

電子化コモン・テクニカル・ドキュメント（eCTD） 作成の手引き

第 4.1 版 英訳版

（平成 28 年 10 月発行）

編 集 日本製薬工業協会 医薬品評価委員会
電子化情報部会

本書の内容を無断で複写・転載することを禁じます。

1. eCTD 作成の手引き第 4.1 版の英訳版にあたって

日本製薬工業協会医薬品評価委員会 電子化情報部会（医薬品評価委員会電子化情報部会）では、平成 23 年 8 月医薬出版センターより「eCTD 作成の手引き（第 4 版）」の頒布を開始し、多くの方に活用いただいているところです。

その後、4 年以上の歳月が経過し、一部記載内容と実際の運用の間に相違する点が生じてきたため、平成 28 年 2 月に、第 1 部（基本情報）、第 2 部（eCTD の作成準備から承認まで）について、最新情報を反映し、4.1 版を発行しました。

医薬品開発のグローバル化が加速し、日米欧において eCTD での同時申請を行う企業も現れてきています。また、タイや GCC 諸国でも eCTD での申請が開始されており、申請企業においては、海外関係者との eCTD に関する情報共有の機会が益々高まっています。日本の eCTD の概要及び eCTD の作成から承認のプロセスを説明する機会が増えてきています。

そこで今回、eCTD 作成の手引き（第 4.1 版）の第 2 部（eCTD の作成準備から承認まで）を英訳いたしました。なお、eCTD の内容と直接関係しない部分などを一部翻訳対象から外しておりますが、オリジナル（日本語版）との比較の利便性を考慮し、項番号だけは残しています。

海外関係者との情報共有の機会において、日本の eCTD の概要及び eCTD の作成から承認のプロセスを理解していただくために、ご利用いただければと存じます。

平成 28 年 10 月 4 日

日本製薬工業協会医薬品評価委員会

電子化情報部会

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本記載内容には、現時点の情報に基づき、製薬協電子化情報部会としての見解を記載した部分が含まれています。そのため、eCTD 申請が受理されることを保証するものではありません。eCTD 申請する際の不明点は、直接 PMDA に確認ください。

第 4.1 版（第 2 部）英訳版

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Part 2

Preparation to Approval for eCTD

In Part 2, the outlines of processes of preparing eCTD as well as eCTD submission until approval are described in an easy-to-understand manner for those who are involved in preparing eCTD such as medical writers, eCTD assemblers, and regulatory experts.

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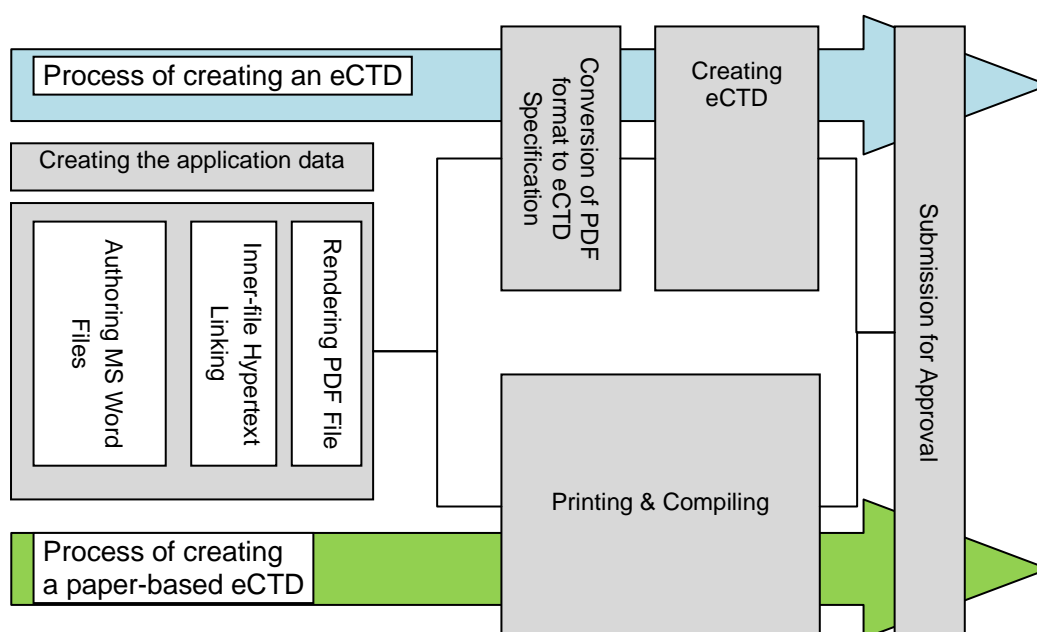
1. Handling on the preparation to approval of eCTD

This Part 2 deals with the matters regarding eCTD preparation up to the application in Chapter 2 to 4, the matters regarding the application in Chapter 5, the matters regarding authority compliance review in Chapter 6, the matters regarding revision of eCTD during authority review in Chapter 7, the matters to be considered at the time of approval and the later in Chapter 8, and the matters regarding inquiries to the regulatory authority in Chapter 9.

1.1 Processes of creating eCTD

The eCTD is basically a computerized CTD and eCTD has many common processes that paper-based CTD has. The flow of creating the application dossier is no difference between the eCTD and the paper-based CTD. While the application with paper-based CTD is conducted with printed paper after completing electronic files, the application with eCTD is conducted with electronically assembling the completed files after making some corrections to conform to eCTD specifications (Fig 1-1).

Fig 1-1 Comparison of eCTD process and paper-based CTD process



1.2 Processes of authority review and approval on eCTD application

The process of reviewing an eCTD application is basically same as that of reviewing a paper-based CTD.

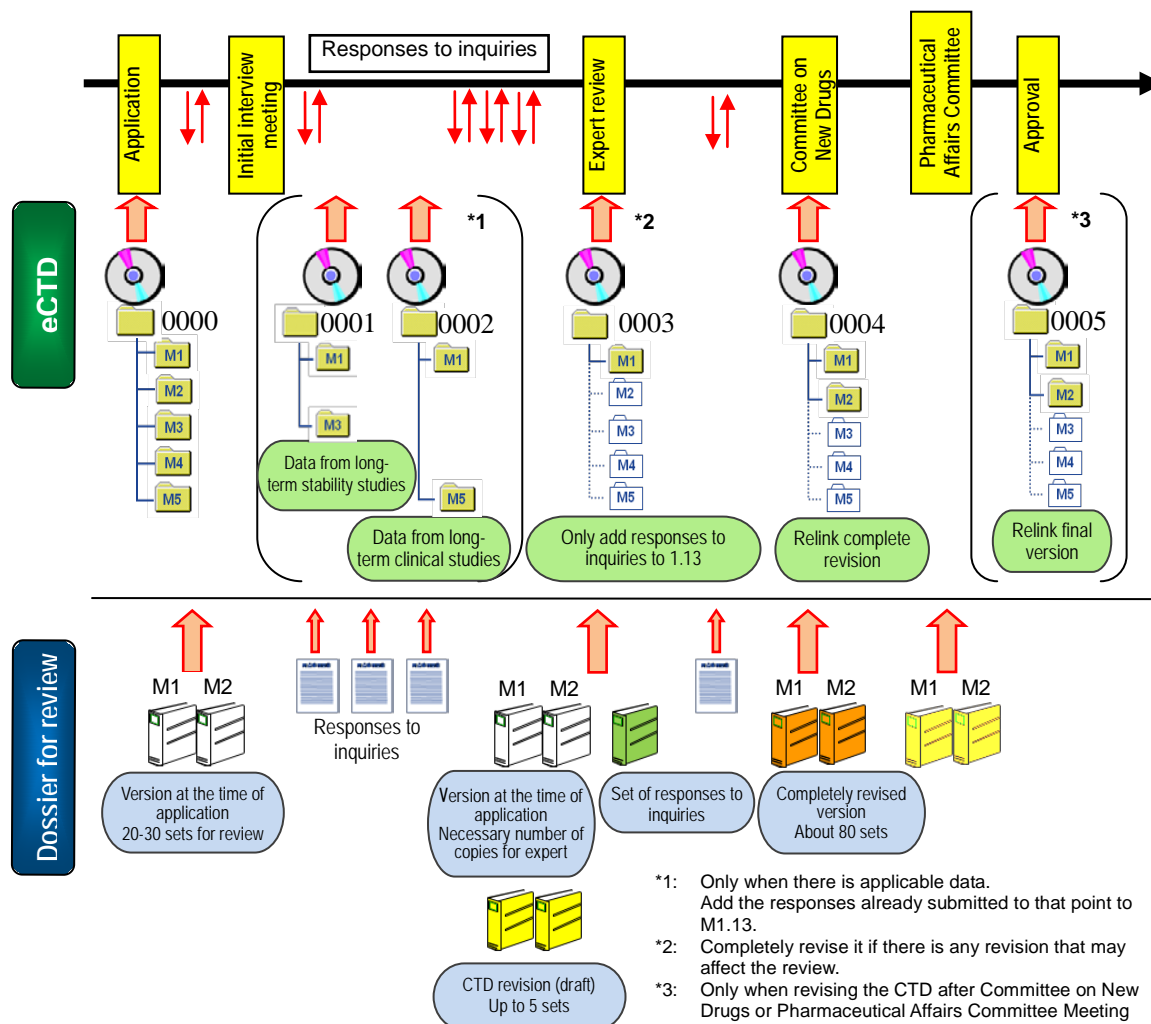
When an application is filed with eCTD format, Classification IV needs the submission with the paper format as the authority review purpose, though other Classification does not need it. Besides the responses to inquiries, the dossier for Expert Review as well as the dossier for Deliberations at the Pharmaceutical Affairs and Food Sanitation Council (Committees on Drugs, Subcommittees).

The timing and volume for submitting the eCTD and printed paper in the process from application to approval when the application is filed with eCTD format are shown below (Fig 1-2). Since the number of required copies of printed materials depends on the office and review team of PMDA, it should be checked at the respective events to the corresponding window person (usually Assistant Section Chief) in PMDA.

Also, only authorized persons in charge can do the procedures for receipt and confirmation of the eCTD at the regulatory authority. Therefore it is necessary to make an appointment for a revised eCTD submission after the first submission. For Expert Reviews and Committees on Drugs, you must make an appointment with the First Administration Section of the Office of Review Administration when the schedule for carry-in of materials is determined.

The website of the regulatory authority, which provides the domestic information on eCTD, has the reference material on the operation of eCTD in Japan, titled “Operation for CTD and eCTD (dated September 21, 2010)” on September 24, 2010. You should refer to this material as it illustrates the composition of eCTD to be submitted during the review and timing for submission.

Fig 1-2 Timing and volume for submission of eCTD and review data in the application process



(1) At the time of the first submission

Once the submission date is determined and you make the appointment for submission with the regulatory authorities by fax, you will receive a returning call from the regulatory authority and be informed of the eCTD receipt number issued by the regulatory authority. When making the appointment for submission, you should state that it is the “application of original eCTD”.

On the day of application, you should submit one set of original eCTD (recording media such as DVD-R) to the First Administration Section of the Office of Review Administration. The submission of copy is not necessary. Once the eCTD is submitted, it is imported and verified. Then, if there is no problem, the procedures for accepting the application (FD application) are followed.

(2) At the time of authority paper compliance review and on-site GCP inspection

When the application is filed with eCTD format, the submission of CTD M1 to M5 in electronic format will be exempted in the authority paper compliance review. Also in the on-site GCP inspection, the submission of CTD M2 in electronic format will be exempted.

