CTD Module 1 Verification Questions Based on Country-Specific Requirements

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Step 1: Country Determination

1. **Country Identification Based on Application Form:**
    - **Q1:** "Identify the country based on the application form provided. Does the document contain one of the following application forms?"
        - **For the United States (FDA):** "FDA Form 356h"
        - **For the European Union (EMA):** "EU Application Form"
        - **For Japan (PMDA):** "PMDA Application Form"
        - **For Canada (Health Canada):** "Drug Submission Application Form"

Country-Specific Document Checks Based on Identified Country

After determining the country, proceed with the following questions according to the specific requirements for each regulatory region:

United States (FDA) - Specific Verification

2. **Required Files for FDA Compliance:**
    - **Q2:** "If FDA Form 356h is present, does the document contain all required FDA files? Verify each item is present and list any missing ones."
        - **Required files for FDA:** "Cover Letter, Comprehensive TOC, Labeling, Patent Information, REMS, Environmental Assessment/Categorical Exclusion, Financial Disclosure, Field Copy Certification, User Fee Cover Sheet (Form FDA 3397), Debarment Certification, Administrative Information"
3. **Expiration Date Check for FDA Certificates:**
    - **Q3:** "Are all FDA certificates up-to-date with valid expiration dates? List any that are expired or invalid."

European Union (EMA) - Specific Verification

4. **Required Files for EMA Compliance:**

- **Q4:** “If the EU Application Form is present, does the document include all required EMA files? Verify each item is present and list any missing ones.”
    - **Required files for EMA:** “Application Form, Cover Letter, SmPC, Labeling, Environmental Risk Assessment (ERA), Patent Information, Product Information, Risk Management Plan (RMP), Orphan Drug Designation”

5. **Consistency Check for EMA ERA and RMP Files:**
    - **Q5:** “If the Environmental Risk Assessment (ERA) and Risk Management Plan (RMP) are included, are they consistent and complete in all parts? List any inconsistencies found.”
6. **Expiration Date Check for EMA Certificates:**
    - **Q6:** “Are all EMA certificates up-to-date with valid expiration dates? List any that are expired or invalid.”

Japan (PMDA) - Specific Verification

7. **Required Files for PMDA Compliance:**
    - **Q7:** “If the PMDA Application Form is present, does the document contain all necessary Japanese regulatory files? Verify each item is present and list any missing ones.”
        - **Required files for PMDA:** “Application Form, Drug Master File (DMF) Registration, Labeling, Patent Information, GMP Compliance Certification, Risk Management Plan (RMP), Financial Disclosure”
8. **Translation and Labeling Consistency Check for Japan:**
    - **Q8:** “If Japanese translations are present (such as labeling), are they consistent with the English version? Note any inconsistencies in translation.”
9. **Expiration Date Check for PMDA Certificates:**
    - **Q9:** “Are all PMDA certificates up-to-date with valid expiration dates? List any that are expired or invalid.”

Canada (Health Canada) - Specific Verification

10. **Required Files for Health Canada Compliance:**
    - **Q10:** “If the Canadian Drug Submission Application Form is present, does the document contain all required Canadian regulatory files? Verify each item is present and list any missing ones.”
        - **Required files for Health Canada:** “Drug Submission Application Form, Cover Letter, Submission Certification, Labeling, Patent Information, Risk Management Plan (RMP), Environmental Assessment”
11. **Consistency Check for Canadian Certification and RMP Files:**

- **Q11:** “If the Submission Certification and RMP are included, are they consistent and complete in all parts? List any inconsistencies found.”

12. **Expiration Date Check for Canadian Certificates:**
    - **Q12:** “Are all Health Canada certificates up-to-date with valid expiration dates? List any that are expired or invalid.”

Common Document Checks Across All Regions

Regardless of the region, certain elements should be consistent and verified across all Module 1 submissions:

13. **Cross-Check of Cover Letter Presence:**
    - **Q13:** “Is a cover letter included, tailored for each regulatory authority specified in the document?”
14. **GMP Certificates and Expiration Dates:**
    - **Q14:** “Are GMP certificates included for each region, with up-to-date expiration dates?”
15. **Consistency Check for Labeling and Prescribing Information:**
    - **Q15:** “Are labeling and prescribing information consistent and accurately reflected across all sections?”
16. **Expiration and Date Validation for All Certificates:**
    - **Q16:** “Are all certificates across regions current, with no expired dates? List any that are outdated or inconsistent with the expected expiration.”

