceptable for Japan?**

- A1 PMDA judges acceptable on the premise that the impact of changes made during stage 2 on product quality is assessed and process consistency and comparability are demonstrated by sufficient supporting data.

Outcome from Consultation

- **Q2 Does PMDA agree that Stage 2 of process validation for API is complete, subject to regulatory approval, the batches produced support the point of commercialisation?**
- A2 PMDA judges acceptable based on the three points listed below:
  - The manufacturing processing conditions used between campaigns 1 and 2 were unchanged.
  - Changes to control strategy were made based on verification studies.
  - For changes made to the drug substance CQAs, it has been confirmed that all batches manufactured during stage 2 met the specification limits for drug substance CQAs.

Final Reminder

- Concept of 3-stage lifecycle approach to process validation is applicable.
- Validation approach should be proven to be equal to or greater the conventional 3 batch PQ approach.
- The approach taken to Performance Qualification will be product specific, based on risk assessment, e.g. number of batches will vary, scale may vary, control strategy may be enhanced during PQ. PMDA will accept all batches in PQ as long as we have acceptable supporting knowledge that justifies the change and confirms no adverse impact on quality.

Questions