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An Impact assessment of Post-Approval Regulatory and Quality Compliance at a UK – Only Pharmaceutical Manufacturer

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Abstract

Purpose: To assess the regulatory compliance of operational processes at a British pharmaceutical manufacturing company (Company X). Provide remediation strategies for any compliance gaps identified to align operations with regulatory approvals. Ultimately, to assure Qualified Persons that finished pharmaceutical products released for sale are compliant with regulatory approvals and manufactured to current quality standards.

Materials and methods: A gap analysis between regulatory-approved CTD sections and operational documentation is conducted for a single marketed product at Company X. Inclusion of CTD sections for review is determined according to those likely to contain Established Conditions (EC) as specified in the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Q12 guideline. A three-tiered review process is used to identify Established Conditions and describe compliance. Tier 3 (Student) identifies Established Conditions by comparing like-for-like (compliant), equivocal (further assessment required) and opposing (non-compliant) terminology in the CTD sections compared to operational documentation. Tier 2 (Subject Matter Experts (SMEs)) reviews and approves Tier 1 outputs. Equivocal terminology is assessed as either compliant or non-compliant. Non-compliant conditions are assessed as regulatory gaps if they deviate from the CTD or quality gaps if they are compliant with the CTD but deviate from Good Manufacturing Practices (GMP). A risk assessment is conducted using a risk priority numbering (RPN) tool and remediation proposals are made. Tier 1 (Governance) reviews and confirms Tier 2 compliance gap outputs and ratifies a final adjudication and remediation strategy.

Results and discussion: Data outputs for this study could only be generated at Tier 3 and Tier 2 levels due to time constraints. A total of 62 compliance-related Established Conditions (EC) were identified with 37 representing compliance gaps. 49% (30 conditions) related to regulatory compliance gaps, 40% (25 conditions) were compliant and 11% (7 conditions) were quality compliance gaps. Six categories of regulatory compliance gaps were identified with the most commonly observed being the unavailability of regulatory-approved CTD sections for review. Three categories of quality compliance gaps were identified with the most commonly observed being the misalignment of operational and validating documentation.

Conclusions: Company X is presently in a state of non-compliance. The unavailability of regulatory-approved documentation emerges as the most common compliance issue suggesting insufficiencies in regulatory document control may currently exist. A root cause analysis coupled with a corrective and preventative action plan may be beneficial to support sustained compliance. Further work is required to remediate identified compliance gaps to bring operations into regulatory compliance.

Keywords: Post - approval variations; Established Conditions (EC); Failure Mode Effect Analysis (FMEA); Risk Priority Numbering (RPN); Regulatory compliance gap categories; Regulatory document control system (RDCS); GMP; CTD; ICH; risk priority numbering (RPN) tool

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1. Introduction

Have you ever had to take medicine? How did you know that it was safe? Did you trust that the pharmaceutical manufacturer(s) made a quality product? Who ensures that the medicine you, your family and friends take will make you better and not worse? The availability of safe and efficacious pharmaceutical finished products is an entitlement that should be afforded without question to the public. These provocative questions highlight the importance of the pharmaceutical industry and medicines regulators to the interests of public health. A cooperative relationship must exist between the government and the pharmaceutical industry to achieve the unified goal of

supplying safe and effective medicines to the public. The pharmaceutical industry in the United Kingdom (UK) is regulated by the Medicine and Healthcare products Regulatory Agency (MHRA), the UK government's public health licensing authority. (1) The MHRA are responsible for "ensuring that medicines meet applicable standards of safety, quality and efficacy" and "the supply chain for medicines is safe and secure". One of the ways the MHRA safeguard their responsibility to the public is through the issuance of licences before a pharmaceutical product can be sold in the UK market.

1.1 The Legal Basis for the Approval and Supply of Medicines in the United Kingdom

The exit of the United Kingdom from the European Union (EU) has had a significant impact on the regulatory landscape of the British pharmaceutical industry. At the time of writing, the sale of medicinal products in Northern Ireland is subject to the laws of the EU. (2) The Windsor Framework is an agreement ratified in February 2023 between the UK and EU to enable a single licence and pack of medicines to be approved solely by the MHRA across the UK. The specific arrangements for the supply of medicine in line with the Windsor Framework are due to come into effect from the 1st of January 2025. (3) For this reason, this paper will focus on the UK-only approval regulatory landscape under this imminent legal basis.

The lawful supply of authorised pharmaceutical products in the United Kingdom is set out in the Human Medicines Regulations (HMRs) 2012 [Statutory Instrument 2012 No.1916]. Part 1 Regulation 6 Paragraph 1 states the legal basis for the MHRA to be '*responsible for the grant, renewal, variation, suspension and revocation of licences, authorisation, certificates, designations, opinions and registration*' of human medicines throughout the product's lifecycle. (4)

1.2 Regulatory Approval to Sell Marketed Medicines in the United Kingdom

The regulatory approval lifecycle for a pharmaceutical product is a lifelong journey. *Figure 1* provides a high-level overview of the regulatory approval phases through a pharmaceutical product lifecycle. Whilst the pre-approval, submission, evaluation and approval phases are discreet, it is pertinent to note that the post-approval phase is a continual obligation until the product is discontinued from the market. The approved technical dossier is a comprehensive document outlining the evidence and conditions to justify the safety, quality and efficacy of the marketed product. The terms within the technical dossier stipulate the conditions that allow a company to market and sell a medicinal product in the UK.

1.3 The Common Technical Document

Due to the potential global functionality, complexity and comprehensive nature of the information required in a technical dossier for medicine approval, harmonised guidelines on the presentation and format have been recommended by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to promote Good Review Practices. (5) The Common Technical Document (CTD) layout is the mandatory format for regulatory MA submissions in the UK. Figure 2 provides an overview of the organisation of the CTD. It is divided into five Modules: Module 1 contains region-specific administrative and prescribing information whilst Modules 2 to 5 are harmonised, in countries that adopt the CTD regulatory format, and provide the foundation for the quality, safety and efficacy aspects of the dossier.

1.4 Post-Approval Obligations of the Marketing Authorisation Holder

The ultimate responsibility for the quality, safety and efficacy of a pharmaceutical product over its lifecycle lies with the MAH. (6) Part 5 Sections 73 to 78B of the HMR 2012 outline the legal obligations of MAH post-approval. In summary, they are:

- Obligation to notify placing on the market
- Obligation to provide information relating to safety
- Retention of any documents or information that will facilitate the withdrawal or recall
- Obligation to ensure appropriate and continued supplies

Additional obligations are required for the provision of paediatric pharmaceutical products and advanced therapy medicinal products, which will not be reviewed within the course of this dissertation however, warrant noting.

1.5 Post-Approval Marketing Authorisation Changes: Variations and Established Conditions

Of significance for MAH is the 'obligation to take account of scientific and technical progress' as per HMR, 2012. (5) A MAH is required to continuously review and update the product information, manufacturing and control methods, to reflect the latest scientific and technical advancements. Where a change to the registered MA details is required as a result, a variation of change must be submitted to the MHRA. As a consequence, any changes to ECs necessitates a submission to the regulatory authority'. (2,9) It is an expectation that MAH identify ECs within CMC operations and include them in the Module 3 (Quality) dossier. Figure 3 provides a decision tree for the determination of ECs and relevant regulatory reporting categories.

The GMP compliance is achieved through the implementation of a robust quality management system, in pragmatic terms, the commitment of senior management and employees to adopt and adhere to policies, procedures and practices that reduce the potential for adverse impact on the quality of the pharmaceutical product. Figure **4** provides a schematic of the elements that form an effective pharmaceutical quality management system. Non-compliance with GMP increases the risk for an MAH of potential regulatory discipline, lost revenue and reputational impairment.

1.6 Rationale for the Project

Operational compliance with the approved MA for pharmaceutical products is essential for ensuring quality, safety and efficacy to protect public health. It is within the legal responsibilities of a QP to ensure that batches of medicines are released according to the terms and specifications outlined in the MA for a marketed product.