Common Questions for Module 1 Verification (Applicable Across All Regions)

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1. **Country Identification Based on Application Form**
    - **Q1:** “Identify the country of submission based on the application form provided. (e.g., FDA Form 356h for the United States, EU Application Form for EMA, PMDA Application Form for Japan, Drug Submission Application Form for Canada).”
2. **Verification of Cover Letter Presence**
    - **Q2:** “Is a cover letter included in the document? This should be customized for the specific regulatory authority (e.g., FDA, EMA, PMDA, or Health Canada).”
3. **Table of Contents (TOC) Completeness Check**
    - **Q3:** “Is a comprehensive Table of Contents (TOC) included for Module 1, listing all required sections relevant to the submission guidelines of each region?”
4. **Consistency Check for Labeling and Prescribing Information**

    - **Q4:** “Are labeling and prescribing information sections present and consistent across the document, without discrepancies in content between sections?”
5. **Verification of GMP Certificates and Expiration Dates**
    - **Q5:** “Are GMP certificates included, and are their expiration dates current and valid? Confirm there are no expired certificates.”
6. **Expiration and Validity Check for All Certificates**
    - **Q6:** “Are all certificates up-to-date with valid expiration dates, and have any anomalies or inconsistencies in dates been identified? If yes, list any certificates that are expired or lack expiration dates.”
7. **Cross-Verification of Required Patent Information**
    - **Q7:** “Is patent information included in the document, and does it meet the regulatory requirements for all regions?”
8. **Risk Management Plan (RMP) Presence and Consistency**
    - **Q8:** “If an RMP is required, is it included, and is it consistent with the regional requirements specified for risk assessment documentation?”
9. **Verification of Financial Disclosure Statements**
    - **Q9:** “Is a financial disclosure statement included, and does it meet all required standards for each regulatory region’s guidelines?”
10. **Administrative Information Check**
    - **Q10:** “Is administrative information (e.g., applicant contact details, correspondence details) present and accurate for each specific regional regulatory body?”
11. **Environmental Assessment/Claims Verification**
    - **Q11:** “If an Environmental Risk Assessment (ERA) or Categorical Exclusion is required, is it present and complete, meeting the environmental standards for each region?”
12. **User Fee Cover Sheet (as applicable)**
    - **Q12:** “If a user fee cover sheet is required (e.g., FDA Form FDA 3397 in the United States), is it included and accurately completed?”

Module 2

Detailed Question Set for Module 2 Verification

General Structure and TOC Completeness

1. **TOC Completeness for Module 2**
   - **Q1:** "Does the Table of Contents for Module 2 include all sections listed in the reference TOC, with each section present in the correct order?"
2. **Section Label Accuracy**
   - **Q2:** "Are all sections correctly labeled according to the provided Module 2 structure (e.g., 2.1, 2.2, etc.) with no mislabeled or missing headers?"
3. **Color Code Compliance Check**
   - **Q3:** "Does each section in Module 2 comply with its respective color code? Verify that yellow sections have no documents, pink sections have exactly one document, and green sections allow one or multiple documents."

Section 2.1: TOC Applicability

4. **Section 2.1 Content Compliance**
   - **Q4:** "Is Section 2.1 labeled as 'A TOC is not applicable for eCTD' with no additional content included, following the red color code requirement?"

Section 2.2: Summary of Clinical Overall

5. **Single Document Requirement for Section 2.2**
    - **Q5:** "Is there exactly one document included in Section 2.2 'Summary of Clinical Overall' as required by the pink color code?"
6. **Document Completeness for Section 2.2**
    - **Q6:** "Does the single document in Section 2.2 cover all aspects of the clinical summary as required by the regulatory guidelines?"

Section 2.3 and Subsections: Summaries and Introduction

Section 2.3: Introduction and General Notes

7. **Single Document Requirement for Section 2.3 Introduction**
    - **Q7:** "Is there only one document included in Section 2.3 'Introduction' as required by the pink color code?"
8. **Note Application for Section 2.3**
    - **Q8:** "Are Notes 1 and 2 accurately applied to Section 2.3, ensuring all instructions related to granularity and document splitting are followed?"

Section 2.3.S: Drug Substance

9. **Document Count Compliance for Section 2.3.S**
    - **Q9:** "Does Section 2.3.S 'Drug Substance' allow for one or multiple documents, following the green color code requirement?"
10. **Note Verification for Section 2.3.S**
    - **Q10:** "Are Notes 1 and 3 accurately applied in Section 2.3.S, ensuring the correct use of keyword guidance and separation by drug substance where applicable?"
11. **Keyword Guidance for Drug Substance**
    - **Q11:** "For multi-substance products in Section 2.3.S, has each substance been documented separately according to the keyword guidance in Appendix A?"