(3) At the time of Initial Interview Meeting

You must submit the printed paper of CTD M1 and M2 as the dossier for the Review Team before the initial interview meeting after the first submission. Since you are required to submit this dossier for the Review Team as soon as possible, it is better to produce it at the same time of first submission. Even in the case of submission with eCTD format, you need to separately submit other dossier in paper format except for the CTD, such as the data on new additives.

[Guidelines on creation of printed paper of M1 and M2 (in paper format)]

- Print the eCTD leaf file as it is and file it with index/tab paper (divider) attached.
- Put together each of the printed leaf files (handle in the same manner as in the case with paper CTD).
- You do not need to create the each module cover and M2.1 exclusively for the paper dossier.

(4) At the time of Expert Review

About 2 weeks before the scheduled date of the Expert Review (designated date), you should add the inquiries (copies) and responses to the inquiries (copies) issued before the Expert Review to M1.13.3, update the life cycle of eCTD, and submit it along with a request for change of eCTD. At this time, you do not need to set a hypertext link. If there is any additional data that may affect the review (e.g., report on long-term stability studies, report on long-term clinical studies) or some change in the contents of summaries, you may be required to submit the revised version of eCTD even before the Expert Review.

As for the dossier for Expert Review (printed paper), you must submit the leaf files of M1 (usually excluding 1.3, 1.4, and 1.13) and M2 at the time of application according to the procedures described in (3). You do not need to submit the printed paper of M3 to M5. Furthermore, you must submit the revised CTD (draft) (marker version) that reflects the responses to the inquiries issued by the Expert Review and clearly states the corrected parts in paper format for the reviewers (maximum 5 sets of copies). At this time, you may be required to submit the revised CTD (draft) that clearly states the corrected parts in eCTD format. However, you do not need to set a hypertext link at this point and you are allowed to prepare it by the time of official revision before the Committee.

(5) At the time of Committee on New Drugs

You must submit the revised version of eCTD that have incorporated all corrections including the inquiries issued after the Expert Review by the carry-in date of submission dossier for the Committee (it will be designated by the person in charge at the regulatory authorities in 2 weeks before the Committee on New Drugs is held) in principle. Since you need to include the hypertext link at this revision, if it takes time to work on the revision, you should consult the review team when necessary (you may be allowed to submit it by the day before the Committee in some cases).

As for the printed dossier for the Committee on New Drugs, in the case of “Discussion”, you must file the written request for “Discussion” and Authority Review Report for the application, M1 (usually excluding 1.3, 1.4, and 1.13) and M2 of the CTD according to the designated method. You do not need to import the written request for “Discussion” and Authority Review Report into the eCTD by scanning, etc. In the case of drugs to be reported to but not reviewed by the Committee, you do not need to submit the applicable dossier of CTD in print format.

(6) At the time of Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

At the time of PAFSC, you must submit the written request for “Discussion” and Authority Review Report for the application, printed paper of M1 (usually excluding 1.3, 1.4, and 1.13) and M2 of the CTD about 2 weeks before the scheduled date of the Committee (designated date), as in the case of Committee on New Drugs. In the case of drugs to be reported to but not reviewed by the Committee, you do not need to submit the relevant dossier of CTD. If the revision of CTD is necessary, i.e., if you are required by the Committee on New Drugs to correct the review data, you must submit the eCTD after updating its life cycle. The hypertext links need to be included at this point, too.

(7) At the time of CTD revision after the Committee on New Drugs or PAFSC

If you are going to revise the CTD after the Committee on New Drugs or PAFSC, you need to submit the final version of eCTD after updating the life cycle of it. You should consult the review team about the necessity of submitting the final version of eCTD and the timing for submission. You should submit it to the Director of the Evaluation and Licensing Division, and it will be received by each review team.

If you are going to revise only M1.8 or M1.11, you do not need to submit the revised version of eCTD.

(8) At the time of publication of information

You must redact the leaf files (PDF) of eCTD where necessary. You must delete external link(s) beforehand and arrange the redacted parts so that the text information cannot be copied. Once the redact is completed, you should segment the eCTD leaf files into pieces of 10MB or less and change the file name according to the authority notification.

(9) If there are any additional data during review

In “Points to Consider for Reducing Total Review Time for New Drug Applications” (PFSB/ELD-CND Administrative Notice dated June 9, 2010), for “Data from long-term clinical studies”, it was decided that data obtained on completion of administration to all patients for at least 6 months should be appended as application data, and the final report (including data on completion of administration to all patients for at least one year) and the revised draft of the CTD should be submitted at the latest by 6 months before the end of the targeted total PMDA review period. For “Data from long-term stability studies”, it was decided that additional data should be submitted at the latest by 6 months before the end of the total targeted PMDA review period and additional data obtained thereafter should be submitted by the time of data submission to the Expert Review.

Therefore, when handling the above data, you need to update the life cycle of eCTD in order to add the additional data to M3 or M5, in addition to the aforementioned life cycle of eCTD (at the time of application, expert review, Committee on New Drugs, final version). In doing so, although you do not need to set the hypertext link to additional data, you must create the eCTD with M1.13 including the responses already submitted by then.

Furthermore, you must submit the documents that need to be changed due to the submission of the additional data (M2.3, M2.5, M2.7, and already submitted responses) as “responses” in paper format. It is preferable that these additional data should be submitted at the same time when you update the life cycle of eCTD, but you should consult the review team on the basis of situation. For the revised versions of M2.3, M2.5, and M2.7 that you submit as the responses, you must properly include the revised documents in the CTD revision before the Committee on New Drugs.

- 2. Preparation for company structure to create eCTD (this chapter is excluded from translated item)**

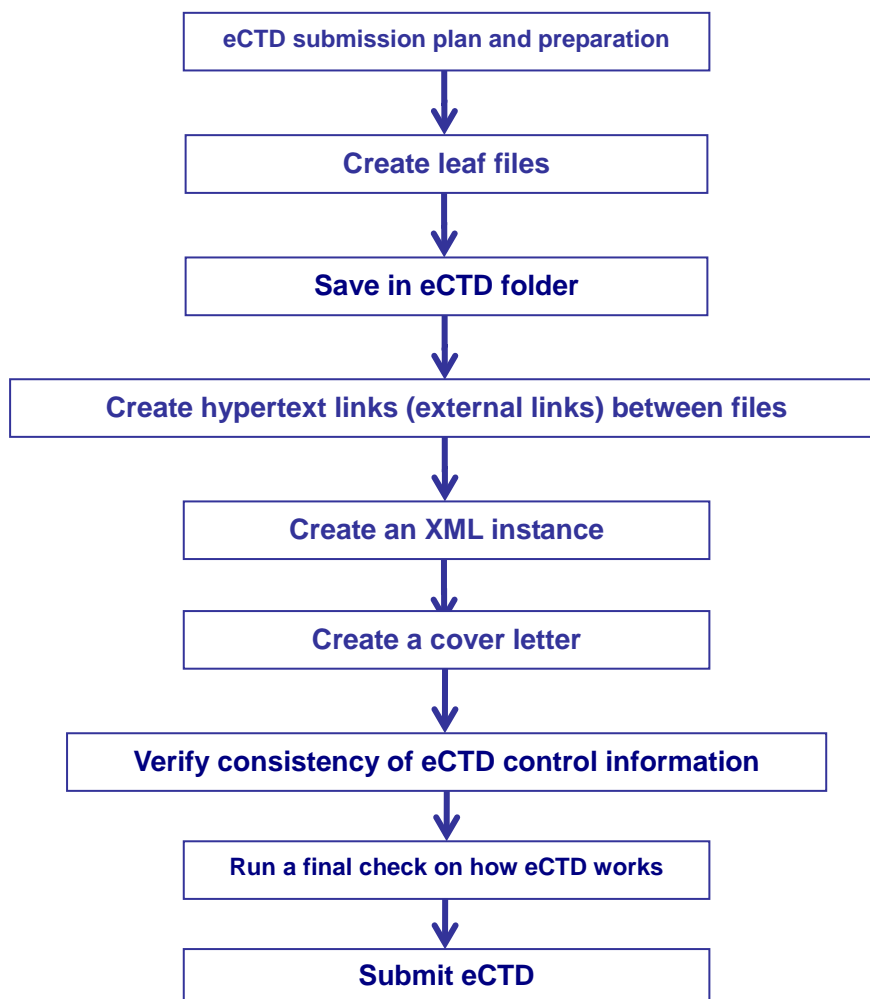
3. Creation of eCTD

3.1 eCTD submission plan and preparation

Since the eCTD is CTD modules with the addition of electronic requirements, the data are composed on the basis of the CTD structure. You should create M1 based on “Notification of eCTD Implementation,” and M2 to M5 based on “Notification of eCTD specification” and “Notification of eCTD Implementation.” The electronic specifications specific to each region are defined in M1, and the related information is described in “3.5” and “3.6” of this document.

In principle, eCTD should be created according to the flow shown in Fig 3-1.

Fig 3-1 Flow of creating an eCTD



In order to create the submission dossier efficiently according to the flow shown in Fig 3-1, it is convenient if you prepare the eCTD Module Structure Table (Fig 3-2) that lists the folder structure, file name, revision information (operation attribute) of each leaf file, etc. based on the composition of application data (package), “Notification of Granularity Documents,” and “Notification of eCTD specification.”

Fig 3-2 Example of eCTD Module Structure Table

Folder Structure				File name	Title name (XML name)	Operation 0000	Operation 0001
m1							
	jp						
m2							
	22-intro						
				introduction.pdf	2.2 緒言	new	
	23-qos						
				introduction.pdf	2.3 緒言	new	
				drug-substance-tokyo.pdf	2.3 S 原薬(イーアイ塩酸塩、日本製薬工業東京工場)	new	
				drug-product-tablet-10mg.pdf	2.3 P 製剤(セイヤクキョール錠 10mg、錠剤)	new	
				drug-product-tablet-20mg.pdf	2.3 P 製剤(セイヤクキョール錠 20mg、錠剤)	new	
				appendices.pdf	2.3 A その他	new	
	24-nonclin-over						
				nonclinical-overview.pdf	2.4 非臨床試験の概括評価	new	
	25-clin-over						
				clinical-overview.pdf	2.5 臨床に関する概括評価	new	
	26-nonclin-sum						
				introduction.pdf	2.6.1 緒言	new	
				pharmacol-written-summary.pdf	2.6.2 薬理試験の概要文	new	
				pharmacol-tabulated-summary.pdf	2.6.3 薬理試験概要表	new	
				pharmacokin-written-summary.pdf	2.6.4 薬物動態試験の概要文	new	
				pharmacokin-tabulated-summary.pdf	2.6.5 薬物動態試験概要表	new	
				toxicology-written-summary.pdf	2.6.6 毒性試験の概要文	new	
				toxicology-tabulated-summary.pdf	2.6.7 毒性試験概要表	new	
	27-clin-sum						
				summary-biopharm.pdf	2.7.1 生物薬剤学試験及び関連する分析法	new	
				summary-clin-pharm.pdf	2.7.2 臨床薬理試験	new	
				summary-clin-efficacy-hypertension.pdf	2.7.3 臨床的有効性 - 高血圧	new	
				summary-clin-safety.pdf	2.7.4 臨床的安全性	new	
				literature-references.pdf	2.7.5 参考文献	new	
				synopses-indiv-studies.pdf	2.7.6 個々の試験のまとめ	new	
m3							
	32-body-data						
	32s-drug-sub						
	lei-hydrochloride-tokyo						
	32s1-gen-info						
				nomenclature.pdf	3.2.S.1.1 名称(イーアイ塩酸塩、日本製薬工業東京工場)	new	
				structure.pdf	3.2.S.1.2 構造(イーアイ塩酸塩、日本製薬工業東京工場)	new	

3.2 Creation of leaf files

An electronic document file of submission dossier is called a “leaf file,” which is one of the components of eCTD. The specifications on the format are defined in detail by the Notifications so that the regulatory authorities can effectively review the application data using eCTD. In particular, whether you start giving careful consideration to the electronic requirements such as page size, margin, font, bookmark, and hypertext link at the time of writing the text for submission dossier will significantly affect whether you can efficiently perform the subsequent PDF processing work or not. We will show examples for these requirements in this Chapter, and we provide the points to consider and detailed technical explanation in “Chapter 1” and “Chapter 2” of Part 3 of this document (refer to “2.1” of Part 1 of this document for regulatory requirements on leaf files).