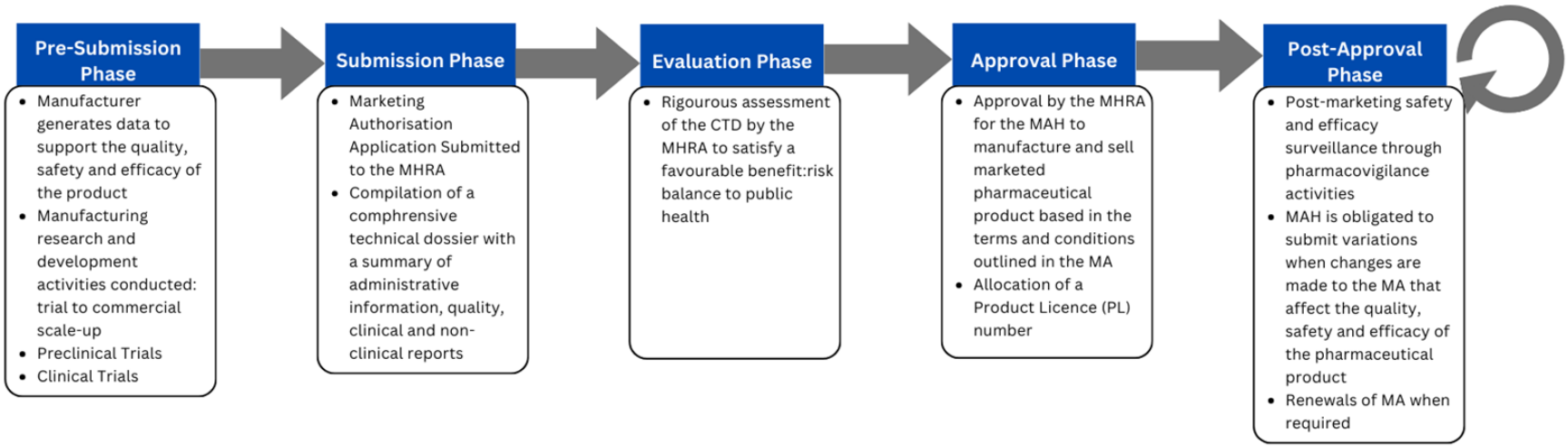

Figure 1. Overview of the Regulatory Approval Phases of Marketed Medicines for Human Therapeutic Use in the United Kingdom (3,4,8)

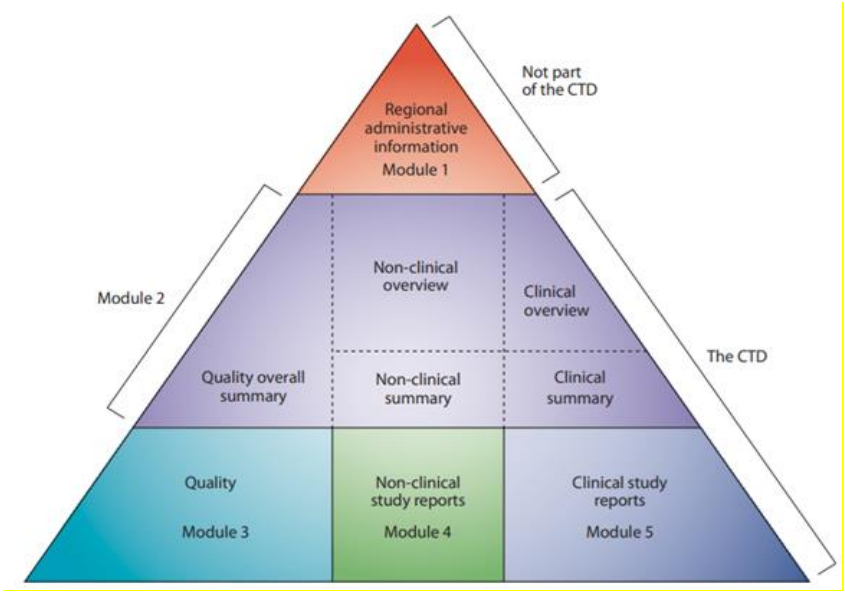

Figure 2. The Common Technical Document Triangle provides a visual summary of the harmonised structure of regulatory documents for medicine approval submission in the United Kingdom (9)

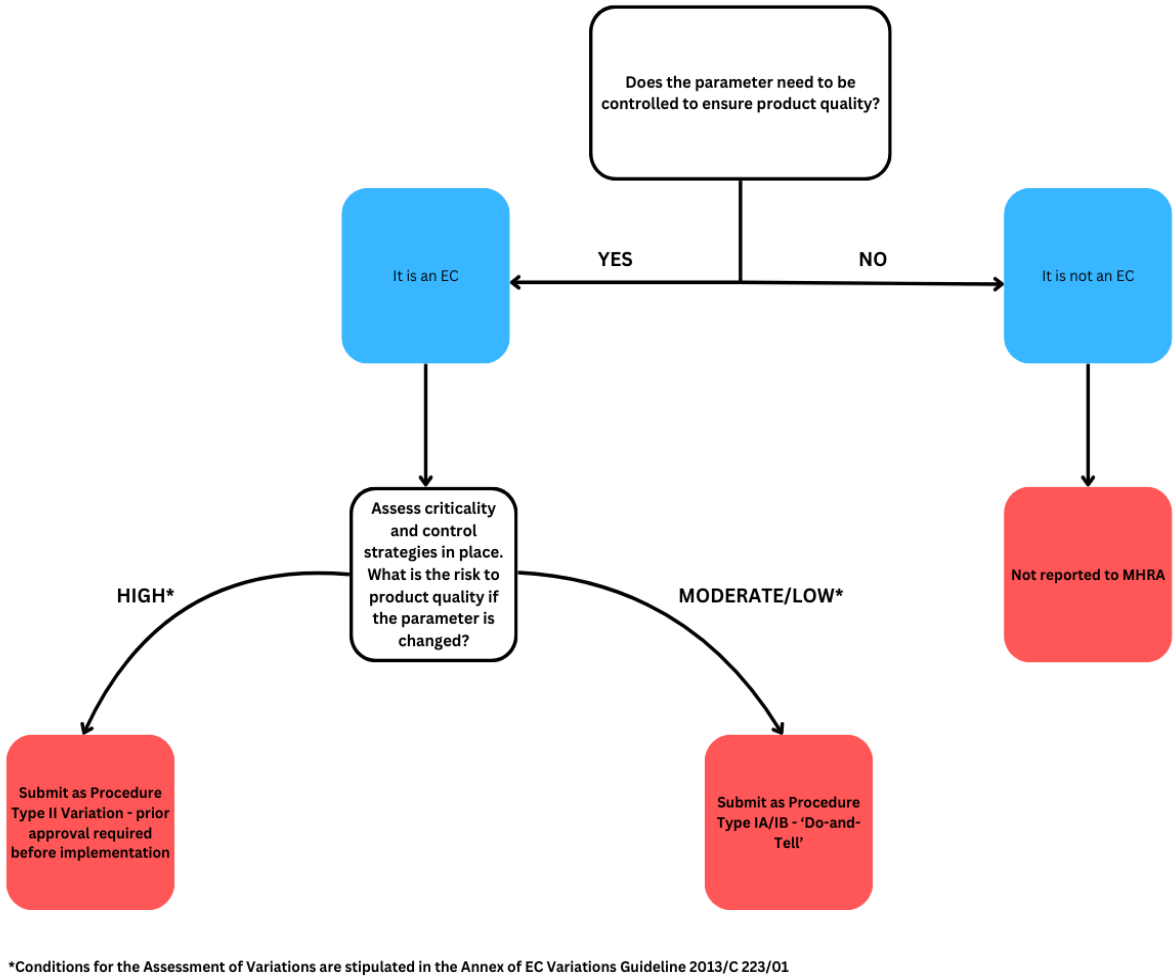

Figure 3. Decision Tree for the Identification of Chemistry, Manufacturing and Controls Established Conditions and Regulatory Reporting Categories (adapted from (1,10)

Figure 4. Elements of the Pharmaceutical Quality Management System (adapted from (3,11).

Of most bearing to the certification of batches for release is concordance with currently MHRA-approved Module 3 (Quality) MA dossier sections. This section of the MA will detail the Chemistry, Manufacturing, and Control (CMC) terms and conditions for the sale and supply of finished pharmaceutical products. Module 1 (Administrative and Prescribing Information) of the MA dossier is also of importance as it contains product information on the terms and conditions for leaflets and packaging of finished pharmaceutical products (FPP).