Section 2.3.P: Drug Product

12. **Document Count Compliance for Section 2.3.P**
    - **Q12:** "Does Section 2.3.P 'Drug Product' allow for one or multiple documents, following the green color code requirement?"
13. **Note Verification for Section 2.3.P**
    - **Q13:** "Are Notes 1 and 4 applied accurately to Section 2.3.P, ensuring compliance with product-specific keyword guidance and granularity options?"
14. **Keyword Guidance for Drug Product**

- **Q14:** "For combination products or multiple dosage forms, does Section 2.3.P follow the keyword guidance in Appendix A, ensuring separation for each component?"

Section 2.3.A and Subsections: Appendices and Facilities

Section 2.3.A: Appendices

15. **Yellow Color Code Adherence in Section 2.3.A**
    - **Q15:** "Is Section 2.3.A 'Appendices' marked with a yellow color code, confirming that no documents are submitted at this level?"

Section 2.3.A.1: Facilities

16. **Single Document Requirement for Section 2.3.A.1**
    - **Q16:** "Does Section 2.3.A.1 'Facilities' include only one document as per the pink color code requirement?"
17. **Note Application in Section 2.3.A.1**
    - **Q17:** "Are Notes 1 and 5 correctly applied in Section 2.3.A.1, ensuring that documents for multiple facilities are organized by facility keyword as per Appendix F?"

Section 2.3.A.2: Component(s) for Combination Product

18. **Single Document Requirement for Section 2.3.A.2**
    - **Q18:** "Does Section 2.3.A.2 'Component(s) for Combination Product' include only one document as required by the pink color code?"
19. **Note Application in Section 2.3.A.2**
    - **Q19:** "Are Notes 1 and 6 correctly applied in Section 2.3.A.2, ensuring that each combination product component has a separate document when applicable?"

Section 2.3.A.3: Indications

20. **Single Document Requirement for Section 2.3.A.3**
    - **Q20:** "Does Section 2.3.A.3 'Indications' include only one document as required by the pink color code?"
21. **Note Application in Section 2.3.A.3**
    - **Q21:** "Is Note 1 applied accurately in Section 2.3.A.3, confirming that each indication is documented separately when appropriate?"

Section 2.3.R: Regional Information

22. **Single Document Requirement for Section 2.3.R**
    - **Q22:** "Does Section 2.3.R 'Regional Information' contain only one document as per the pink color code requirement?"
23. **Note Application in Section 2.3.R**
    - **Q23:** "Is Note 1 applied accurately in Section 2.3.R, ensuring that regional-specific information is included as needed?"

Sections 2.4 - 2.5: Nonclinical and Clinical Summaries

Section 2.4: Nonclinical Summary

24. **Yellow Color Code Adherence in Section 2.4**
    - **Q24:** "Is Section 2.4 'Nonclinical Summary' marked with a yellow color code, confirming that no documents are included?"

Section 2.5: Clinical Summary

25. **Yellow Color Code Adherence in Section 2.5**
    - **Q25:** "Is Section 2.5 'Clinical Summary' marked with a yellow color code, confirming that no documents are included?"

Section 2.6: Clinical Overview and Subsections

Section 2.6: Clinical Overview

26. **Yellow Color Code Adherence in Section 2.6**
    - **Q26:** "Is Section 2.6 'Clinical Overview' marked with a yellow color code, ensuring no documents are included?"

Sections 2.6.1 - 2.6.7: Clinical Overview Subsections

27. **Single Document Requirement for Clinical Overview Subsections**
    - **Q27:** "For Sections 2.6.1 to 2.6.7, does each subsection contain exactly one document as per the pink color code requirement?"

Section 2.7: Clinical Summary and Subsections

Section 2.7: Clinical Summary

28. **Yellow Color Code Adherence in Section 2.7**

- **Q28:** "Is Section 2.7 'Clinical Summary' marked with a yellow color code, ensuring no documents are included?"

Sections 2.7.1 - 2.7.6: Clinical Summary Subsections

29. **Single Document Requirement for Clinical Summary Subsections**
    - **Q29:** "For Sections 2.7.1 to 2.7.6, does each subsection contain exactly one document as required by the pink color code?"
30. **Note 7 Application for Section 2.7.3**
    - **Q30:** "For Section 2.7.3 'Summary of Biopharmaceuticals,' is Note 7 correctly applied, confirming each indication is documented separately if needed?"

Final Consistency and Note Verification

Overall Note Application Across Module 2

31. **Note Application Accuracy Check**
    - **Q31:** "Are all applicable notes (1–7) accurately applied in their respective sections throughout Module 2, with no missing or incorrectly applied notes?"
32. **Compliance with Granularity and Splitting Requirements**
    - **Q32:** "Does each section follow granularity and document splitting requirements as per Notes 1 and 2? Confirm that larger documents are split where appropriate to accommodate complexity."