3.2.1 Points to note for file name

When giving a file name to a leaf file, there are restrictions for the length of file name and characters to be used (refer to “2.1” of Part 1 of this document). It is useful to give some meaning as an identifier with the use of the limited number of characters. The file structure and list of recommended file names are shown in “3.5” of Part 3 of this document.

3.2.2 Creation by MS Word file

In most cases of eCTD submission, authors create CTD manuscripts with MS Word as native format and the files are converted to PDFs that are used as leaf files. Therefore, the cooperation with authors through, for example, setting, and complying with the rules for the use of templates and writing, is at least as important as in the case of CTD at the stage of creating the texts with MS Word.

In the writing rules, especially about the description of external references, how to describe citations should be properly stated and uniformed terms should be established so that the persons in charge of

placing links will be properly informed of the intention, which not only improves the efficiency of link-placing work in PDF files but also leads to better readability for the reviewers.

It is also efficient to stipulate and use a document template for submission dossier by each company whether it is eCTD or CTD. The document template should contain the “page setting” to unify the layout such as paper size and margin according to the eCTD requirements, “style” that stipulates the font to be used and unifies the text format, and “examples of description” that includes the guidance that helps to write the submission dossier. These will lead to better visibility and readability of the entire data. In addition, the template should also contain “tool buttons” that enable macro operation of MS Word, etc. to improve the working efficiency of writing texts, etc. according to the rules of each company.

The style is used when setting the format of documents. As shown in Table 3-1 and Table 3-2, if you define the style and page setting to be used in the submission dossier as a document template, you can save the effort to adjust the layout during the creating process. Since this is relevant not only to eCTD but also to CTD, it is assumed that each company has already adopted its own original document template. By setting the application of a header style and how to use a cross-reference function, you can also streamline the work of creating the bookmarks and hypertext links, which are requirements for the leaf files, because the items shown in Table 3-3 will be automatically converted to PDF files with a PDF-converting software when you need to convert them later.

The examples of rules for the style and document template are shown below. Since not only the values shown in the related notifications but also the values to be set at each company’s discretion will be included, you should review each setting value by checking with the related notifications Please refer to “Chapter 1” of Part 3 of this document for more information.

Table 3-1 Examples of rules for style

Setting item	Setting value
Font	Use MS Mincho for the text in Japanese and Times New Roman for the text in alphanumeric characters. Use Times New Roman for symbols and special characters. Use MS Gothic for the header in Japanese and Arial in alphanumeric characters, etc. Set them by taking into account the document format.
Font size	Use 10.5 pt for the text in Japanese document (10.5 pt for alphanumeric characters in the Japanese document) and 12 pt for the text in English document. Set the font size of a header text bigger than the text of page body by 2 to 6 pt, considering the document format. Set the font size of a figure/table at 8 pt or more, considering legibility and the document format.
Font color	Use black for the color of characters. When using the color other than black, attention should be paid so that the text is legible without any problem when it is output in gray scale (black and white tone) as specified in “Notification of eCTD specification.”
Line spacing before and after paragraph	Set it after taking into account the document format.
Style to be applied to the next paragraph	Set it after taking into account the document format.

Table 3-2 Examples of rules for document template

Setting item	Setting contents
Page setting	Paper size, margin, header/footer size, etc.
Style	Style for header, style for main body, style for paragraph number/itemization, style for text in a table, style for title of a figure/table, etc.
Header / footer	CTD module number, document number, product name, page number, etc.
Guidance	Commentary based on the notifications/regulations for evidence, in-house rules

Setting item	Setting contents
	for description of CTD, etc.

Table 3-3 Items to be converted at the time of PDF formatting

Response in text	Requirements for leaf file to be converted at the time of PDF formatting
Cross-reference	Hypertext link in the same file
Header style	Bookmark

3.2.3 Graphic file

Graphic file formats are shown as one of common formats that can be used for eCTD submission. However, since the access to documents is easy in the review process and the adjustment of layout is not necessary when printing it out, you must always use the PDF format unless it is impossible to use a PDF file; provided, however, it is not applied to the cases when the use of a detailed photo is indispensable or when it is impossible to attach a graphic to the document due to the limited file capacity. In such cases, you should save the graphic file as a leaf file and make it linkable from the document file.

Because there are several graphic formats with different characteristics, you can select a format as needed (refer to Table 2-1 in “2.1.2.2” of Part 3 of this document).

3.2.4 Excel file

You are required to attach an Excel file for “M1.12 List of Attachments.”

In an Excel file, the access and printing records are automatically recorded as meta information and the contents in the file are updated even if there is no change in an entry in the worksheet. Therefore, MD5 check sum values change even when the document is only opened or printed. For this reason, you must set the Excel file as “read only” once the contents are determined.

You should refer to “4.2.2.4” of Part 3 of this document for more information on check sum values.

You should also refer to “3.6.1” of Part 2 of this document for more information on points to consider when creating the list of attachments with Excel, etc.

3.2.5 PDF file

PDF is a file format in which documents, images, etc. can be viewed uniformly under almost any environment without being affected by a specific environment, and broadly used in electronic application. For this reason, most of the files to be included in eCTD are PDF files and the requirements for the PDF file are shown in the “Notification of eCTD specification” and “Notification on eCTD Implementation” so that the regulatory authority can effectively review them.

PDF file has two kinds of types. One is a file which an electronic source document such as a Word file or Excel file is converted with the original character information intact (hereinafter referred to as “text PDF”), and the other is a file which is created by scanning a paper material (hereinafter referred to as “scanned PDF”). In both PDF files, you can obtain the electronic advantage that expedites the review, i.e., you can display a relevant page instantly by setting the navigation such as bookmarks and hypertext links.

Also, there are requirements for PDF files such as file size, PDF version, expansion setting, setting of hypertext link and bookmark, and optimization for Web display. You need to create a PDF file after fully understanding the requirements shown in the Notices (refer to “2.1” of Part 1 of this document). If a prepared PDF file does not meet the eCTD requirements by the time of submission, you may need to redo it from preparing the text again. Therefore, PDF conversion is one of the important operations in the process of creating an eCTD.

Because many PDF files are used for eCTD, it is very useful to introduce a system or tool that can manage settings of the PDF files. With such a system or tool, you can optimize the PDF files or check or change the settings collectively at the final stage when all leaf files are ready on the table. You should refer to “2.8” of Part 3 of this document for more information. You should also refer to “Chapter 2” of Part 3 of this document for more information on procedures for creating and editing PDF and points to consider.

3.2.5.1 PDF formatting of texts of electronic source documents

As for a text PDF file created from an electronic source document, the reviewers can use the search function of a string in the review environment and copy & paste the string to the materials created by the

reviewers. Since it is very useful for the operations on the reviewer's side, it is required to convert an electronic source documents into a text PDF as many as possible. The "Notification on eCTD Implementation" also clearly state that "the text PDF should be created for the materials that will be created after April 2006".

One of the advantages that a text PDF has on the applicant's side is that, since a PDF processing tool can generally recognize characters, when the applicant processes a leaf file, for example, he or she can define the settings collectively, e.g., converting the setting of all hypertext links into blue characters. In addition, if the electronic data filed in eCTD format are made available for in-house viewing in a company, the text PDF can be used in the same manner as the regulatory authorities to create the secondary data in the company.

3.2.5.2 PDF formatting of paper data

When scanning paper data, you need to set the resolution and color mode according to the type of the text (refer to Table 2-2 in "2.1.2.2" of Part 3 of this document). All values shown in the Notifications are recommended setting values. Thus, if the paper data turned out to be an illegible PDF file due to these settings, you need to scan it again with increased resolution, etc.

In scanned PDF, since the PDF processing tool recognizes the scanned information as images, it will become impossible to search a string, but the risk of garbled characters disappears. Since it is impossible to use the search function in the review process, you are required to convert documents other than those listed below into text PDF as many as possible.

Examples of PDF formatting of paper data are shown below:

- (1) References (if the electronic files obtained are locked for security)
- (2) Old application-related data stored only in paper
- (3) Various types of certificates including handwritten signatures/printed names and seals

The "Notification of eCTD Implementation" clearly state that you can include data created in the past in eCTD even if they are Scanned PDF. The conditions are shown below:

- (1) Among reports, etc. to be attached to M3 to M5, those which were already created as paper version before March 2006
- (2) They are legible

3.2.6 Creation of bookmark and hypertext link

Bookmarks and hypertext links are one of the settings to enhance the navigation of a PDF file, and both the "Notification of eCTD Specification" and "Notification of eCTD Implementation" present the hierarchy of bookmarks and requirements for setting hypertext links, etc. You should also refer to "2.1" of Part 1 of this document for these requirements and "2.4" and "2.5" of Part 3 of this document for the procedures for creating bookmarks and hypertext links.

Among tasks related to eCTD, creation of bookmarks and hypertext links takes time and labor most. The applicants should set them, after considering where in the submission dossier they should navigate to, in order to make them useful in the review process.

The author of a CTD document can help to reduce the burden of creating bookmarks and hypertext links by doing what is described in "3.2.2" of Part 2 of this document at the stage of writing the text. However, the work after converting to PDF might not be the author's role. For this reason, it is necessary to establish a system based on efficiency and to make adequate preparation, for example, by clarifying the roles between the work when writing the text and the work after PDF formatting.

3.2.6.1 Points to consider for setting bookmarks

Bookmarks have a role as a table of contents and allow you to navigate the PDF file. You can automatically produce a bookmark at the time of PDF formatting by setting a header style in the electronic source document (Table 3-3). Also, some PDF processing tools can produce bookmarks based on the information in the text PDF.

You should refer to "2.1" of Part 1 of this document for the requirements concerning bookmarks.

3.2.6.2 Points to consider for setting hypertext links

There are two types of hypertext links; a “link within a document” to refer to within the same file and an “external link” to refer to another file. Since hypertext links can enhance the efficiency of inspecting a document by giving it a navigation to refer to notes, related sections, references, appendixes, tables or figures and are very useful in the review process, you are required to appropriately set hypertext links to make the review more efficient. The Notifications indicate that you are required to set hypertext links especially to CTD M2 to M3-M5 wherever possible. However, it does not mean that it is better to set as many hypertext links as possible, but you should create them considering the efficiency of the review.

Depending on the method of creating external links, the link may not properly function in some cases when the file is moved from the PC environment where the eCTD was created to another PC environment. The use of a “relative path” is stipulated to maintain links after a submitted eCTD is registered to the system of the regulatory authorities.

You should refer to “2.1” of Part 1 of this document for more information on the requirements for hypertext links.

3.2.6.3 Timing to create hypertext links

As stated earlier, there are two types of hypertext links; a “link within a document” and an “external link” and they are different in the timing to create them.