Established Conditions are legally binding details related to CMC processes that are considered to affect the quality of finished pharmaceutical products and must be reported to the MHRA. Adherence to these conditions within CMC operations and in the Marketing Authorisation is essential to maintaining FPP quality and meeting the legal responsibilities of a Marketing Authorization Holder. Company X is a medium-sized pharmaceutical manufacturer of finished pharmaceutical products in the UK. They supply FPP to a UK-only market. It has been identified at Company X that compliance with the MA may have drifted for marketed products. A comprehensive analysis of any regulatory compliance gaps needs to be conducted and remediation enacted to assure QPs that products are being released according to the requirements of National Law. This forms the basis of the current study. The outcomes of this work are intended to provide a position on the current state of regulatory and quality compliance, as well as to provide an impact assessment of any potential compliance gaps.

2 Aims and Objectives

This project intends to serve as a method development and pilot execution protocol for Company X to assess its current regulatory compliance. It will focus solely on reviewing a single marketed finished pharmaceutical product as determined by Company X.

2.1 Aims

Aims of the project include to:

Assess the state of compliance between the Marketing Authorisation and current operational processes at Company X, Assess the impact of identified compliance gaps on quality

2.2 Objectives

The aims will be achieved by way of:

1 Identifying regulatory compliance and gaps between regulatory approved documentation versus operational documentation
2 Identifying quality compliance and gaps between operational documentation versus supporting documentation
3 Performing a risk assessment on compliance gaps identified to attribute prioritisation for remediation

Proposing remediation strategies for any identified regulatory compliance gaps by ascribing a Variation Regulations Classification Type

3. Materials and Methods

This study was performed by way of a gap analysis between the MHRA-approved Module 1 and Module 3 MA dossier sections against current operational documents at Company X. Figure *5* provides a high-level overview of the review process flow and relevant stakeholders at study milestones.

The softwares and prorgammes used in this study were sourced from UCL Library and collaborative Industry partners included eCTD, eQMS, Q Pulse, ICH Q3 – Q10, EUGMP Part 1 and part 2 of EudraLex Volume 4.

3.1 Inclusion and Exclusion Criteria

CTD sections included for review included Module 1.3.2 Mock-Up and Module 3.2.P Drug Product for a single marketed product at Company X. See Appendix I – Summary of CTD Module Sections, Operational and Supporting Source Documents Identified for Review for an exhaustive list. CTD sections relating to drug substance (i.e. Module 3.2.S) were not included in the scope of this project due to time constraints. The inclusion of CTD module sections for review was guided by criteria for sections that contain Established Conditions specified in the ICH Q12 Guideline Appendix I (see Appendix II – Sections of the Common Technical Document likely to contain Established Conditions).

3.2 Collation of Source Documentation for Review

3.2.1 Regulatory Documentation

All approved CTD dossier sections were made available in project-dedicated folders in the electronic Quality Management System by the Regulatory Affairs Manager (or delegate). A standardised folder directory naming convention was established to ensure auditability and document control in line with Good Documentation Practice.

3.2.2 Operational and Supporting Documentation

Operational department leads at Company X identified the need to review operational and supporting documentation. *Table 1* summarises the subject matter experts involved in this process. A full list of the reviewed documents is available in Appendix I – Summary of CTD Module Sections, Operational and Supporting Source Documents Identified for Review. A three-tiered review method was developed to ensure a robust yield of principal data outputs and review assessments. *Figure 6* provides a high-level overview of the review outputs flow. Data were documented on standardised forms created specifically for this project to ensure compliance with Good Documentation Practices. These forms included key details such as approval traceability, unique identifiers and numbers on all pages.

3.3 Tier 3 Review (Student)

This review aimed to generate principal data for the project. Outputs from this review were then escalated for a Tier 2 review by subject matter experts for assessment.

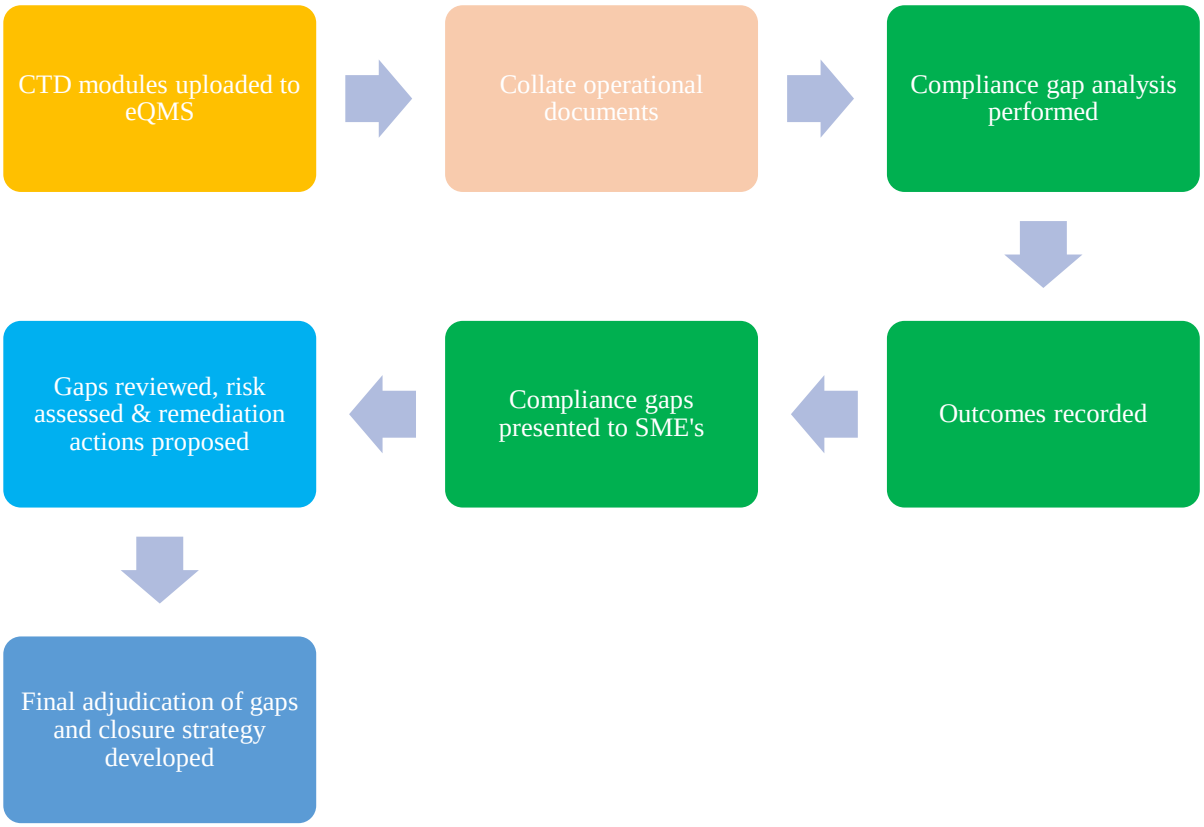

Figure 5. High-level project design and review process flow

Table 1. Operational Leads Responsible for Providing Source Documents

Module Heading Number	Module Section Heading	Subject Matter Expert Lead
1.3.2	Mock-ups	Quality Assurance
3.2.P.1	Description and Composition of the Drug Product	Quality Assurance
3.2.P.3	Manufacture	Manufacturing
3.2.P.4	Control of Excipients	Quality Control
3.2.P.5	Control of Drug Product	Quality Control
3.2.P.6	Reference Standards of Materials	Quality Control
3.2.P.7	Container Closure System	Quality Control
3.2.P.8	Stability	Quality Control