Consistency and Completeness Checks

33. **Overall Completeness of Module 2**
    - **Q33:** "Is Module 2 complete with all sections and subsections included, and does it fully adhere to the specified structure and guidelines?"
34. **Summarized List of Any Issues Found**
    - **Q34:** "Summarize any missing documents, incorrect note applications,

Module 3:

Detailed Question Set for Module 3 Verification

General Structure and TOC Completeness

1. **TOC Completeness for Module 3**
    - **Q1:** "Does the Table of Contents for Module 3 include all sections and subsections as outlined in the reference TOC, with each section present in the correct order?"
2. **Section Label Accuracy**

- **Q2:** "Are all sections in Module 3 correctly labeled according to the provided structure (e.g., 3.1, 3.2, etc.) with no mislabeled or missing headers?"

3. **Color Code Compliance Check**
   - **Q3:** "Does each section in Module 3 comply with its respective color code? Verify that yellow sections have no documents, blue sections allow documents but they are optional, and green sections contain at least one document."

Section 3.1: TOC Applicability

4. **Section 3.1 Content Compliance**
   - **Q4:** "Is Section 3.1 labeled as 'A TOC is not applicable for eCTD' with no additional content, following the yellow color code requirement?"
5. **Note 1 Application for Granularity in Section 3.1**
   - **Q5:** "Is Note 1 applied in Section 3.1, ensuring that if relevant information changes in the product's lifecycle, a complete replacement document will be provided as per the granularity guidelines?"

Section 3.2 and Subsections: Overall Drug Substance and Product Documentation

Section 3.2: Overall Drug Substance and Product Documentation

6. **Blue Color Code Adherence in Section 3.2**
   - **Q6:** "Is Section 3.2 correctly marked with the blue color code, indicating documents are optional at this level but may also exist at lower levels?"
7. **Note 2 Application in Section 3.2**
   - **Q7:** "Is Note 2 accurately applied in Section 3.2, confirming that documents can be present at this level and/or at lower levels, as per Appendix B?"

Section 3.2.S: Drug Substance and Related Subsections

8. **Section 3.2.S Document Compliance**
   - **Q8:** "Is Section 3.2.S labeled correctly with the blue color code, indicating that documents can be included here as well as at lower levels?"
9. **Note 3 for Multi-Substance Products in Section 3.2.S**
   - **Q9:** "Is Note 3 applied in Section 3.2.S, ensuring that if the drug product contains more than one drug substance, a separate 'S' document is provided for each substance, as outlined in Appendix A?"
10. **Consistency of Granularity in Subsections of Section 3.2.S**
    - **Q10:** "Do all subsections of Section 3.2.S maintain a consistent level of granularity, ensuring information can be updated separately if any changes occur in the future?"

11. **Lower-Level Document Presence for Section 3.2.S Subsections**
    - **Q11:** "For each subsection within 3.2.S (e.g., 3.2.S.1, 3.2.S.2, etc.), is it verified that they follow the blue and green color coding guidelines, with optional documents at the blue levels and at least one document at green levels?"

Section 3.2.S.1: General Information

12. **Document Presence in Section 3.2.S.1**
    - **Q12:** "Is Section 3.2.S.1 'General Information' appropriately marked with the green color code, ensuring at least one document is included?"
13. **Note 4 Compliance for Subsection Document Expectations**
    - **Q13:** "Does Section 3.2.S.1 follow Note 4, which states that lower levels of each heading within CTD-Q are unlikely to have individual documents?"

Section 3.2.S.4: Control of Drug Substance

14. **Document Compliance in Section 3.2.S.4**
    - **Q14:** "Is Section 3.2.S.4 'Control of Drug Substance' correctly marked with the green color code, ensuring at least one document is present?"
15. **Consistency with Note 2 in Section 3.2.S.4**
    - **Q15:** "Is Note 2 applied to Section 3.2.S.4, allowing documents at this level as well as at lower levels, if applicable?"

Section 3.2.P and Subsections: Drug Product Documentation

Section 3.2.P: Drug Product

16. **Document Presence in Section 3.2.P**
    - **Q16:** "Is Section 3.2.P 'Drug Product' appropriately marked with the blue color code, making documents optional here but required in lower levels?"
17. **Note 6 Compliance for Diluent Information in Section 3.2.P**
    - **Q17:** "Does Section 3.2.P follow Note 6, ensuring that for products supplied with reconstitution diluents, separate documents for the diluent are included as required?"

Section 3.2.P.2: Pharmaceutical Development

18. **Green Color Code Adherence in Section 3.2.P.2**
    - **Q18:** "Is Section 3.2.P.2 'Pharmaceutical Development' correctly marked with the green color code, ensuring at least one document is included?"
19. **Note 7 Compliance for Quality by Design in Section 3.2.P.2**
    - **Q19:** "Is Note 7 applied in Section 3.2.P.2, verifying that a single document is not used for Quality by Design applications or large molecules, as per guidance?"