While it is possible to set a link within a document even after creating the PDF file, if the electronic source document is a Word file, it is efficient to automatically create the link by using the “cross-reference function” (Table 3-3) at the stage of creating the Word document. Since the setting of cross-reference is converted to the link within a document at the time of PDF formatting, you can reduce the workload of creating the link within a document after the PDF formatting.

On the other hand, you should create an external link after determining the location to store the leaf file. The conditions for creating an external link are shown below:

<Conditions for creating an external link>

- The folder structure of eCTD has been finalized
- The file name to be referred has been finalized
- If the reference of an external link is specified up to a specific page of a specific file, the file to be referred has been finalized

3.2.6.4 Streamlining of work to create hypertext links

Considering efficiency of the review, a hypertext link should be set in a location which is intended to be useful for inspecting the contents of data that are not listed on the same page. It is the author who can judge whether the data to be inspected for the review is useful or not. If the person in charge of creating a link is another person or a staff of a subcontractor, the measures to accurately convey the author’s intention will be necessary. For the person in charge of creating hypertext links, whether he/she is an in-house staff or subcontractor, he/she can smoothly create hypertext links if an in-house rule for hypertext links is made and known by employees including the author.

The points for creating hypertext links are (1) to post a link in one direction from upstream to downstream (M1→M2→M3, M4 or M5) and (2) to limit the number of links to the minimum. For example, each company should contrive ways such as “do not post links from study numbers or CTD numbers in the document to attachments in M4 or M5”, “do not post links from 1.12 List of Attachments to attachments in M4 or M5”, “do not post links within a document of the Scanned PDF such as references”.

The point (1) is to minimize the time and effort to post a relink at the time of life cycle, and the point (2) is to reduce the workload and make it easier for the reviewers to inspect important links.

The examples of directing the location of setting links at the time of writing a text are shown below. However, the rules for writing and creating links should be stipulated at each company’s discretion, and the working system for useful links can be clear by accumulating experience of creating an eCTD and can lead to a high quality eCTD by improving the process. Therefore, you should be flexible by reexamining the rules so that they conform to each company’s system as needed.

<Rules for writing and link setting at the time of creating a text when directing the location of setting links (examples)>

- If the reference is a figure/table: Describe it as “Attachment 5.3.4.1-1 Figure 12-1” or “Excerpted from Attachment 5.3.4.1-1 Figure 12-1” and post a link to the underlined portion.
- Use blue for the color of a string to which a link is set or circle the string with enclosed letters or parentheses [] and post a link to the blue portion, enclosed letters or letters in parentheses
- If the citation of a reference is stated: Post a link with either of the following patterns
<Pattern 1> Text of CTD M2 → List of references in M2 → References in M5
<Pattern 2> Text of CTD M2 → References in M5

3.3 Creation of folder

A folder is one of elements that compose an eCTD application, and the “Notification of eCTD specification” offers an explanation of it using a concept of “directory structure”. A directory structure is a structure composed of a directory (folder) and a file, which refers to a leaf file. Since many leaf files will be used for an eCTD application, a folder is indispensable to gather the related information.

While the “Notification of eCTD specification” describes it using both a “directory” and a “folder”, the “Notification of eCTD Implementation,” describe it using only a “folder”. Since both words mean the same, the words are integrated as a “folder” in this document. You should refer to the ICH website since the templates for folder structures of M2 to M5 are downloadable from the website.

3.3.1 Points to consider for folder name

Both the “Notification of eCTD specification” and “Notification of eCTD Implementation,” provide considerations concerning a folder. The Notifications offer strongly recommended folder structures and folder names and it is desirable that you should maintain the specifications wherever possible (refer to “2.2” of Part 1 of this document for regulations for folders).

What you should keep in mind when using a folder name is to collect the information on items that will be reflected in the folder name at the stage of planning the creation of eCTD. You should refer to “3.3.2” of Part 2 of this document for a list of necessary information. You should record the collected information in the eCTD Module Structure Table (Fig 3-2) to be managed by Excel, etc.

Also, since a folder structure and folder name will affect the work to create hypertext links, you should understand that you are not allowed to change the name through the life cycle once adopted, and it is important to determine it as early as possible.

3.3.2 Review of folder name

As stated earlier, it is desirable to determine a folder name when planning and preparing a submission in the process of creating an eCTD. Since there are items whose folder names are decided by an applicant, you should identify target folders by referring to the “Notification of eCTD specification” and “Notification of eCTD Implementation,” and set the folder names that you do not need to change through the life cycle from the first submission to approval.

If the folder name you set exceeds 64 characters, it must be shortened at the applicant’s discretion as needed.

(1) Information to be collected at the stage of planning and preparation

Because the Japanese characters cannot be used as a folder name, you should collect the information in English.

Module to be reflected in a folder name	Information to be collected at the stage of planning and preparation
3.2.S	Substance
	Manufacturer
3.2.P	Product
	Dosage Form
	Manufacturer

Module to be reflected in a folder name	Information to be collected at the stage of planning and preparation
3.2.P.4	Excipient
3.2.A.1	Manufacturer
3.2.A.2	Product Dosage Form Manufacturer
3.2.A.3	Novel Excipient
5.3.5	Indication

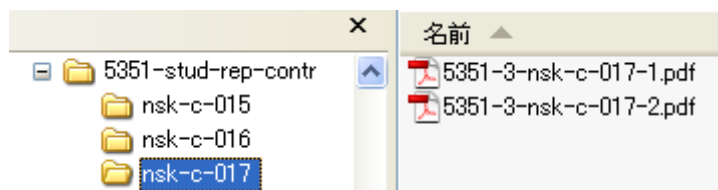
(2) Study report of M4

Concerning study reports to be contained in the “m4” folder, one study report may be submitted as multiple files. In principle, however, it is desirable to provide one report as one file. While there is no need to create anything other than the folders specified by the “Notification of eCTD specification” if you create one file, it is recommended to manage each report in a folder if you submit the report as multiple files. You should refer to “Chapter 3” of Part 3 of this document for more information.

(3) Study report of M5

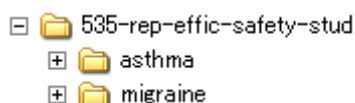
As in the case with the “m4” folder, it is desirable to provide a study report to be contained in the “m5” folder as one file for each report in principle. Including the case when you provide a report as multiple files (summary, text, and appropriate appendixes), it is recommended that you should create a folder using the study report number, etc. as a folder name and manage each report in a folder.

Fig 3-3 Example of folder structure for “study report”



You should use an indication as a folder name of a folder below the “5.3.5” folder, a part of the “m5” folder structure. The indication to be used as a folder name can be appropriately abbreviated. If you apply for multiple indications, for example, asthma and migraine, you should name the first folder “asthma” and the second folder “migraine.”

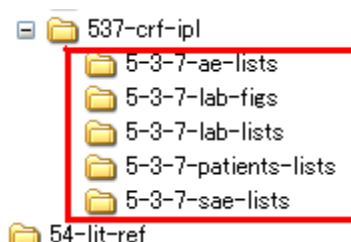
Fig 3-4 Example of “5.3.5” folder structure



Concerning “5.3.7”, a folder for a list of cases should be created below the “537-crf-ipl” folder, and various types of lists and figures should be stored in it for each study. In principle, folder names should be in accordance with Fig. 3-5 .

You should refer to “Chapter 3” of Part 3 of this document for more information.

Fig 3-5 Example of folder structure for “5.3.7 Patient data listings and case report form”



3.3.3 Addition of folders not specified in the “Notification of eCTD specification” and “Notification of eCTD Implementation,”

If you need to add a folder other than ones in the template for eCTD folder structure, which is provided by the ICH, due to the structure of submission dossier, it is allowable to add an appropriate folder at the applicant’s discretion. For example, if there are too many data to be attached to M1.13, you can use additional folders. You should refer to “3.3” of Part 3 of this document for more information.

3.3.4 Handling of overseas application data

When using overseas approval application data, you may submit them while keeping the folder structure and leaf files (e.g., data set, case card for individual patient) which are not required for approval application in Japan. However, it is desirable to delete them wherever possible for the regulatory authorities to effectively use the data storage area. If the STF (to be stated in “5.6.1” of Part 3 of this document) is used in the application data submitted to the FDA, you should delete the XML file contained below the “m4” and “m5” folders. After deleting the STF, if necessary, recreate the leaf files which are divided according to the STF specifications and turn them into one file. You should remember that the relink will be necessary because this work will cause the external links to be broken. If the files are divided because of the file size, etc., you can efficiently associate the divided files with each other using a bookmark of each file, etc.

3.4 Creation of XML instance (this section is excluded from translated item)

3.5 Creation of M1

When creating M1, there are requirements specific to each region in both aspects of the contents of data to be attached to the approval application data and electronic specifications. The electronic specifications specific to each region are provided in the “Notification of eCTD Implementation”. The summary of the electronic specifications are offered in this section. You should refer to Part 3 of this document for more information.

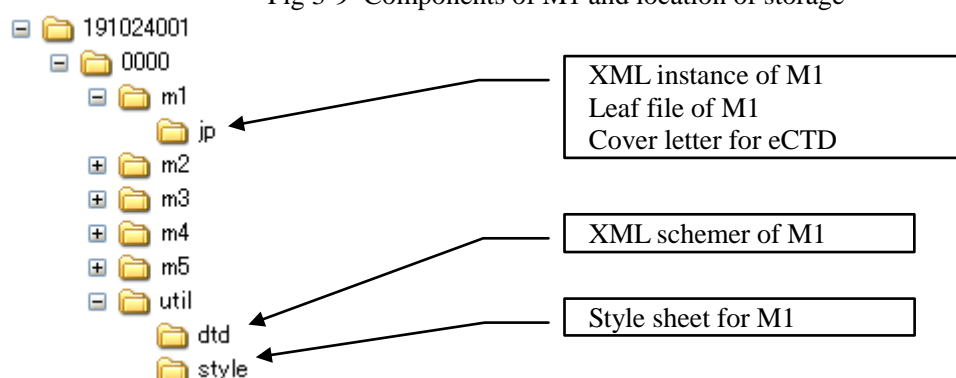
3.5.1 Components of M1 and location of storage

M1 has the following 5 components.

Table 3-4 Components of M1

Components of M1	Explanation
Leaf file of M1	Refer to “3.5.2” of Part 2 of this document for outline of creating a leaf file of M1
Folder structure of M1	Refer to “3.5.3” of Part 2 of this document for outline of creating the part of m1/jp folder
XML instance of M1 jp-regional-index.xml	Refer to “3.5.4” of Part 2 of this document for outline of creating an XML instance of M1
XML schemer of M1 jp-regional-1-0.xsd, xlink.xsd	Download an XML schemer of M1 from the website of the regulatory authorities and store it in the designated sub folder (refer to Fig 3-9) within the util folder without changing it.
Style sheet for M1 jp-regional-1-0.xsl	

Fig 3-9 Components of M1 and location of storage



3.5.2 Leaf file of M1

The leaf files that should be attached to M1 include the contents of M1^{*1} and files specifically necessary for eCTD. The files specifically necessary for eCTD are a cover letter for eCTD (refer to “3.6.4” of Part 2 of this document) and a statement of scanning process (refer to “3.6.5” of Part 2 of this document). While the table of contents for M2 to M5 is not necessary for eCTD, the table of contents for the application data including M1 (M1.1) is necessary.

*1: The contents of M1 are shown in the Appendix 2 of “Notification No. 899” (Part 1 Guidelines for preparation of data concerning the administrative information such as application form and information on package insert), and the electronic specifications corresponding to these contents are described in the “Notification of eCTD Implementation.”

3.5.3 Folder structure of M1

As for the folder structure of M1, it is essential to create up to a jp folder and all leaf files that should be attached to M1 must be stored in the jp folder^{*1}.