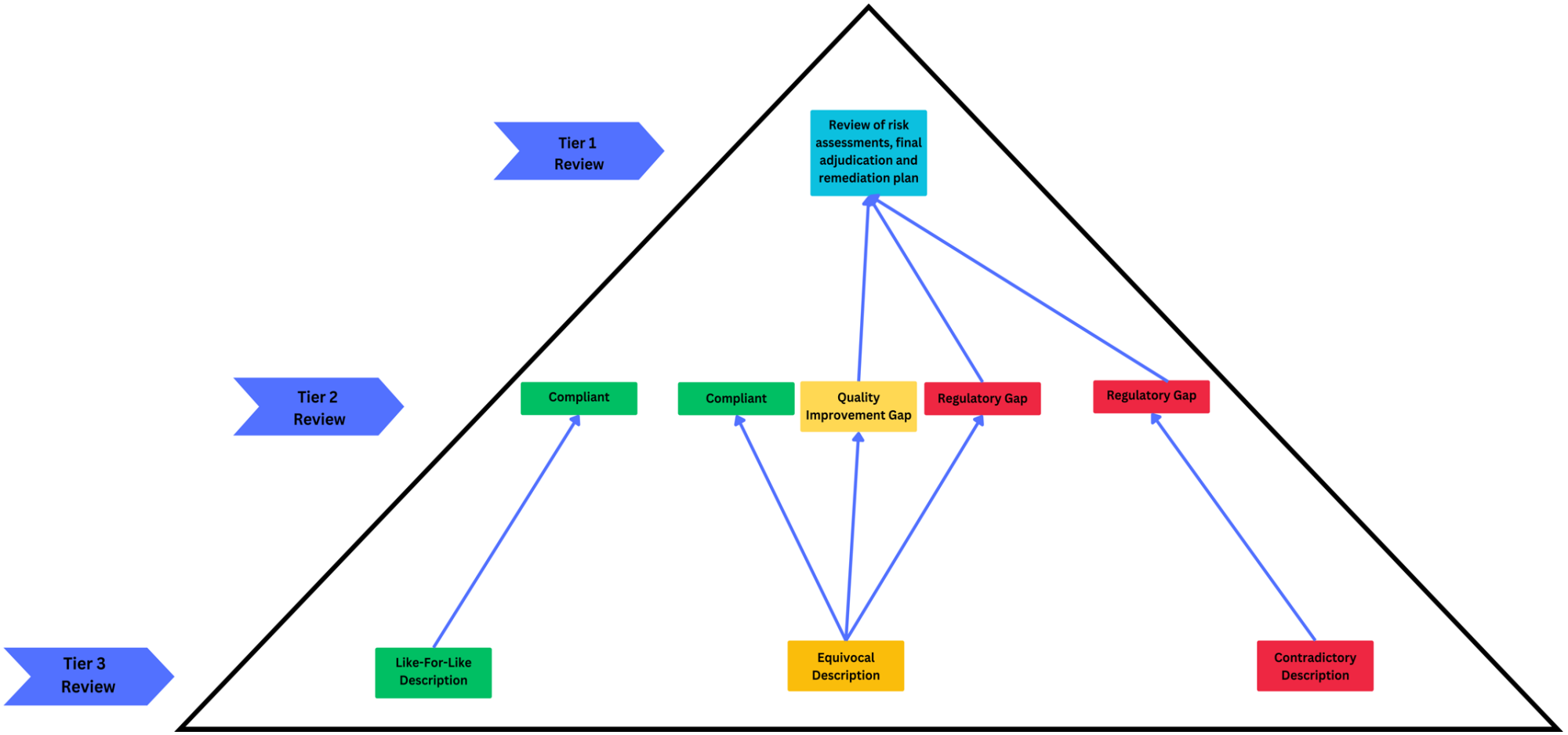

Figure 6. Overview of Data Collection, Assessment, Adjudication and Remediation Process Flow

A two-arm gap analysis was conducted to assess:

1. Regulatory Compliance between CTD sections and Operational Documentation; AND
2. Quality Compliance between Operational Documentation and Supporting Documentation

Compliance Gap Analysis Review

A word-for-word review was carried out between documentation. Information in regulatory and operational documentation was assessed and recorded in line with a Red-Amber-Green (RAG) risk assessment tool developed by the author (see Table 2) to identify regulatory conditions. Information in operational documentation was then assessed against supporting documentation to identify quality conditions.

Table 2. Red-Amber-Green (RAG) Risk Assessment Tool for Tier 1 Review

Compliant	'Like-for-Like' terminology was used across regulatory and operational documentation.
Equivocal Terminology	Equivocal terminology was used requiring further assessment of the perceived regulatory and/or quality compliance gap by subject matter expert(s).
Non-Compliance	Opposing terminology was used across regulatory and operational documentation.

3.4 Tier 2 Review (Subject Matter Experts)

The purpose of this review was to evaluate the Tier 3 data outputs, establish EC, conduct a risk analysis, and propose remediation strategies for any identified compliance gaps from a multidisciplinary perspective. Tier 3 data was presented to the SME group by the student in a formalised meeting. Tier 2 outcomes were captured as minutes, approved by the workstream lead and saved to the project folder directory in the eQMS for auditability purposes.

3.4.1 Assessment of Tier 3 Data Outputs

Qualitative data collected in the Tier 3 review were coded into 3 categories: Regulatory Gap (R), Quality Gap (Q) or Compliant (C). Regulatory and Quality Compliance Gaps were further assessed and described as per 'Appendix III – Description of Regulatory and Quality Compliance Gaps'.

3.4.2 Risk Assessment of Compliance Gaps

Quality risk management is the systematic process for the "*assessment, control, communication and review of risks to the quality of a medicine*" and has been identified as a valuable component to an effective quality management system. A risk is determined by the combination of the probability of the occurrence of harm and the severity of the outcome should it occur. Decision makers in this review should include persons with the competence and authority to make appropriate verdicts. The RAG system was used to attribute all compliance gaps identified a priority ranking for remediation. All regulatory compliance gaps identified were allocated a red priority as these are deemed to require immediate remediation due to being a deviation from the MA registered details. A risk ranking assessment tool (see Table 3) was developed in collaboration with the CMC compliance specialist at Company X, to prioritise and communicate compliance gaps identified at the subsequent tier 1 review by the governance team. Gaps were attributed to a Risk Priority Number (RPN) determined by the severity multiplied by the probability. *Table 3: Risk Priority Assessment and Risk Priority Number Tool*

Table 3. Risk Priority Assessment and Risk Priority Number Tool

Severity	The level to which the issue can cause harm
1	Minor inconsistency no impact on GMP
2	Significant inconsistency no impact on GMP
3	GAP would lead to a minor impact on product quality and/or minor inconvenience to the patient
4	GAP could lead to moderate impact on product quality and/or supply issues and/or recall
5	GAP could lead to patient harm and/or a significant deviation from GMP. Significant quality, safety and/or efficacy issues.
Probability	The level to which the issue if realised will lead to the severity
1	Almost zero chance of the issue being realised
2	20% certainty the risk will be realised
3	50% certainty the risk will be realised
4	80% certainty the risk will be realised
5	100% certain the risk will be realised

	Severity				
Probability	1	2	3	4	5
1	1	2	3	4	5
2	2	4	6	8	10
3	3	6	9	12	15
4	4	8	12	16	20
5	5	10	15	20	25

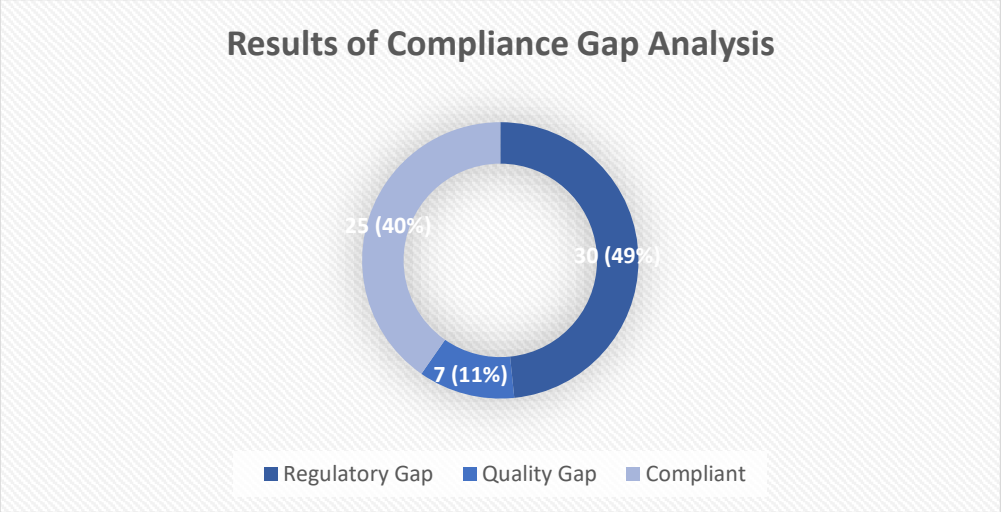

Figure 7. Results of compliance and compliance gap outcomes identified in MA sections reviewed

3.5 Tier 1 Review (Governance Board)

The purpose of this review was to assess the Tier 2 regulatory and quality compliance risk assessment and remediation proposal outputs, conduct a further risk assessment and ratify a final adjudication and remediation strategy. Tier 2 data was to be summarised and presented to the governance team by the CMC project lead and author in a formalised meeting. Outcomes were to be captured as minutes, approved and saved to the project folder directory in the eQMS for auditability purposes. Method development and execution of the Tier 1 pilot review was unable to be completed due to time constraints.