Section 3.2.P.4: Control of Excipients

20. **Document Requirements for Section 3.2.P.4**
    - **Q20:** "Does Section 3.2.P.4 'Control of Excipients' meet the requirements of the blue color code, where documents are optional but allowed at lower levels?"
21. **Note 8 Application for Excipient Documentation**
    - **Q21:** "Is Note 8 followed in Section 3.2.P.4, ensuring excipients are documented according to Appendix D guidelines?"

Section 3.2.P.7: Container Closure System

22. **Section 3.2.P.7 Document Compliance**
    - **Q22:** "Does Section 3.2.P.7 'Container Closure System' include documents per the green color code, requiring at least one document?"
23. **Note 9 Application for Multiple Closure Systems in Section 3.2.P.7**
    - **Q23:** "Is Note 9 followed in Section 3.2.P.7, providing separate documentation for each container closure system if there is more than one?"

Section 3.2.P.8: Stability

24. **Document Inclusion in Section 3.2.P.8**
    - **Q24:** "Is Section 3.2.P.8 'Stability' correctly marked with the blue color code, allowing optional documents at this level?"
25. **Stability Documentation Consistency with Note 10**
    - **Q25:** "Does Section 3.2.P.8 follow Note 10, confirming stability information is provided based on container closure systems, manufacturer, strength, and stability protocols, as needed?"

Section 3.2.A and Related Subsections

Section 3.2.A: Appendices

26. **Blue Color Code Adherence in Section 3.2.A**
    - **Q26:** "Is Section 3.2.A 'Appendices' marked with the blue color code, allowing documents at this level optionally?"
27. **Note 2 Application in Section 3.2.A**
    - **Q27:** "Is Note 2 followed in Section 3.2.A, allowing for documents at this level as well as lower levels if necessary?"

Section 3.2.A.1: Facilities and Equipment

28. **Document Requirement in Section 3.2.A.1**
    - **Q28:** "Does Section 3.2.A.1 'Facilities and Equipment' contain at least one document as required by the green color code?"

29. **Note 11 Compliance for Multiple Facilities in Section 3.2.A.1**
    - **Q29:** "Is Note 11 applied, confirming that for multiple facilities, documents are provided per facility as per Appendix F?"

Section 3.2.R and Section 3.3

Section 3.2.R: Regional Information

30. **Document Presence in Section 3.2.R**
    - **Q30:** "Is Section 3.2.R 'Regional Information' compliant with the green color code, ensuring at least one document is included?"
31. **Note 14 Application for Regional Requirements in Section 3.2.R**
    - **Q31:** "Is Note 14 applied to Section 3.2.R, ensuring regional information is provided as required by regional guidelines?"

Section 3.3: References

32. **Single Document per Reference in Section 3.3**
    - **Q32:** "Does Section 3.3 'References' comply with the requirement that each reference be provided in a separate file, as stated in the guidelines?"

Final Consistency and Completeness Checks

Overall Note Application Across Module 3

33. **Note Compliance Check**
    - **Q33:** "Are all applicable notes (1–14) correctly applied throughout Module 3, with no missing or incorrectly applied notes?"
34. **Granularity Consistency in Module 3**
    - **Q34:** "Is the granularity consistent across Module 3, allowing document replacement as per lifecycle changes without compromising the document structure?"

Module 4:

Initial Exclusion Check for Module 4

1. **Product Type Verification Against Exclusion List**
    - **Q1:** "Does the product type fall under the exclusion list of drug types where Module 4 content is not required (e.g., Generic drug, Biosimilar, Orphan drug, Well-established use application, Herbal medicine)?"
2. **Exclusion Confirmation for Module 4 Content**
    - **Q2:** "If the product type is in the exclusion list, has Module 4 been left intentionally empty, and has a justification for this exclusion been provided?"

General Structure and TOC Completeness for Module 4

1. **TOC Completeness for Module 4**
    - **Q1:** "Does the Table of Contents (TOC) for Module 4 include all the required sections and subsections, arranged in the correct order?"
2. **Section Label Accuracy**
    - **Q2:** "Are all section labels in Module 4 accurate and consistent with the standard TOC structure, with no mislabeled or missing headers?"
3. **Color Code Compliance Check**
    - **Q3:** "Does each section in Module 4 adhere to its assigned color code, ensuring that sections marked as essential include required documents, while optional sections remain optional?"