In the case that there are many files to be attached to M1.13, it is allowable to create a sub folder under the jp folder as needed at the applicant’s discretion.

*1: The XML schemers and style sheets of M1 (jp-regional-1-0.xsd, xlink.xsd, jp-regional-1-0.xsl) should be stored separately in a sub folder under the util folder.

3.5.4 XML instance of M1

The XML instance of M1 shall be created according to the contents defined in the XML schemers (jp-regional-1-0.xsd and xlink.xsd). In reality, you can create the XML instance of M1 by referring to the sample of MI instance (also called “sample instance”) even if you do not understand the XML schemer. You can find a sample of XML instance of M1 in the “Notification of eCTD Implementation,” and also download from the website of the regulatory authorities.

If you want to deepen the understanding of the method of creating the XML instance of M1, you may refer to the “Domestic eCTD Q&A”, “Notices for eCTD Checklist” and operating manual for eCTD validator in addition to the “Notification of eCTD Implementation.”

3.6 Creation of data specifically necessary in Japan

3.6.1 List of attachments (m1.12)

You should create a list of attachments according to the “Notification of eCTD Implementation,” and store the PDF file (m1-12-01.pdf) and Excel file (m1-12-02.xls^{*1}) in the “m1/jp” folder. It is desirable that the Excel file should be formatted to the PDF file so that the contents of the Excel and PDF files will be identical.

*1: You may submit the list of attachments for M1.12 (Excel) using the Excel file of Office 2013 format.

When creating the list with the Excel file, you must include the following items in one line so that the data can be sorted or extracted in the reviewing process.

- (1) Reference Number
- (2) Title
- (3) Author
- (4) Study period
- (5) Site of study implementation
- (6) Report type (domestic / overseas)
- (7) Journal to be posted
- (8) Whether it is evaluation data or reference data
- (9) Presence or absence of submission of electronic application data ^{*2}

^{*2}: It will be necessary when submitting the electronic application data (to be effective in October 2016).

Although the data is divided into multiple worksheets in the example shown in Fig 3-10, you may put together all data in one sheet.

Also, since this Excel file is the data to be attached to M1.12, each company may prescribe the format, e.g., describing “1.12 List of attachments” of CTD in the first line.

Fig 3-10 Example of list of attachments

	A	B	C	D	E	F
1	Module 5	Clinical study report list of attachment				
2						
3	5.2	All clinical study list				
4	CTD No.	Title	Study period	Study Site	Publication	Evaluation data/No evaluation data
5	5.2	All clinical study list	-	-	Internal material	-

3.6.2 List of cases (m5.3.7)

For the list of cases, the PDF file will be the leaf file. However, if it is judged necessary in the review process, you are required to separately submit the electronic file in the Excel format etc. For this reason, it is desirable that you create the leaf file in the Excel format etc. and include the necessary information in one line per item as in the case with the list of attachments. When you submit the list of cases in the Excel format etc., although you do not need to make the appearance completely consistent with the leaf file (PDF file) for the eCTD application, you must keep the contents of both files consistent.

If the list of cases is created in English because, for example, the CSR in other countries is used, you may attach the English list as it is on condition that you provide the translation table for abbreviations both in Japanese and English. If you create the Japanese-English translation table common to all lists, you should establish a file (537-reference.pdf) immediately below 537-crf-ipl (same hierarchy as the folder).

You will be exempted to submit the list of cases for m5.3.7.1 and m5.3.7.5 in studies for which the submission of the electronic application data (to be effective in October 2016) is required.

3.6.3 Approval application (copy) (m1.2)

For the approval application (copy), you need to submit the information which is output from FD application software as a leaf file of the eCTD after formatting it to a PDF file. Other points to consider are shown below:

- (1) You may use whichever the text PDF or the scanned PDF. However, scanned PDF if there is a printed seal, you should use the Scanned PDF. If there is no printed seal, you should use the text PDF.
- (2) You should name the file as “m1-02-01.pdf” and store it in the m1/jp folder.
- (3) When you create the text PDF using FD application software, lines may disappear and letter or line spacing may differ from the paper version. However, you must keep the contents consistent since it is the “copy”. You must also make the layout as similar to that of the paper version as possible. As a means to prevent the problem of inconsistency, you can use the paper version printed from the text

PDF which is created from FD application software or use the paper-version Scanned PDF printed from FD application software.

3.6.4 Cover letter for eCTD

A cover letter for eCTD is the format used for an eCTD application and will be necessary when you submit an eCTD each time. The points to consider are shown below:

- (1) The text PDF before affixing the company seal will do (refer to Fig 3-11).
- (2) You should name the file as “cover.pdf” and store it in the m1/jp folder.
At the time of life cycle, there may be no correction to make for M1. Even in such a case, you must create the m1/jp folder and store the cover letter below the folder.
- (3) Do not describe the cover letter file for eCTD in the XML instance for M1.
- (4) You should not only include the cover letter in the eCTD as a leaf file but also submit it in the paper version.
You should create 2 copies of the paper version, get the receipt stamp if the eCTD is imported without any problem, submit one copy to the regulatory authority, and keep the other copy returned from the regulatory authority for your company’s record.
- (5) For the signature or printed name and seal on the paper-version cover letter for eCTD, you would need the company seal or president’s seal as in the case with the application form (for both original and duplicate).

These rules will be applied only when the eCTD is submitted in person. If it is submitted via the gateway system (to be effective in October 2016), you do not need to submit the paper version described in the above (4) and below it. However, you will need to submit the paper version described in the above (4) and below it, if required by the authority.

The sample of the cover letter for eCTD is shown below and the contents to be included in the cover letter and points to consider are summarized in Table 3-5. Each company should create the cover letter for eCTD based on the form attached to the “Notification of eCTD Implementation,” as Form 1.

Fig 3-11 Sample of the cover letter for eCTD

様式 1 eCTD 用カバーレター	
eCTD 受付番号	230525001
提出連続番号	0000
様式 (コード)	E01
申請区分	1-(1) : 新有効成分含有医薬品
申請日	2011 年 6 月 8 日
名称	一般的名称
	イーアイ塩酸塩
	販売名
	セイヤクキョール錠 10mg, 同錠 20mg
申請書セクション一覧	第 1 部、第 2 部、第 3 部、第 4 部、第 5 部
電子媒体の種類	DVD-R
提出枚数	1 枚
サイズ (提出媒体ごと)	46.3 MB
ウイルスチェックに関する陳述	McAfee VirusScan Enterprise によりウイルス非感染を確認した。 スキャンエンジン : 5400 ウイルス定義ファイル : 6369
Index.xml のチェックサム 関数値	a0c2d63836849c8b87e8f72cf5df3800
動作確認環境	CPU : Intel(R)Core(TM)2Duo 2.66 GHz メモリ (RAM) 容量 : 1 GB OS : Windows XP Professional SP3 ブラウザ : Internet Explorer (Ver. : 6.0 SP3) Acrobat Ver. : Adobe Acrobat 9.0 Professional Excel Ver. : Excel 2007 SP2
連絡先	(薬事担当者名) 日本橋太郎 Tel: 03-5403-1411 Fax: 03-5403-1417
	(技術担当者名) 中央花子 Tel: 03-5403-1411 Fax: 03-5403-1417
備考	eCTD の位置づけ : 正本

上記により、医薬品製造販売承認における電子申請資料を提出いたします。

2011 年 6 月 8 日

(申請者)
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 代表取締役 社長 神田一郎 印

厚生労働大臣 殿

Table 3-5 Contents to be included in the cover letter for eCTD and points to consider

Items to be included	Contents to be included / points to consider
eCTD receipt number	Enter the eCTD receipt number issued by the Pharmaceuticals and Medical Devices Agency (PMDA).
Serial number for submission	Enter the serial number of the life cycle. Enter “0000” at the time of application, and then increase it incrementally by 1 at each revision as “0001”, “0002”.
Form (code)	Enter the form code for the flexible disc (FD) application. E01 Application Form for Marketing Approval of Drug E11 Application Form for Partial Changes in Approved Items for Marketing Approval of Drug
Application category	Enter the application category as follows (note that it is different from the description method for application category code at the time of FD application): 1-(1): Drugs containing new active ingredients 1-(2): New prescription combination drugs 1-(3): Drugs with new routes of administration 1-(4): Drugs with new indications 1-(5): Prescription drugs with new dosage forms 1-(6): Drugs with new dosages 1-(7): Biosimilar Products 1-(8): Prescription drugs with additional dosage forms (during reexamination period) 1-(8-2): Prescription drugs with additional dosage forms (not during reexamination period) 1-(9): Prescription combination drugs with similar formulations (during reexamination period) 1-(9-2): Prescription combination drugs with similar formulations (not during reexamination period) 1-(10): Other prescription drugs (during reexamination period) 1-(10-2): Other prescription drugs (Same with (10), changes in manufacturing method of biological products, etc.) 1-(10-3): Other prescription drugs (not during reexamination period) 1-(10-4): Other prescription drugs (Same with (10-3), changes in manufacturing method of biological products, etc.)
Date of application	Enter the date of application. If the date of application is different from the date of submission in the case of life cycle submission of eCTD, enter the date of submission in the date section outside the table. In the sample of description shown in Fig 3-8 the initial eCTD is submitted on the date of application, and therefore, the date of application is the same as the date of submission.
List of sections for application form	Refer to the sample shown in Fig 3-8 as one example.
Check sum value for index.xml	Enter the check sum value for eCTD XML instance (index.xml). Enter the value stated in the index-md5.txt.
Environment for operation check	Enter the environment in which the operation of eCTD was checked.
Remarks	Enter whether original or reference as a status of eCTD.

3.6.5 Statement of scanning process

A statement of scanning process is a statement which demonstrates that a page such as the handwritten signature or printed name/seal was scanned without failure (Fig 3-12). This statement will be necessary for the initial application and you also need to resubmit it at the time of revision if the scanned page is included in the application data. You should pay attention to the following points.

- (1) The head of the responsible department (e.g., General Manager of Regulatory Affairs Department, Director of Development Department) for the applicable data must sign or affix his/her printed name and seal on the statement of scanning process in the paper version.
- (2) Create the scanned PDF after signing or affixing the printed name/seal. Name the file as “m1-03-XX.pdf” and store it in the m1/jp folder.
- (3) The statement will be classified as the certificate for M1.3.
- (4) Submit the original paper version after importing it into the eCTD as a leaf file.

These rules will be applied only when the eCTD is submitted in person. If it is submitted via the gateway system (to be effective in October 2016), you do not need to submit the paper version described in the above (4). However, you will need to submit the paper version, if required by the authority.

Fig 3-12 Sample of statement of scanning process

<div><h2>スキャンに関する陳述書</h2><p>申請品目名：セイヤクキョール錠 10mg、同錠 20mg</p><p>本電子化コモン・テクニカル・ドキュメント中のスキャンにより作成した資料（署名ページ等）に関しては、原本を忠実に電子化したページを挿入して作成したものに相違ありません。なお、原本に関しては別途適切に保管しており、要求に応じて提出することは可能です。</p><p>日本製薬工業株式会社 薬事部長</p><p>署 名： ○○ ○○</p><p>日 付： 2011 年 6 月 6 日</p></div>

3.6.6 Data to be attached to M1.13 Others

The “Notification No. 899” was revised on July 7, 2009 and the data (following (1) to (5)) to be attached to “Others” in M1.13 were stipulated. The following data should be attached in the numerical order as other reference data.

You should refer to “Chapter 5” of Part 3 of this document for more information.