4. Results

Due to the commercially sensitive nature of the data generated from this project, the results reported are presented in generalised terms. The original raw data remains the intellectual property of Company X. After Tier 1 and Tier 2 reviews, 62 compliance-related ECs were identified in the MA sections available for review. 49% (30 conditions) reflected regulatory compliance gaps, 40% (25 conditions) were compliant and 11% (7 conditions) reflected quality compliance gaps (see Figure 7: Results of compliance and compliance gap outcomes identified and *Table 5: Summary of Compliance Gaps and Risk Priority*).

4.1 Types of Regulatory Compliance Gaps

Six categories of regulatory compliance gaps were adjudicated at the Tier 2 review and grouped as per *Figure 8: Types of Regulatory Gaps Identified*.

Of the 15 CTD module sections included for review in this study, 10 were unavailable. See Appendix I for a list of the CTD dossier sections unavailable. One EC was identified where the registered test in the MA has been superseded by technical progress and reflected in the operational documentation. Eight ECs were identified where the registered information in the MA was not in alignment with the operational processes. Conditions included:

- The MA registered qualitative description for the finished pharmaceutical product embossing was not aligned with the description in the operational and supporting documentation
- MA registered manufacturing equipment type was not aligned with that being used operationally
- MA registered manufacturing in-process control specification not in alignment with operations
- MA registered release specification not in alignment with operations
- Two MA-registered shelf-life specifications were not in alignment with operations
- A MA registered container closure system specification was not in alignment with operations
- A MA registered container closure system component not in alignment with operations

Five ECs were identified that were not registered in the MA. Conditions included:

- The omission of the primary packaging process description
- A lack of descriptions for three closed container system component specifications
- An absence of specifications for a closed container system componentFour registered ECs were identified that were not incorporated into the operational procedure. Conditions included:

- An MA-registered in-process visual appearance specification was missing from the operational procedure
- An MA-registered in-process moisture specification was not included in the operational procedure
- An MA-registered shelf-life specification was absent from the operational procedure
- Several MA-registered closed container system specifications were not included in the operational procedure

Three typographical errors were noted in the registered MA. Whilst not strictly a regulatory EC, these particulars were recorded to promote Good Review Practices. Conditions included outdated terminology for a registered specification test, incorrect legal classification stated in a CTD section where it is not required to be registered and duplication of wording.

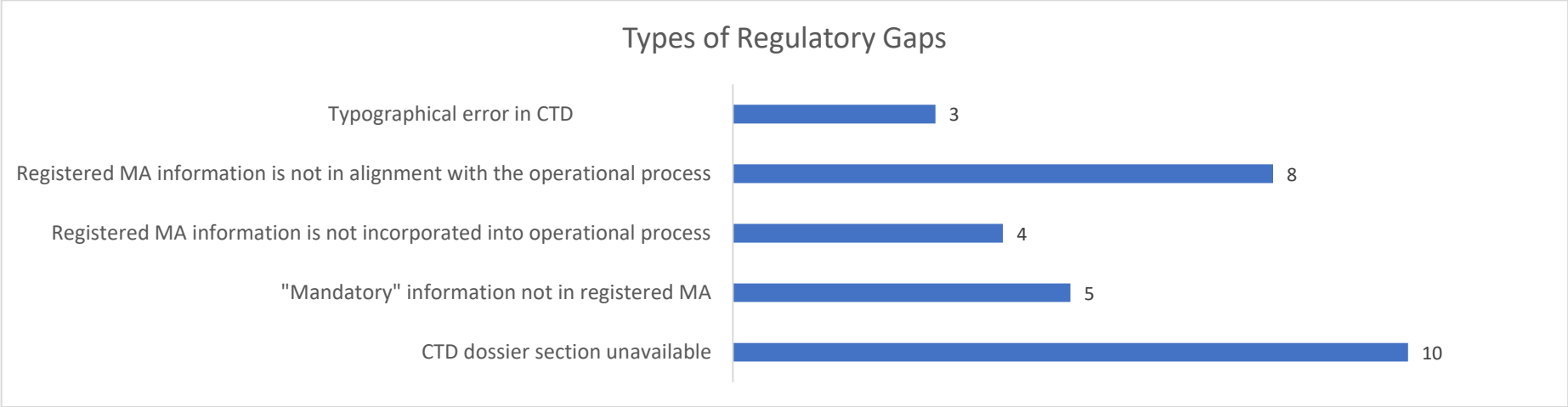

Figure 8. Types of Regulatory Gaps Identified

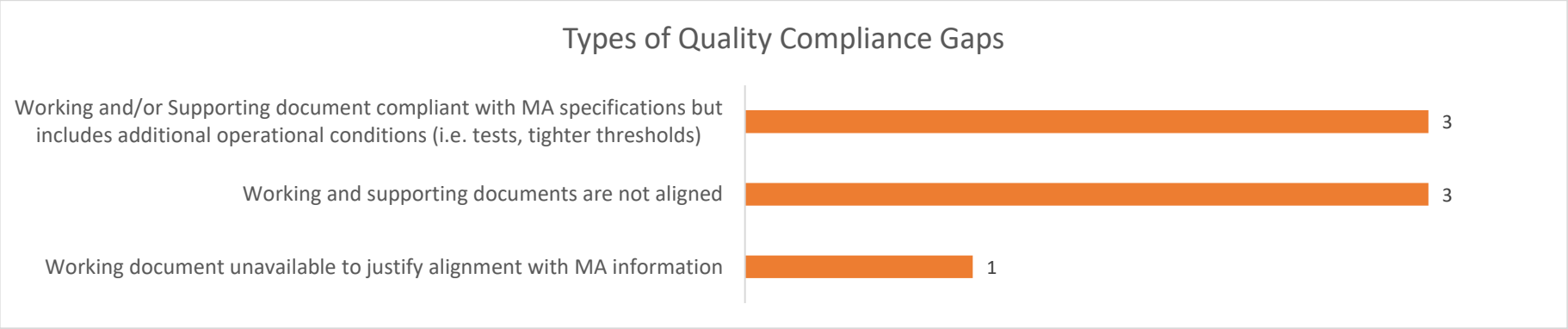

Figure 9. Types of Quality Compliance Gaps Identified

Table 4. Summary of Compliance Gaps and Risk Priority

Sequence	CTD Module	Compliance Gap Type*	Description of Compliance Gap	Risk Priority
1	1.3.2	R1	CTD section not available for review	High
2	3.2.P.1	R4	Discordance between qualitative description of finished pharmaceutical product embossing in CTD and operational documentation	High
7	3.2.P.3.1	R1	CTD section not available for review	High
8	3.2.P.3.2	R1	CTD section not available for review	High
9	3.2.P.3.3	R4	Variance between manufacturing equipment type described in CTD and operational documentation	High