Specific Section Checks for Nonclinical Study Reports (4.1 – 4.4)

Section 4.1: Table of Contents for Nonclinical Study Reports

4. **Section 4.1 Content Compliance**
    - **Q4:** "Is Section 4.1 'Table of Contents for Nonclinical Study Reports' present and correctly labeled, ensuring it provides a structured TOC for all nonclinical study documents included in Module 4?"

Section 4.2: Study Reports (Primary and Secondary Pharmacodynamics)

5. **Primary Pharmacodynamics Study Reports Presence**
    - **Q5:** "Does Section 4.2.1 'Primary Pharmacodynamics Study Reports' contain at least one document as required by its green color code?"
6. **Secondary Pharmacodynamics Study Reports Inclusion**
    - **Q6:** "Are documents included under Section 4.2.2 'Secondary Pharmacodynamics Study Reports' as required, ensuring they meet the regulatory standards?"
7. **Consistency with Granularity for Pharmacodynamics Studies**

- **Q7:** "Is the granularity of the pharmacodynamics study reports consistent with Note 1, ensuring complete replacement of documents if changes occur in the product lifecycle?"

Section 4.3: Safety Pharmacology and Pharmacodynamic Drug Interaction

8. **Safety Pharmacology Study Reports Inclusion**
   - **Q8:** "Is Section 4.3.1 'Safety Pharmacology Study Reports' complete with all required documents, following the assigned color code guidelines?"
9. **Pharmacodynamic Drug Interaction Study Reports Presence**
   - **Q9:** "Does Section 4.3.2 'Pharmacodynamic Drug Interaction Study Reports' contain relevant study reports, ensuring no missing or incomplete documents?"
10. **Safety Documentation for Pharmacodynamics**
    - **Q10:** "Is all safety documentation in the pharmacodynamics reports aligned with current guidelines, ensuring any safety risks are clearly documented and addressed?"

Section 4.4: Pharmacokinetics Study Reports (Absorption, Distribution, Metabolism, Excretion)

11. **Absorption Study Reports Compliance**

- **Q11:** "Is Section 4.4.1 'Absorption Study Reports' present and complete, containing all required documents as per regulatory guidelines?"

12. **Distribution Study Reports Verification**

- **Q12:** "Does Section 4.4.2 'Distribution Study Reports' include all necessary documentation to ensure a comprehensive review of distribution data?"

13. **Metabolism Study Reports Completeness**

- **Q13:** "Are all documents under Section 4.4.3 'Metabolism Study Reports' included, and do they accurately represent the pharmacokinetics of the drug?"

14. **Excretion Study Reports Presence**

- **Q14:** "Is Section 4.4.4 'Excretion Study Reports' complete with all required documents, providing comprehensive data on drug excretion?"

15. **Granularity Consistency in Pharmacokinetics Sections**

- **Q15:** "Is the level of granularity in the pharmacokinetics sections (absorption, distribution, metabolism, excretion) consistent with the guidance in Note 1, allowing for lifecycle-based document replacement if needed?"

Toxicology Study Reports and Supporting Studies (4.5 – 4.8)

Section 4.5: Toxicology Study Reports

16. **Single-Dose Toxicity Reports Presence**

- **Q16:** "Is Section 4.5.1 'Single-Dose Toxicity Study Reports' present, including all relevant documents to support single-dose toxicity data?"

17. **Repeat-Dose Toxicity Study Reports Verification**

- **Q17:** "Does Section 4.5.2 'Repeat-Dose Toxicity Study Reports' include comprehensive data for repeat-dose toxicity, with no missing reports?"

18. **Genotoxicity Study Reports Completeness**

- **Q18:** "Are all genotoxicity study reports included under Section 4.5.3, ensuring there are no gaps in the data provided for genotoxicity analysis?"

19. **Carcinogenicity Study Reports Verification**

- **Q19:** "Does Section 4.5.4 'Carcinogenicity Study Reports' contain all necessary documents, including both short- and long-term studies as required?"

20. **Reproductive and Developmental Toxicity Study Reports**

- **Q20:** "Is Section 4.5.5 'Reproductive and Developmental Toxicity Study Reports' complete, covering all necessary aspects of reproductive and developmental safety?"

21. **Consistency in Toxicity Study Reports**

- **Q21:** "Do all toxicity study reports under Section 4.5 maintain a consistent level of detail and granularity, allowing for future updates if needed?"

Section 4.6: Toxicokinetics and Local Tolerance Studies

22. **Toxicokinetics Study Reports Verification**

- **Q22:** "Does Section 4.6.1 'Toxicokinetics Study Reports' include all necessary reports, with a focus on both acute and chronic toxicokinetics data?"

23. **Local Tolerance Study Reports Completeness**

- **Q23:** "Is Section 4.6.2 'Local Tolerance Study Reports' complete with all required documents, providing sufficient evidence for local tolerance evaluation?"