(1) Data related to approved drugs

In the case of approval application for partial changes in approved items such as additional indication or change in dosage and administration, copies of approval forms and related data for the approved items (review report, materials corresponding to M2 [CTD summary] and list of attachments for M1.12) should be attached. Also, the minor change notifications submitted from the latest approval for the relevant application item until this application (including the description improvement notifications to be submitted based on the No. 4 of “Guidelines for Description Matters of the Marketing Approval Application of Drugs, etc. based on the Revised Pharmaceutical Affairs Law,” Yakushokushinsahatsu Notification No. 0210001 of February 10, 2005) should be attached where necessary.

(2) Clinical trial consultation records (copies)

Copies of clinical trial consultation records with the PMDA for the application should be attached.

(3) Inquiries (copies) and responses to the inquiries (copies)

Copies of inquiries in writing received from the PMDA in the process of review for approval from the time of application, and copies of responses to the inquiries in writing submitted to the PMDA (including the case when the inquiries were sent by an electronic method).

(4) Other data

[1] Data submitted to the PMDA (copies)

Among the data submitted to the PMDA in the process of review for approval, copies of other submitted data not included in the CTD for this application.

[2] Data submitted to the MHLW (copies)

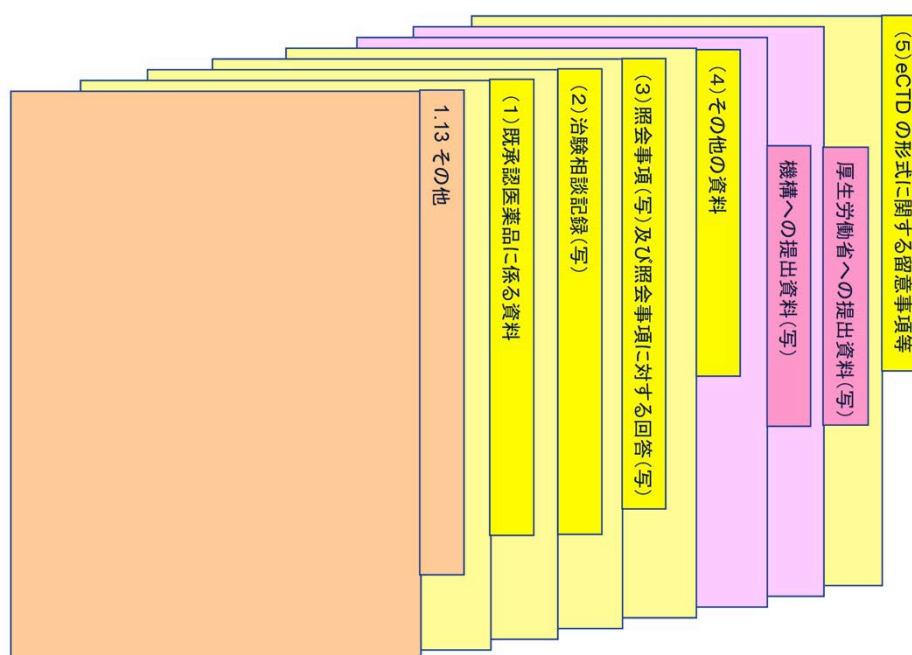
Copies of the data if there is any data submitted to the MHLW in the process of review for approval for this application.

(5) Points to consider about format of eCTD

If you use a format different from the operation shown in the “Notification of eCTD specification” and “Notification of eCTD Implementation,” when submitting the eCTD for this application such as the use of Node Extension and addition of a folder, the reason, points to consider, etc. should be attached.

Concerning the above data, an example of compiling the printed paper is shown in Fig 3-13.

Fig 3-13 Example of compilation the printed paper for M1.13



3.6.6.1 Data related to approved drugs for M1.13.1

As long as the original has been applied and approved with the eCTD in the past, you can omit the submission of data corresponding to M2 [CTD summary] and list of attachments for M1.12 by including the leaf file that contains the eCTD receipt number, etc. (*1,*2) (refer to the “Notification of eCTD Implementation,”). However, since the copies of approval forms and review reports at the time of approval are not the “attachments for approved application”, you need to import the actually scanned data.

*1: For the eCTD submitted for reference, you cannot quote the eCTD receipt number because the strict consistency with the original paper CTD is not required.

*2: Only when the latest eCTD has been submitted to the regulatory authority can you quote the eCTD receipt number.

The examples of import when an application for partial changes is planned are shown below:

Table 3-6 Examples of application and approval status for partial change

1st application	Obtain the approval as a drug containing new active ingredients (Approved on October 23, 2006)	Application with original paper CTD
2nd application	Obtain the partial change in the indication (Approved on May 1, 2009)	Application with original eCTD
3rd application	Application for partial change is planned using the original eCTD	Application with original eCTD

The data will be assembled in the following manner for M1.13.1 in the 3rd eCTD application:

- Copies of approval forms and review reports at the time of approval
Import the data approved on October 23, 2006 and May 1, 2009 by scanning them.
- Data corresponding to M2 [CTD summary] and list of attachments
While you need to import the data approved on October 23, 2006 by scanning them, you can omit the data approved on May 1, 2009.

The following figure (Fig 3-14) shows the example of a leaf file when the data corresponding to M2 [CTD summary] and list of attachments are omitted.

Fig 3-14 Example of a leaf file when quoting the data attached to an approved application
Approved as a drug containing new active ingredients (Approved on July 25, 2012)

セイヤクキョール錠 10mg, 同錠 20mg, 同錠 40mg
(イーアイ塩酸塩)

1.13.1-3 第2部に相当する資料（CTDの概要（サマリー））及び添付資料一覧

【高血圧】

<平成24年7月25日承認時資料>

eCTD 受付番号：230525001

【01】承認日	2012-07-25
【02】販売名	01. セイヤクキョール錠 10mg 02. セイヤクキョール錠 20mg
【03】一般名	イーアイ塩酸塩
【04】申請者名	日本製薬工業
【05】申請日	2011-06-08
【06】申請区分	1-(1)：新有効成分含有医薬品

日本製薬工業株式会社

3.6.6.2 Clinical trial consultation records (copies) for M1.13.2

They used to be attached to CTD M5.4, but now they must be attached to M1.13 “Others”.

3.6.6.3 Inquiries (copies) and responses to the inquiries (copies) for M1.13.3

If there is any relevant data at the time of eCTD revision, the additional attachment will be necessary.

Since it is considered appropriate in some cases that the reference data attached to the responses to inquiries should be included in M1.13.3, you may need to consult the review team about individual cases for preparation of data.

You should refer to “Chapter 7” of Part 2 of this document for responses at the time of eCTD revision.

3.6.6.4 Other data for M1.13.4

You should submit other data after dividing them into “(1) Data submitted to the PMDA (copies)” and “(2) Data submitted to the MHLW (copies)”. Currently, “review data on new additives” and “data on quality” are specified as (1) Data submitted to the PMDA (copies). You should refer to the following “(3) Other data” for data other than the data on new additives and data on quality.

(1) Data on new additives

With the issuance of the “Submission of Review Data on New Additives” (dated September 21, 2010), it was decided that you should include the review data on new additives for drugs in “1.13.4.1 Data submitted to the PMDA (copies)”. However, you do not need to include the review data on new additives which were included in M1.13.4.1 in the data for reviewers (paper versions of CTD M1 and M2) to be submitted to the review team for the time being.

As for the data on new additives to be submitted to the review team for reviewers, you need to submit a set of the review data on new additives in paper as in the past for the time being.

The review data on new additives should be included in “1.13.4.1 Data submitted to the PMDA (copies)” in the following order.

- [1] List of review data on new additives
Not only (5) Data on new additives but also (2) Summary table of individual items for deliberations, (3) Approval application (copy), and (4) Summary of new additives should be stated in the list of application review data on new additives and made available for the table of contents.
- [2] Summary table of individual items for deliberations
- [3] Approval application (copy)
- [4] Summary of new additives
- [5] Review data on new additives

You should also put together and submit the data for reviewers in the same order.

(2) Data on quality

With the issuance of the “CTD Format for Reducing Total Review Time for New Drugs” (dated January 17, 2011), it was decided that you should create data on setting the acceptable range of parameters and operating conditions as the background information for the entry of the manufacturing method section in the approval application and attach it to “1.13.4.1 Data submitted to the PMDA (copies)” at the time of approval application which includes the entry of the manufacturing method section among approval application for new marketing authorization and for partial changes in the approved items (excluding the biological products).

(3) Other data

You should attach data which is necessary for the review and judgment for approval and especially for which there is no other place than CTD to store it.

However, you do not need to attach the data which is prepared as the references for M3 to M5.

Necessary data (specific examples)

- Review data other than usual CTD M2 - M5 (e.g., review data for AIDS drugs)
- Data submitted to each Office as reference for review (e.g., document that shows the trends of regulatory authorities in other countries, applicant’s overseas corporations)
- Copies of errata, written pledges, circumstantial reports, etc. submitted to the Evaluation and Licensing Division of the Ministry of Health, Labor and Welfare

Unnecessary data (specific examples)

- Data not directly related to the review such as time clock management table, FAX forms, list of competitive items, list of members involved, and data on international birth date
- Data used for presentation at the time of initial interview meeting
- Data related to compliance review such as GLP site form and GCP site form (paper compliance review and on-site GCP inspection), data related to GMP inspection.

4. Securing of quality of eCTD

4.1 Check of file quality (this section is excluded from translated item)

4.2 Check of package structure (this section is excluded from translated item)

4.3 Check of XML quality

You should check whether the XML instance has been created without any violation of the XML grammar.

In essence, you can consider that there is no error in the XML grammar if you can display the XML instance with Microsoft Internet Explorer 5.0 or later which comes with an XML parser. Also, there will be no problem if you can clear various check items presented by the regulatory authorities (e.g., Notice on Checklist for eCTD). You can also check them by making sure that neither NG nor warning for the XML is detected using the eCTD validator provided by the regulatory authorities (http://www.pmda.go.jp/ich/m/eCTD/ectd_validator.htm). By the way, it is OK even if the warning is detected with the eCTD validator if there is any appropriate reason (e.g., change in the brand name). So you should consult the regulatory authorities about whether such warning is acceptable or not.

4.4 Virus check

You should confirm that electronic files to be submitted are not infected with any virus. You should store all leaf files in a folder and execute the virus check using virus check software immediately before writing them to a media for submission. You should then state the checking results that the files are not infected with any virus and information on the scan engine and virus definition files in the eCTD cover letter (Fig 3-8).

4.5 Check of consistency with eCTD management information

The XML instance, approval application, and eCTD cover letter for M1 contain the items to describe common management information. You should check the consistency of the contents among these documents.

4.6 Final check of operation of eCTD

Prior to the submission of eCTD to the regulatory authorities, the applicant should check the operation of eCTD considering the review environment at the regulatory authorities. The environment, in which the applicants check the operation of eCTD, should be described in the section of “environment of operation check” of the eCTD cover letter. You should refer to Part 3 of this document for more information.

The eCTD validator is made public on the website of the PMDA dated February 1, 2008 (http://www.pmda.go.jp/ich/m/eCTD/ectd_validator.htm) (February 28, 2011, posting of Ver2.0 which reinforced the check function, etc. of PDF files). Since the regulatory authority conducts the operation check of eCTD with the same contents as this tool, the applicant should check the files using this tool beforehand.