13	3.2.P.3.3	R4	CTD registered manufacturing process out of alignment with operational documentation	High
14	3.2.P.3.3	R2	Primary packaging process not registered in the CTD	High
19	3.2.P.3.4	R3	CTD registered test A not described in operational documentation	High
20	3.2.P.3.4	R3	CTD registered test B not described in operational documentation	High
28	3.2.P.4.1	R1	CTD section not available for review	High
29	3.2.P.4.2	R1	CTD section not available for review	High
30	3.2.P.4.5	R1	CTD section not available for review	High
31	3.2.P.4.6	R1	CTD section not available for review	High
33	3.2.P.5.1	R4	Variance between release specification limits for test C in CTD and operational documentation	High
34	3.2.P.5.1	R3	CTD registered shelf-life test not reflected in operational documentation	High
35	3.2.P.5.1	R4	CTD registered shelf-Life specification not in alignment with operational document resulting in non-compliance of significant figures for ranges reported operationally.	High
36	3.2.P.5.1	R6	Typographical error in CTD section for name of release test	High
37	3.2.P.5.1	R6	Erroneous/superfluous inclusion of legal classification in CTD section	High
38	3.2.P.5.1	R4	Typographical error in CTD section resulting in duplication of statement	High
39	3.2.P.5.1	R4	Operational specification range not registered in the CTD	High
48	3.2.P.5.2	R1	CTD section not available for review	High
Sequence	CTD Module	Compliance Gap Type*	Description of Compliance Gap	Risk Priority
49	3.2.P.6	R1	CTD section not available for review	High
50	3.2.P.7	R2	Operational specification A not registered in the CTD	High
51	3.2.P.7	R2	Operational specification B not registered in the CTD	High
52	3.2.P.7	R4	Variance in specification C limits between CTD and operational documentation	High
53	3.2.P.7	R3	Various CTD registered specifications not reflected in operational documentation	High
54	3.2.P.7	R2	Operational specification C not registered in the CTD	High
56	3.2.P.7	R2	Various operational specifications for closed container system A not registered in the CTD	High
57	3.2.P.7	R4	Variance between type of closed container system component in CTD and operational documentation	High
55	3.2.P.7	Q1	For closed container system A, no operational document is available to verify the identity or material specifications of each primary packaging component	High
62	3.2.P.8.1	R1	CTD section not available for review	High
10	3.2.P.3.3	Q2	Variance between particle size separation technique in operational and validation document	Medium
21	3.2.P.3.4	Q3	In-house specification A threshold tighter versus CTD	Low
22	3.2.P.3.4	Q3	In-house specification B threshold tighter versus CTD	Low
32	3.2.P.5.1	Q3	Operational release test A not registered in MA. Test A superseded by technical advancement and approved in MA, however operational document not updated and continues to apply both test methods.	Low
58	3.2.P.7	Q2	Storage conditions for closed container systems A, B ,C and D not described in operational documentation. Stored in environmentally controlled warehouse.	Low
59	3.2.P.7	Q2	Product code specified in analytical report not listed in packaging material specification document.	Low

**See* Appendix III – Description of Regulatory and Quality Compliance Gaps for definitions of 'Compliance Gap Type'

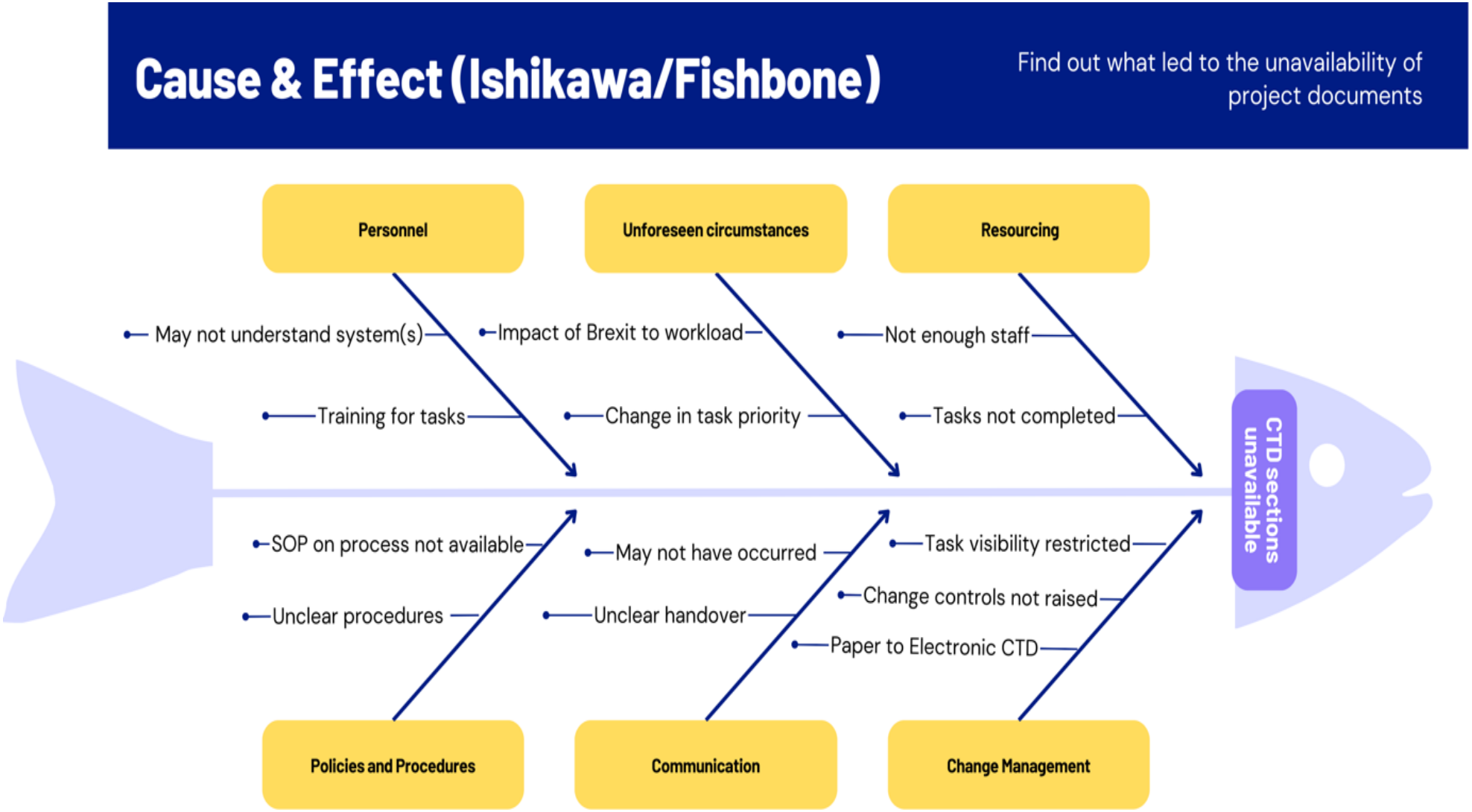

Figure 10. Cause and Effect (Ishikawa/Fishbone) Diagram for Unavailability of CTD Sections (12)

Table 5. Summary of Compliance Gaps and Proposed Remediation Strategies (1)

Sequence	CTD Module	Change Type	Description of Compliance Gap	Risk Priority	Variation Code
2	3.2.P.1	Regulatory Variation	Minor typographical discordance between qualitative description of finished pharmaceutical product embossing in CTD and operational documentation	High	"B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking a) Changes in imprints, bossing or other markings" Procedure Type IA_{IN}
Conditions to be Fulfilled					
"1. Finished product release and end of shelf life specifications have not been changed (except for appearance). 2. Any ink must comply with the relevant pharmaceutical legislation. 3. The scoring/break lines are not intended to divide into equal doses. 4. Any product markings used to differentiate strengths should not be completely deleted."					
Documents to be Supplied					
"1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a detailed drawing or written description of the current and new appearance, and including revised product information as appropriate. 2. Samples of the finished product where applicable"					

Sequence	CTD Module	Change Type	Description of Compliance Gap	Risk Priority	Variation Code
9	3.2.P.3.3	Regulatory Variation	Variance between manufacturing equipment type described in CTD and operational documentation	High	"B.II.b.3 Change in the manufacturing process of the finished product a) Minor change in the manufacturing process"
14			Primary packaging process not registered in the CTD		Procedure Type IA
Conditions to be Fulfilled					
"1. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product; or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form). 3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process. 4 The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls. 5. The specifications of the finished product or intermediates are unchanged. 6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy. 7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least 3 months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action)."				