24. **Consistency in Toxicokinetics and Local Tolerance Reports**

- **Q24:** "Do all toxicokinetics and local tolerance study reports maintain consistent granularity and completeness, meeting the regulatory guidelines?"

Additional Checks for Module 4

Application of Notes and Granularity Standards

25. **Note 1 Compliance Across Module 4**

- **Q25:** "Is Note 1 consistently applied across Module 4, ensuring that changes in relevant information result in complete document replacements for accurate lifecycle management?"

26. **Document Presence as per Appendix References**

- **Q26:** "Is Note 2 followed where applicable in Module 4, allowing documents at multiple levels as outlined in Appendix B?"

27. **Separate Documentation for Multi-Substance Products**

- **Q27:** "If the product contains more than one active substance, is Note 3 applied by providing separate 'S' documentation for each substance as per Appendix A?"

Expiration and Validity of Certificates

28. **Expiration Date Verification for All Certificates**

- **Q28:** "Are the expiration dates of all certificates in Module 4 up-to-date, with none expired or approaching expiration without renewal?"

29. **Manufacturing Date Validation for Toxicology Studies**

- **Q29:** "Do all certificates in the toxicology study reports include valid manufacturing dates, and are any outdated certificates replaced as necessary?"

30. **Renewal Tracking for All Study Certificates**

- **Q30:** "Is there a system in place to track certificate renewals for nonclinical study reports, ensuring that all certificates in Module 4 are current and valid?"

Granularity and Document Replacement Rules

31. **Lifecycle Management of Nonclinical Study Reports**

- **Q31:** "Does Module 4 follow guidelines for lifecycle management, ensuring documents can be replaced at the appropriate level if study data or findings are updated?"

32. **Replacement Standards for Updated Study Data**

- **Q32:** "If study data in Module 4 is updated, does the document replacement follow granularity standards, allowing complete replacement at the individual document level?"

Final Review and Consistency Checks

33. **Consistency Across All Toxicology and Pharmacology Reports**

- **Q33:** "Are all toxicology and pharmacology reports consistent in format, detail, and granularity, ensuring each report meets the required regulatory standards?"

34. **Overall Compliance with Notes in Module 4**

- **Q34:** "Is each section of Module 4 compliant with all applicable notes (1-14), ensuring no missing or incorrectly applied guidelines?"

35. **Final TOC and Document Cross-Verification**

- **Q35:** "Is the final TOC for Module 4 cross-verified with the included documents, ensuring all required documents are present and correctly filed?"

Module 5:

Initial Exclusion Check for Module 5

1. **Product Type Verification Against Exclusion List**
    - **Q1:** "Does the product type fall under the exclusion list of drug types where Module 5 content is not required (e.g., Generic drug, Biosimilar, Orphan drug, Well-established use application, Herbal medicine)?"
2. **Exclusion Confirmation for Module 5 Content**
    - **Q2:** "If the product type is in the exclusion list, has Module 5 been intentionally left empty, and has a justification for this exclusion been provided in the documentation?"

If the product **does not fall** under the exclusion list, the assistant proceeds with the following questions to ensure the content and completeness of **Module 5**.

General Structure and TOC Completeness for Module 5 (Non-Excluded Products)

3. **TOC Completeness for Module 5**

    - **Q3:** "Is the Table of Contents (TOC) for Module 5 complete, with all required sections and subsections listed in the correct order according to the standard guidelines?"
4. **Section Label Accuracy**
    - **Q4:** "Are all section labels in Module 5 accurate and consistent with the standard TOC structure, with no mislabeled or missing headers?"
5. **Color Code Compliance Check**
    - **Q5:** "Does each section in Module 5 adhere to its assigned color code, ensuring that essential sections contain required documents while optional sections remain optional?"

Specific Section Checks for Clinical Study Reports (5.1 – 5.4)

Section 5.1: Table of Contents for Clinical Study Reports

6. **Section 5.1 Content Compliance**
    - **Q6:** "Is Section 5.1 'Table of Contents for Clinical Study Reports' present and correctly labeled, providing a structured TOC for all clinical study documents included in Module 5?"

Section 5.2: Clinical Study Reports (Phase I – III and Additional Studies)

7. **Phase I Study Reports Presence**
    - **Q7:** "Does Section 5.2.1 'Phase I Study Reports (Human Pharmacology)' contain at least one document, as required by its assigned color code, to provide initial human pharmacology data?"
8. **Phase II Study Reports Inclusion**
    - **Q8:** "Is Section 5.2.2 'Phase II Study Reports (Therapeutic Exploratory)' complete with all required documents, detailing exploratory clinical trials and efficacy data?"
9. **Phase III Study Reports Verification**
    - **Q9:** "Are all required documents included in Section 5.2.3 'Phase III Study Reports (Therapeutic Confirmatory)' to support therapeutic confirmatory data?"
10. **Additional Study Reports Presence (Phase IV)**
    - **Q10:** "If applicable, does Section 5.2.4 'Post-Marketing Study Reports' include relevant documents for post-approval studies, meeting regulatory expectations for post-marketing safety data?"