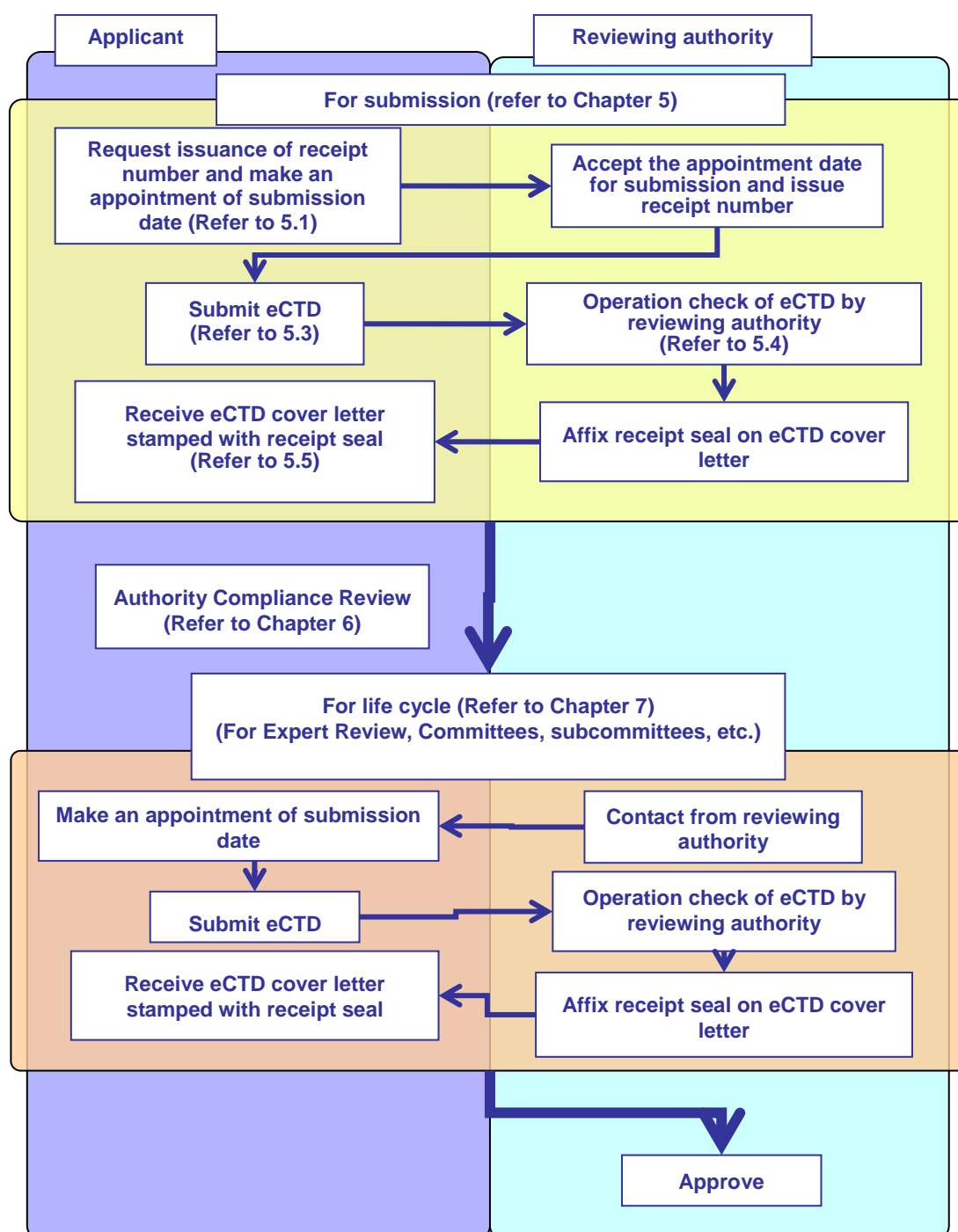
4.7 Consideration of eCTD quality (this section is excluded from translated item)

5. Submission of eCTD

Except for the fact that the operation check of eCTD will be conducted by the regulatory authority when an applicant's obtaining the eCTD receipt number or submitting the eCTD cover letter and eCTD, the procedures for application of eCTD are basically the same as those for application of paper-based CTD. We offer commentaries centering on the processes specific to eCTD in the application process below.

The actions specific to eCTD application in the flow from submission to approval are shown in Fig 5-1 including the section numbers that provide the detailed information in this document.

Fig 5-1 Flow of eCTD from submission to approval



5.1 Acquisition of eCTD receipt number

You should notify the First Administration Section of the Office of Review Administration of PMDA of your plan to file an eCTD application by fax about 2 weeks before the planned date of eCTD submission. You will receive a return call and be notified of an eCTD receipt number.

It is desirable that you should initiate this procedure once the planned date of eCTD submission is determined in-house. You may have an eCTD receipt number issued, even if it is more than 2 weeks before the planned date of eCTD application in some cases. If there is any change in the planned date of eCTD submission or if you want to cancel the eCTD application, you should promptly notify the regulatory authority.

The eCTD receipt number is a number that you need for the eCTD assembling. It is issued in a total of 9 digits; “year^{*1}, month and date (yymmdd) + 3-digit serial number”. For example, the eCTD receipt number that was issued first on October 24, 2007 will be “191024001”. This receipt number will be not only set as the management information of M1 but also used as a folder name of the highest-ranked folder that contains the eCTD to be submitted.

When notifying the planned date of eCTD submission, you should also notify the number of files to be submitted and also estimated volume of the entire files. Because the regulatory authority now checks annotations in the PDF files when it verifies the operation of eCTD at the time when the data is submitted and its verification work takes longer than before, such information is necessary for the regulatory authority to adjust the schedule for receiving the eCTD.

*1: year of Japanese era

5.2 Electronic media for eCTD submission

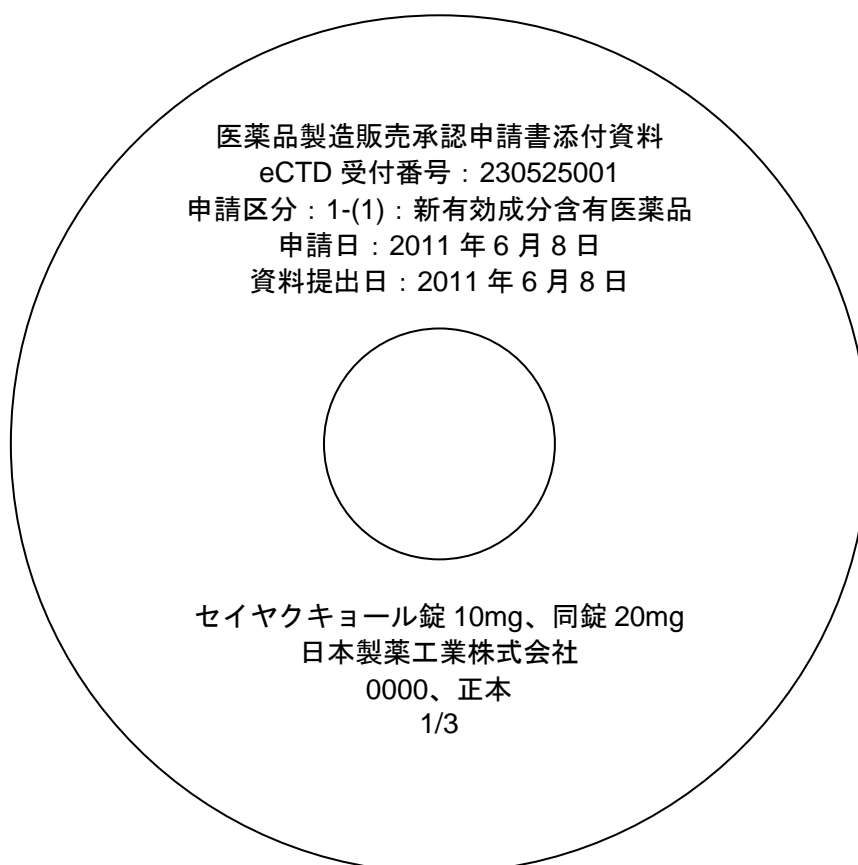
You should submit the eCTD to the regulatory authority’s section responsible for receiving it after storing it in an electronic media for submission.

CD-ROM or DVD-ROM (non-rewritable CD or DVD) are desirable as an electronic media for eCTD submission. In the current situation, however, an eCTD is generally submitted in CD-R or DVD-R. In addition to these media, you may also use CD-RW, DVD-RAM/RW, PCMCIA Type 2 card (memory media such as hard disc and memory), USB flash memory, or floppy disc. However, considering that you must describe the application information on an electronic media for submission, PCMCIA Type 2 card and USB flash memory are not suitable because of their forms. Also, a floppy disc does not have enough capacity. You do not always need to follow the example and you may modify the contents and the order (Fig 5-2).

Once submitted, an electronic media will not be returned to you.

- (1) eCTD receipt number
- (2) Categories on drug approval applications
- (3) Submission date
- (4) Filing date (enter the date of data submission for this life cycle)
- (5) Brand name
- (6) Applicant name
- (7) Serial number to identify the order of the media when there are multiple media (serial number/total number of media)
- (8) Serial number for submission
- (9) Remarks (Describe whether original or reference as a status of eCTD.)

Fig 5-2 Example of description on an electronic media for eCTD submission



In order to display the application information on an electronic media, you may paste a label so that it does not come off or you may directly write the information without pasting any label.

5.3 Submission of eCTD

The procedures for submitting eCTD are the same as the procedures for submitting paper CTD. In the case of eCTD, however, you need an eCTD cover letter (original and duplicate) and statement on scanning process. The submission data necessary at the time of application and detailed guidelines for submission are shown in Table 5-1.

Table 5-1 Guidelines for submission of eCTD and appendixes for eCTD

Submission data		Guidelines for submission
eCTD		1 copy of electronic medium
Appendixes for eCTD	eCTD cover letter	Set up a file for the eCTD and submit a copy of the original and duplicate (2 copies in total) in paper format. If the regulatory authority judges it acceptable after conducting the operation check of the eCTD, it affixes the receipt seal on the eCTD cover letter (duplicate) and returns it to the applicant. <ul style="list-style-type: none"> • Original: To be kept by the regulatory authority • Duplicate: To be kept by the applicant (for confirmation of the eCTD receipt)
	Statement on scanning process	Include a statement on scanning process in the eCTD of M1.3 as a leaf file and submit 1 copy (original) in paper format.

5.4 Operation check of eCTD by regulatory authority

After the applicant submits an eCTD, the regulatory authority will conduct the operation check to see whether the eCTD operates without any issue in the environment at the regulatory authority and determine whether the eCTD is acceptable or not. This check includes the check with the eCTD validator which is made public on the website of the PMDA. If the eCTD does not operate properly in the environment at the regulatory authority, the eCTD will be pushed back to the applicant. The applicant must correct the eCTD according to the instructions by the regulatory authority and resubmit it.

The operation check by the regulatory authority may be completed on the submission date of the eCTD in some cases but may last until the following date or later in other cases. Since the time to verify the operation depends on the CTD volume (number of total files, total volume) and the number of persons in charge of reception is limited, you must make an appointment for the date and time slot of the eCTD submission in order to make the reception expedite smoothly. If you want the operation check for acceptance that needs to be certainly completed on the submission date, you may have to submit it early in the morning.

5.5 Notification of receipt to the applicant

Once it is confirmed that the eCTD operates properly in the reviewing environment, the status of eCTD will be “received” and the subsequent procedures for receiving the application (FD application) will begin. The regulatory authority will affix the receipt seal on the eCTD cover letter (duplicate) as the proof of receipt and return it to the applicant.