<table>
<tr><td colspan="6">Documents to be Supplied</td></tr>
<tr><td colspan="6">“1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a direct comparison of the present process and the new process.
2. For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.
3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.
4. Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability.
5. For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.
6. Copy of approved release and end-of-shelf life specifications.
7. Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
8. Declaration that relevant stability studies have been started under ICH/VICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least 3 months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).”</td></tr>
<tr><td>Sequence</td><td>CTD Module</td><td>Change Type</td><td>Description of Compliance Gap</td><td>Risk Priority</td><td>Change Control</td></tr>
<tr><td>35</td><td>3.2.P.5.1</td><td>Internal Change Control</td><td>CTD registered shelf-Life specification not in alignment with operational document resulting in non-compliance of significant figures for ranges reported operationally.</td><td>High</td><td>Include shelf-life specification range to Finished Product Specification procedure to align reporting of significant figures with the MA</td></tr>
<tr><td>Sequence</td><td>CTD Module</td><td>Change Type</td><td>Description of Compliance Gap</td><td>Risk Priority</td><td>Variation Code</td></tr>
<tr><td>36</td><td>3.2.P.5.1</td><td rowspan="3">Regulatory Variation</td><td>Typographical error in CTD section for name of release test</td><td rowspan="3">High</td><td rowspan="3">Not Applicable
Submit as typographical amendment within grouped submission for this Product Licence</td></tr>
<tr><td>37</td><td>3.2.P.5.1</td><td>Erroneous/superfluous inclusion of legal classification in CTD section</td></tr>
<tr><td>38</td><td>3.2.P.5.1</td><td>Typographical error in CTD section resulting in duplication of statement</td></tr>
<tr><td>Sequence</td><td>CTD Module</td><td>Change Type</td><td>Description of Compliance Gap</td><td>Risk Priority</td><td>Variation Code</td></tr>
<tr><td>39</td><td>3.2.P.5.1</td><td>Regulatory Variation</td><td>Operational specification range not registered in the CTD</td><td>High</td><td>“B.II.d.1 Change in the specification parameters and/or limits of the finished product
a) Tightening of specification limits”
Procedure Type
IA</td></tr>
<tr><td colspan="6">Conditions to be Fulfilled</td></tr>
</table>

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor."

Documentation to be Supplied

"1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed specifications."

Sequence	CTD Module	Change Type	Description of Compliance Gap	Risk Priority	Variation Code
50	3.2.P.7	Regulatory Variation	Operational specification A not registered in the CTD	High	"B.II.e.3 Change in test procedure for the immediate packaging of the finished product b) Other changes to a test procedure (including replacement or addition)"
51			Operational specification B not registered in the CTD		Procedure Type
54			Operational specification C not registered in the CTD		IA
56			Various operational specifications for closed container system A not registered in the CTD		

Conditions to be Fulfilled

"1. Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the former test procedure.
3. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
4. The active substance/finished product is not biological/immunological."

Documentation to be Submitted

"1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data.
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure."

Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Variation Code
52	3.2.P.7	TBC	Variance in specification C limits between CTD and operational documentation	High	Root Cause analysis required to determine alignment with current GMP
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
53	3.2.P.7	Internal Change Control	Various CTD registered specifications not reflected in operational documentation	High	Add MA registered specifications to the Finished Product Specification procedure
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control

57	3.2.P.7	To be Determined	Variance between type of closed container system component in CTD and operational documentation	High	Batch Assembly Record refers to a "CRC Cap" whilst the CTD section states "Tamper Evident Flip-Top Cap". Assess what component is in current operation and update either the CTD or operational documentation accordingly.
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
55	3.2.P.7	Internal Change Control	For closed container system A, no operational document is available to verify the identity or material specifications of each primary packaging component	High	Produce Finish Product Specification procedure for closed container system A.
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Variation Code
10	3.2.P.3.3	Internal Change Control	Variance between particle size separation technique in operational and validation document	Medium	Assess what component is in current operation and update operational or supporting document accordingly.
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
21	3.2.P.3.4	Not Required	In-house specification A threshold tighter versus CTD	Low	In-house specification below MA threshold therefore risk to quality, safety and efficacy is of low consequence. Reasonable to leave unchanged.
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
22	3.2.P.3.4	Not required	In-house specification B threshold tighter versus CTD	Low	In-house specification below MA threshold therefore risk to quality, safety and efficacy is of low consequence. Reasonable to leave unchanged.
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
32	3.2.P.5.1	Internal Change Control	Operational release test A not registered in MA. Test A superseded by technical advancement and approved in MA, however operational document not updated and continues to apply both test methods.	Low	Remove superseded test from operational document.
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
58	3.2.P.7	Internal Change Control	Storage conditions for closed container systems A, B ,C and D not described in operational documentation	Low	Update operational procedure to include storage conditions
Sequence	CTD Module	Change Type	Narrative of Compliance Gap	Risk Priority	Change Control
59	3.2.P.7	Internal Change Control	Product code specified in analytical report not listed in packaging material specification procedure	Low	Update packaging material specification procedure to include product code for component

Table 6. Variation Procedure Types to Amend the Terms of an Approved UK-only Marketing Authorisation (adapted from (1, 5, 13)

Procedure Type	Description of Conditions
Type IA (Minor Variation)	Variations of this type, colloquially known as 'do-and-tell', do not require prior examination by the MHRA before implementation. The MAH must submit a notification of the relevant variation(s) within 12 months of implementation. Variations of this nature are considered to have a minimal impact or no impact on the quality, safety or efficacy of the medicinal product concerned.
Type IA_{IN} (Minor Variation)	Variations of a minor nature however, immediate notification to the MHRA is required after implementation for the continuous supervision of the medicinal product of concern.
Type IB (Minor Variation)	A variation that is neither a minor variation of Type IA, not a major variation of Type II nor an Extension. The MHRA must be notified before the change is implemented.
Type II (Major Variation)	Variations which are not an extension of the Marketing Authorisation however, may have a significant impact on the quality safety and efficacy of the medicinal product.
Extensions	Variations which result in changes to the active substance(s), strength, pharmaceutical form and route of administration.
Urgent Safety Restriction	An interim change in the terms of the Marketing Authorisation due to new information relating to the safety of the marketed pharmaceutical product.

4.2 Types of Quality Compliance Gaps

Three categories of quality compliance gaps were adjudicated at the Tier 2 review and grouped as per Figure 9: Types of Quality Compliance Gaps Identified. The most frequently observed quality compliance gap was the misalignment between operational and supporting documentation with three conditions meeting this gap. Conditions included storage for a closed container component that was not specified in the working document, product code specified on the supporting document was not listed on the working document and variance in the particle size separation technique between operational documentation and validation report. Two conditions were observed where tighter in-house specification limits were implemented operationally compared to those registered in the MA. One condition was observed where an operational document was unavailable to support the operational alignment of a manufacturing process with the registered MA details.

4.3 Risk Assessment

All 30 regulatory compliance gaps were attributed to a high-risk (red) priority. Of the quality compliance gaps identified 1 was ranked high risk, 1 medium risk and 5 low risk (see *Table 5*)

4.4 Remediation Outcomes

Due to time constraints, remediation proposals could not be generated at the Tier 2 review. Furthermore, a Tier 1 level review was not commenced.

5. Discussion

Due to time limitations over the project period, a Tier 1 governance review could not be progressed. The governance team is comprised of the company's Head of Quality, Qualified Person, Regulatory Affairs Manager and Project Manager. It is proposed in the methodology that at this milestone the governance team would make a final adjudication and remediation of identified compliance gaps. With this in mind, it is worth noting that the results reported in this dissertation are limited to the scope of the Tier 3 (Student) and Tier 2 (SME) assessment criteria. As remediation is a critical aspect of bringing Company X into regulatory compliance, this Tier review should be prioritised in future. The most frequently observed regulatory compliance gap was the unavailability of CTD sections for review (see Figure 8: Types of Regulatory Gaps Identified) This may suggest that regulatory documentation is presently managed in an uncontrolled manner. Critical documents to pharmaceutical operations should have controls in place to ensure the accuracy, integrity, availability and legibility of the document at all times. The management of regulatory commitments to the MHRA can become a source of MA non-compliance if it is not under an appropriate level of control by the MAH. (14)

Document control is an element of the pharmaceutical Quality Management System. Remediation strategies for this regulatory compliance gap should include a root cause analysis to fully understand the company's current position in accessing MHRA-approved CTD sections. If these sections are unavailable, they may need to be rewritten and submitted to the MHRA for approval. Of the remaining compliance gaps identified (see *Table 5: Summary of Compliance Gaps and Risk Priority*), either a variation of the MA or change to operational documentation is required to align the company's regulatory position into a state of compliance.