Section 5.3: Biopharmaceutical Study Reports

11. **Biopharmaceutical Reports Completeness**
    - **Q11:** "Is Section 5.3.1 'Biopharmaceutical Study Reports' complete, covering essential bioavailability and bioequivalence data for the product?"
12. **Bioavailability Study Reports Verification**

- **Q12:** "Does Section 5.3.1.1 'Bioavailability Study Reports' contain necessary reports to support the bioavailability of the drug product?"

13. **Comparative Bioavailability and Bioequivalence Reports**
    - **Q13:** "Are the comparative bioavailability and bioequivalence study reports included under Section 5.3.1.2, ensuring compliance with regulatory guidelines for product consistency?"
14. **In Vitro - In Vivo Correlation Study Reports**
    - **Q14:** "Does Section 5.3.1.3 'In Vitro - In Vivo Correlation Study Reports' provide data supporting the correlation between in vitro tests and in vivo drug behavior?"
15. **Reports of Bioanalytical and Analytical Methods**
    - **Q15:** "Are all bioanalytical and analytical method study reports included under Section 5.3.1.4, ensuring the accuracy and validity of analytical methods used?"

Pharmacokinetics, Pharmacodynamics, and Safety Summaries (5.4 – 5.6)

Section 5.4: Clinical Pharmacokinetic Study Reports

16. **Pharmacokinetic Study Reports Completeness**
    - **Q16:** "Does Section 5.4 'Clinical Pharmacokinetic Study Reports' include all required reports, detailing pharmacokinetics in humans and meeting regulatory standards?"
17. **Population Pharmacokinetic Study Reports**
    - **Q17:** "Are population pharmacokinetic study reports included under Section 5.4.1, providing data on pharmacokinetics in diverse populations?"
18. **Pharmacodynamic Study Reports Presence**
    - **Q18:** "Is Section 5.5 'Pharmacodynamic Study Reports' complete, including all necessary documents that cover pharmacodynamic studies to illustrate drug action?"

Section 5.6: Post-Marketing Safety Summaries

19. **Post-Marketing Study Reports**
    - **Q19:** "If applicable, are all post-marketing study reports included in Section 5.6, providing evidence of safety and efficacy in real-world use?"
20. **Literature References for Clinical Study Reports**
    - **Q20:** "Does Section 5.7 'Literature References' provide all cited literature that supports clinical study data, ensuring no missing references or gaps in cited information?"

Application of Notes and Granularity Standards

21. **Granularity and Completeness Compliance**

    - **Q21:** "Is each section in Module 5 provided with appropriate granularity, allowing future updates and ensuring complete document replacements if required (as per Note 1)?"
22. **Additional Document Presence Based on Appendix B**
    - **Q22:** "Is Note 2 consistently applied in Module 5, allowing documents at both higher and lower levels if referenced in Appendix B?"

Expiration and Validity of Certificates

23. **Expiration Date Verification for All Certificates**
    - **Q23:** "Are all certificates in Module 5 up-to-date with current expiration dates, ensuring no expired certificates are included in the clinical study reports?"
24. **Manufacturing Date Validation for Study Reports**
    - **Q24:** "Are all certificates in Module 5 issued with valid manufacturing dates, and are any outdated certificates replaced as needed to ensure regulatory compliance?"
25. **Renewal Tracking for Clinical Study Certificates**
    - **Q25:** "Is there a system in place to track certificate renewals for clinical study reports, ensuring no expired or outdated certificates remain unaddressed?"

Final Review and Consistency Checks

26. **Consistency Across All Clinical Study Reports**
    - **Q26:** "Are all clinical study reports consistent in format, detail, and completeness, ensuring each report meets regulatory guidelines and standards?"
27. **Overall Compliance with Notes in Module 5**
    - **Q27:** "Is each section of Module 5 compliant with all applicable notes (1-14), ensuring no missing or incorrectly applied guidelines?"
28. **Final TOC and Document Cross-Verification**
    - **Q28:** "Is the final TOC for Module 5 cross-verified with the included documents, ensuring all required documents are present and correctly filed?"

Conclusion

- **Exclusion Check** (Q1 and Q2) ensures that Module 5 is skipped if the product falls under the **exceptions_list**.
- For products **requiring Module 5**, questions Q3 through Q28 comprehensively verify that all clinical study reports and certificates are present, valid, and complete.