The receipt date of the eCTD will be treated as follows. The operation check by the regulatory authority may not be completed on the submission date of the eCTD in some cases. Thus, the applicant will be informed of the completion of operation check either immediately on the submission date of the eCTD or on a later date. Even if the applicant is informed of the receipt of the eCTD on a later date, the receipt date of the eCTD will be the same as the submission date of the eCTD. If the eCTD is pushed back because the proper operation of it could not be confirmed, the applicant must resubmit the eCTD until the proper operation of it is confirmed. The receipt date of the eCTD will be the submission date of the eCTD which is accepted. In the following example, the receipt date of the eCTD will be July 14.

Date	Transaction between the applicant and the regulatory authority
July 8	Initial submission of the eCTD by the applicant
July 9	Push back of the eCTD by the regulatory authority
July 14	Resubmission of the eCTD by the applicant
July 15	Notification of the receipt by the regulatory authority to the applicant

6. Compliance review (this chapter is excluded from translated item)

7. Revision of eCTD

When a submission is filed with eCTD format, the revision will be necessary at the following timing:

- [1] When submitting the data from long-term stability studies (if necessary)
- [2] When submitting the data from long-term clinical studies (if necessary)
- [3] At the time of Expert Review (only adding responses to inquiries to 1.13)
- [4] At the time of Committee on New Drugs (complete revision)
- [5] At the time of Pharmaceutical Affairs and Food Sanitation Council (if necessary)
- [6] At the time of approval (if necessary)

However, if patient cases in a clinical study are deleted due to some deficient event with authority compliance review, if a new clinical study result that may change the rationale of regulatory submission is presented during the authority review, or if the information that should be included at the time of first submission turns out to be clearly missing, etc., the applicant may be instructed to revise the eCTD regardless of the timing shown above. When the applicant submits the revised eCTD, he or she needs to attach a written request for change for the Director of the Evaluation and Licensing Division.

If it is difficult to adequately prepare the revised eCTD including the preparation of hypertext links due to difficult time frame, the applicant should take appropriate actions such as consulting the regulatory authority beforehand.

7.1 Points to consider at the time of revision

If the revision becomes necessary in the review process after the first submission, the contents of CTD may be updated or new content may be added. In the case of paper-based CTD, you should print out the revised contents and replace the old contents with them or add new one, and then you should compile them again. In the case of eCTD, the old leaf files will be replaced by the revised ones, the hypertext links for the revised portions will be reset^{*1}, and the XML instance will be recreated.

*1: The resetting of hypertext links is unnecessary in following cases:

- [1] When submitting the data from long-term stability studies (if necessary),
- [2] When submitting the data from long-term clinical studies (if necessary)

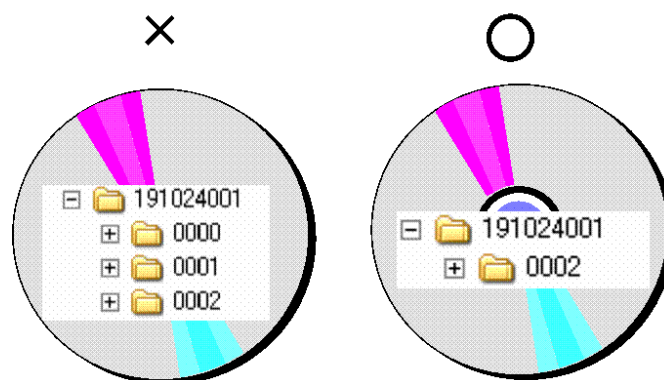
If you have any questions when creating the revised version, you should ask the regulatory authority. You should also check with the regulatory authority, if you have any questions about handling of the data to be attached to the eCTD at the time of revision.

7.1.1 Information to be included in the submission media at the time of revision

When you create a media for the revised version of eCTD (after 0001) during the life cycle of the application, you must not submit the eCTD that you already submitted.

For example, the serial number when you submit the eCTD in the third time will be “0002”, and you should store only the folders under “0002” in the top-level folder of the eCTD (the folder with the number of “191024001” in Fig 7-1) and not submit the already submitted folders under “0000” and “0001”.

Fig 7-1 Folders when submitting the revised version of eCTD



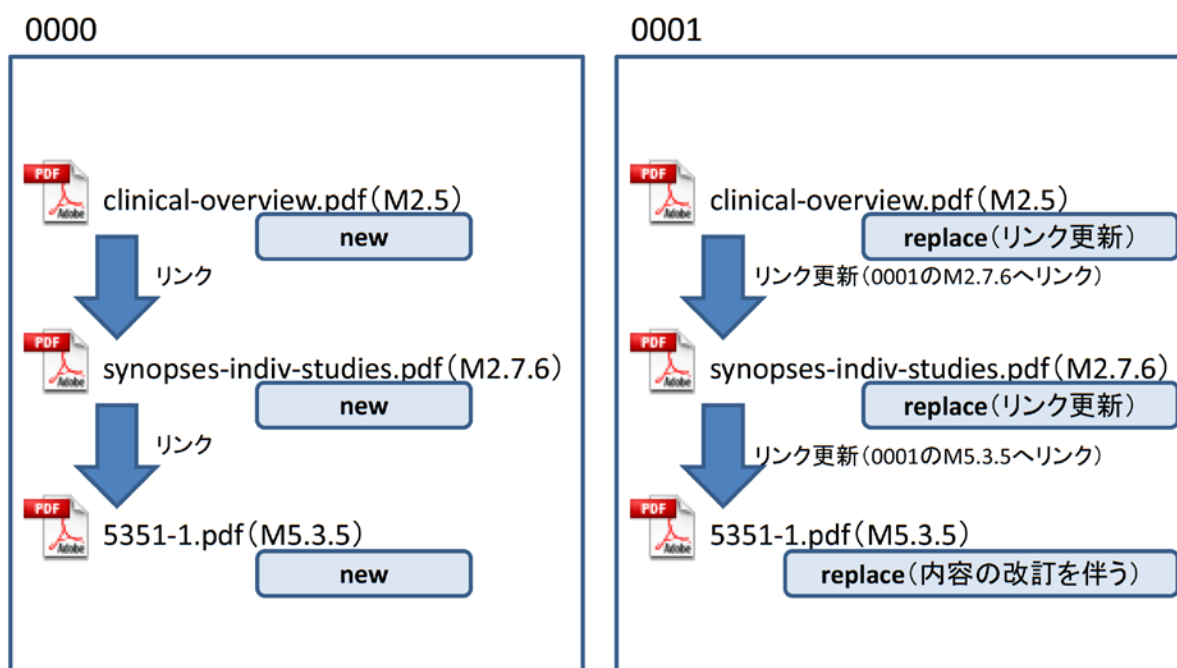
7.1.2 Hypertext link

As for hypertext links, you need to correct not only links within the document on the revised leaf files but also external links on the unrevised leaf files which refer only to the revised leaf files (refer to Fig 7-2).

For example, if a document included at the time of first submission is to be replaced during the authority review process and there is an external link that goes to the document, some external link will not properly work after the replacement. Therefore, you must update the external link information and replace the document. What you should keep in mind is that you need to post a hypertext link again if there is any leaf file in which the link is posted to this original file, and you need to update the leaf file with “replace” as the attribute value of operation attribute. In this way, you must guarantee that all leaf files and hypertext links properly work with the XML instance (index. xml) at the time of revision (please refer to “2.5” of Part 3 of this document).

For this, it is efficient to manage the setting information of hypertext links using a list. Also, in order to handle hypertext links during the life cycle without any delay in a limited amount of time, you should cooperate with the person in charge of writing and share the information on leaf files which may be revised at an early stage and understand the link information in the list.

Fig 7-2 Example of updating of link information



7.1.3 XML instance

When it comes to the XML, you need to pay attention especially to the description of operation attribute. You should refer to “4.2.2.2” of Part 3 of this document for technical details.

7.1.4 Submission of revised eCTD

When you submit a revised eCTD to the regulatory authority, the revised version needs to meet the eCTD requirements that the first submission has. You must confirm that the hypertext links work properly and conduct the operation check using the eCTD validator provided by the regulatory authority in the same manner you have in the first submission.

When you actually submit the revised eCTD, you may also need to file the printed version. So you should consult the reviewer about the procedure. While the printed version may be directly filed to the Office you need to make the appointment with the window person in charge of application and notification at the PMDA beforehand and submit the revised eCTD as in the case with the eCTD first submission. It will be accepted as long as there is no problem with the operation check.

You should submit only the information of relevant life cycle with an electronic media for the revised version (Table 7-1).

Table 7-1 Guidelines for submission of data at the time of revision

Submission data		Guidelines for submission
eCTD		1 copy of electronic medium (only for this life cycle)
Appendixes for eCTD	eCTD cover letter	Set up a file for the eCTD and submit a copy of the original and duplicate (2 copies in total) in paper format. If the regulatory authority judges it acceptable after conducting the operation check of the eCTD, it affixes the receipt seal on the eCTD cover letter (duplicate) and returns it to the applicant. <ul style="list-style-type: none"> • Original: To be kept by the regulatory authority • Duplicate: To be kept by the applicant (for confirmation of the eCTD receipt)
	Statement of scanning process	If the signature page, etc. is added, include a statement on scanning in M1.3 as a leaf file and submit 1 copy (original) in paper format.
Written request for change		When submitting the revised CTD, submit a copy of the original and duplicate (2 copies in total) in paper format addressed to the Director of Evaluation and Licensing Division. Also, mention only the files whose hypertext links are corrected.

8. At the time of obtaining approval/after obtaining approval

What to do at the time of obtaining approval and after obtaining approval will be basically the same as in the case of application with the original CTD in paper format.

8.1 After meeting of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

After the review at the PAFSC, there are slight possibilities that you may be instructed to make the application data on some rectification. Since the relevant contents have to be properly described and adjusted for the approval, you may be required to submit the revised eCTD after updating the relevant contents before the issuance of the written approval. However, if the revised parts are limited to M1.8 “package insert (draft)” and M1.11 “risk management plan (draft)”, you do not need to submit the revised eCTD.

8.2 After obtaining approval

If you have not submitted the final versions of all data to the regulatory authority for some reason when you obtain approval, you may be required to submit the revised eCTD in some cases when the authority takes measures related to the Law Concerning Access to Information concerning the publication of information on approval review and reexamination of new drugs. Also, considering the reusability etc. of the already approved data in eCTD application at the time of additional application which occurs during the product life cycle such as a partial change including the future expansion of indication, you need to submit the revised eCTD by the time of the disclosure of information on approval review as the final version at the time of approval.

8.3 For publication of information

If the data for publication will be created on the basis of the leaf files of M1 and M2 in the eCTD, you should delete the hypertext links from the files, and no text data should be left in the deducted parts. Regarding the deducted parts, as one attention was called in the Administrative Notice dated February 8, 2010 “Masking process of publication of information on approval review of new drugs, etc.”, the text data may be left in some cases depending on the deduct method even if the relevant parts are illegible on the screen or in the printed page. In such a case, some caution should be paid because a third person may be able to recognize the contents which the applicant intends to hide.

Also, the file size of data for publication of information is limited to 10MB (the file size was changed from 1MB to 10MB at the same timing as the amendment of “Notification of eCTD Implementation Notification of eCTD Implementation” on August 25, 2008). If the file size becomes bigger than 10MB, it should be appropriately divided or composed according to the requirements for data for publication of information.

9. Consultation with the regulatory authority about creation of eCTD

If you have any question about creating an eCTD while you are preparing an eCTD application/revision, you should make an inquiry to the PMDA by e-mail (ectd@pmda.go.jp). Although the PMDA cannot accept general questions such as how to create an eCTD, you can get answers to specific questions when preparing an eCTD. You may also consult the PMDA using the opportunity of consultation before license application.