Table 6 provides a summary of proposed remediation strategies for compliance gaps identified. The outcomes highlight how Company X can practically consider the outcomes of results, the implications to business continuity and recommendations for changes in company practice.

For compliance gaps requiring submission of a variation to the approved CTD section, an assessment by the author is given in Table 5 that ascribes a variation code against criteria set in the Annex of the European Commission Variations Classification Guidelines 2013. (15) Specific details of the change have been redacted due to the

commercial-in-confidence nature of the information. It is noted that of all the variations required, all are Type IA or Type IA_{IN} minor variation submissions. Information on other variation types is provided in *Table 7*. Type IA variations, colloquially known as 'do-and-tell', do not require prior examination by the MHRA before implementation. The MAH is expected to submit a notification of the relevant variation(s) within 12 months of implementation. Type IA_{IN} variations are a sub-type of Type IA however, require notification to the MHRA within 2 weeks of change implementation as this type of change may 'interfere with MHRA's ability to continuously supervise the product'. Variations of a Type IA/Type IA_{IN} nature are considered to have a minimal impact or no impact on the quality, safety or efficacy of the medicinal product concerned. This infers a level of confidence, that all of the identified regulatory compliance gaps are of minimal impact to the quality of the presently manufactured product. However, it should be noted that if the implementation period exceeds 12 months for Type IA or 2 months for Type IA_{IN} without the MHRA being notified of the change, the procedure defaults to a Type IB. A Type IB variation will require that the change of concern be ceased and immediate notification to the MHRA. Approval from the MHRA will be required before the change of concern can be re-introduced operationally. Although the MHRA classified this as a minor variation in the product's quality, potential implications for business continuity and revenue impacts are likely.

Consequently, Company X should consider reviewing how long changes have been in operation as they may be lawfully obliged to cease current operations or revert to the previously approved MA terms and conditions until the Type IB application is approved. A Type IB application may require up to 30 days for processing by the MHRA. The identification of operational changes without a change to the MA may suggest deficiencies in the process flow of information between the regulator and Company X. Robust communication processes are an integral aspect of the pharmaceutical industry due to the large number of stakeholders involved throughout a pharmaceutical product's lifecycle. A significant burden lies on an MAH to establish effective communication channels, therefore, a short-term investment in process understanding and procedure establishment may offer long-term efficiencies and reassurance to the regulator that the Quality Management System is robust. As the legally responsible entity for ensuring the performance and regulatory compliance of a pharmaceutical product throughout its lifecycle, they must facilitate mechanisms for the two-way communication of regulatory information. (16)

Two conditions that require further root cause analysis were identified to determine the most appropriate remediation strategy (see Table 5 sequences 33 and 52). For both conditions, a variance in the specification limits between the MA and operational may be due to a historical update in the British Pharmacopoeia (BP). It is common practice in the pharmaceutical industry for product specifications and limits to be set against BP monographs. This may include specifications and limits for active pharmaceutical ingredients, excipients and/or finished products. It is hypothesised that operational documentation was updated when the finished product monograph was updated in the BP however an amendment to the MA was not concurrently submitted. This further suggests deficiencies in the communication of regulatory information at Company X and that processes require robust review. Quality risk management tools are a useful resource for the identification and control of quality issues, such as those reported in this project. The use of quality risk management systems is a regulatory condition as part of GMP requirements. (17) Root cause analysis is a commonly used application that as the name suggests, identifies and addresses the root cause(s) or contributing factors to the issue in question. (18) A cause and effect diagram, also known as an Ishikawa or fishbone diagram is an example of a simple and effective risk management tool to aid identification of possible cause(s) for a specific event. Refer to Figure *10* for a cause-and-effect diagram addressing the most frequently observed regulatory compliance gap—the unavailability of CTD sections—based on preliminary root cause analysis discussions at Company X.

Pharmaceutical quality management systems are a legislative requirement of MAHs to ensure pharmaceutical products are safe and efficacious. A well-designed system also minimises the risk of regulatory non-compliance. (19) This is achieved through the establishment of a systematically designed procedure that incorporates GMP and Quality Risk Management principles. (20) Table 9: Summary of EudraLex Volume 4 Good Manufacturing Practice Chapters, Chapter I – Pharmaceutical Quality Systems, provides a summary of the elements that structure this important pharmaceutical industry framework. Robust controls are required in the pharmaceutical industry to ensure that any changes that impact the quality, safety and efficacy of the pharmaceutical product are appropriately reviewed, justified, approved and monitored through the change control period. Chapter 1 Paragraph 1.4 of EudraLex Volume 4 GMP provides the following change control guidance: "(xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required; and (xiii) After the implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;". (13) To ensure the appropriate review, approval and sustainability of any changes generated from remediation actions they should be raised through the quality management system as formal change control items. Regular review of these change controls should be conducted to ensure barriers to remediation deliverables are resolved, actioned and completed expeditiously.

6. Conclusions

Access to safe and efficacious medications is a privilege owed to all without question. The Medicines and Healthcare products Regulatory Agency acts as the legal authority on behalf of the British government to assess and approve the quality of a pharmaceutical product before it is made available for sale in the UK. The approved terms and conditions for sale of pharmaceutical products are

outlined in a comprehensive dossier known as the Common Technical Document and comprises sections where legally binding information that assures the quality of a pharmaceutical product is found. Regulatory compliance is the legal duty of Qualified Persons within the pharmaceutical industry before releasing pharmaceutical products to the market.

The present study identifies that Company X is in a state of non-compliance with regulatory and quality aspects of operations. In total, 30 regulatory compliance gaps and 7 quality compliance gaps have been identified. The unavailability of regulatory-approved CTD documentation emerged as the most common compliance gap in this study. Good documentation practice is an essential part of the pharmaceutical quality management system due to the instructive requirements necessitated by manufacturing processes and the data-rich outputs they generate. High-quality documentation should yield transparent, easy-to-interpret, reproducible directives and be readily available. A root cause analysis coupled with a corrective and preventative plan for the management of regulatory dossiers may assist with the remediation and sustainability of change in the future for company X.

Due to time constraints, a governance-level review at Company X could not be conducted to assess and approve remediation strategies to address compliance gaps identified in this study. The methodology automatically attributes all regulatory compliance gaps a high risk, on the basis that regulatory non-compliance is a risk to business continuity due to regulatory action. Reassuringly however, all compliance gaps identified requiring changes to the MA are noted as Type IA 'do-and-tell' or Type IA_{IN} 'Immediate Notification' variations (see Table 6) which have minimal impact or no impact on the quality, safety or efficacy to the medicinal product reviewed per regulatory guidance. However, the translation of these variation change proposals needs to be considered when associated changes are implemented. If more than 12 months have elapsed since the Type IA change was implemented or 2 weeks for a Type IA_{IN}, a change in procedure to a Type IB submission is required. This may affect business continuity as the related operational process will need to be ceased or reverted to the currently approved CTD terms and conditions.

7. Future Work

The results of this work have identified that several CTD sections remain unavailable for review. To ensure a holistic assessment of the pilot product a review of these documents is required. Undertaking a formalised cause and effect analysis should be able to offer insights into existing barriers to documentation access. Following this, a corrective and preventative action plan may assist the progression of this pilot review and the future sustainability of regulatory document control at Company X. The success of this project may be constrained by the availability of current personnel resources to conduct a complete review. 37 conditions were identified from 5 CTD sections that require intervention. Assuming this rate of occurrence, an additional 74 conditions could be raised from the remaining 10 CTD sections for this one product review. Future considerations should be made to capture time-in-motion data during the remediation phase, particularly when change controls are raised and actioned. This may offer the company an understanding of the long-term resourcing requirements for this project. The results of this report will be made available to the governance team at Company X to facilitate the Tier 1 review. During this period, it should be noted that the methodology proposed in this project will be piloted for the first time. Considerations for ongoing method improvements at this project milestone may enhance the efficiency of future reviews. The current method ascribes all regulatory compliance gaps to a high-risk ranking. From the results of this study, the majority of outcomes are regulatory compliance gaps. The development of a risk assessment tool at the Tier 1 review may be useful to further risk-rank regulatory compliance gaps to support the prioritisation of change controls.

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