国际人用药品注册技术协调会

ICH M2 专家工作组

电子通用技术文档技术规范

本规范由 ICH M2 专家工作组根据 ICH 工作程序涉及 M2 专家工作组的相关部分制定，并由电子通用技术文档（eCTD）实施工作组根据 ICH 工作程序涉及 eCTD 的变更控制的相关部分进行维护。

文件变更历史记录

版本编号	日期	描述
版本3.0	2003年10月	初始步骤 4 文件
版本3.1	2003年11月	并入的经批准的变更请求 00020, 00030, 00090, 00110, 00190, 00200, 00240, 00260, 00290, 00310, 00380, 00400, 00420, 00450, 00480, 00500, 00510, 00520, 00530
版本3.2	2004年2月	编辑更正和变更以同M4组织文件一致：粒度附件。
版本3.2.1	2008年6月	并入的经批准的变更请求 0120、0130、0140、0210、0270、0300、0390、0560、0590、0600、0620、0640、0670、0700、0710、0720、0730、0750、0760、0770、0780、0810、0820、 0940、0960、1030、1080、01170、1250、1280、1310、1320、1360、1370、1400、1450、1580、1660、1680。 并入的 eCTD 问答 1-3、5-7、9 - 11、13、15、17-19、21、23、24、28-34、37-39 和 41-47。提供操作属性使用说明。转换“叶”为“叶元素”。删除 CTD 未说明的编号（如 4.2.1.1.1）。引入“增补”叶以修改同一顺序的叶。更正拼写错误和其他措辞问题。
版本3.2.2	2008年7月	在步骤 4 的批准和签署后进行较小的编辑更正。

ICH 电子通用技术文档技术规范

引言

ICH M4 专家工作组（EWG）制定了通用技术文档（CTD）的技术标准。ICH M2 专家工作组在当前的文件中制定了电子通用技术文档（eCTD）的技术标准。eCTD 被定义为制造企业传送监管信息到监管机构的界面，同时其兼顾电子文档创建、技术审评、生命周期管理和归档提交的便利化。eCTD 规范列出了使得以电子方式提交文件在技术上有效的标准。本规范的重点是规定从制造企业以电子形式传送注册申请到监管机构的方法。制造企业之间、监管机构之间的传送在此未作阐述。

背景

eCTD 技术规范以 ICH M4 专家工作组制定的 CTD 的具体内容为基础。CTD 描述了模块、章节和文件的组织。CTD 中阐述的结构和详细程度被作为确定 eCTD 结构和内容的基础，在适当时，eCTD 技术规范规定了更详细的内容。

eCTD 的原则是使用开放的标准。开放的标准包括因为广泛使用而被视为事实标准的专有标准，通常情况下该标准均适用。

范围

M4 专家工作组编制的 CTD 并不包括在一个区域需要提交的全部提交文件。它阐述了在所有区域通用的模块 2 至模块 5。CTD 未阐述模块 1 行政文件和药品信息，亦未对初始申请文件的修正或变更内容的提交文件予以阐述。

仅以 CTD 中所述模块为基础制作关于创建电子提交文件的规范的实用性是有限的。因此，M2 专家工作组制作了适用于所有初始注册申请模块的 eCTD 规范和在产品的整个生命周期的其他信息提交的（如，变更和修改）规范。

本文仅对注册申请中的区域通用性部分和产品的某些生命周期要求进行描述。各区域的特定注册申请将在区域性指导中阐述。但，本主干文件可用于处理区域性文件提交也可用于通用部分文件提交。

技术要求

本规范旨在支持诸如下述的高级功能要求：

- 复制和粘贴
- 查看和打印文件
- 注释文件
- 便于向数据库输出信息
- 本次申请和跨申请的搜索

- 整个 eCTD 及其随后的修正/变更导航

变更控制

eCTD 规范可能会随着时间的推移发生变更。可能影响本规范内容的因素包括但不限于：

- CTD 内容的变更，通过在同等细节层次对信息进行修正，或者提供更多的内容和结构说明，
- 不在本 CTD 范围内的区域性申请要求的变更，
- 在本 eCTD 技术规范中已经采用的标准的更新，
- 对创建和/或使用 eCTD 具有重要价值的新标准的确立，
- 新的功能要求的确立，
- 各方使用 eCTD 的经验

变更控制管理的具体规定在对外 ICH 文件中阐述。

附录 1：整体架构

设计指导原则

本附录详细阐述了进行 eCTD 设计和架构的基本原则。详细规范在附录 2 和 6 中阐述。

业务模式

关于支持采用的业务流程，可作如下描述：

制造企业<----->信息<------>监管机构

业务流程详细阐述了对信息的具体要求。eCTD 规范目前仅规定了从申请人到监管机构的单向传输体系。

eCTD 的重点是规定制造企业和监管机构之间的数据交换规范。制造企业通过创建电子 CTD 初始提交文件启动该程序。在此程序的整个生命周期，将会提交附件资料以更新或修改初始提交文件（例如，补充、修改、变更）。监管机构向制造企业提交确认回执、问题和要求。这些被认为是利用电子信箱或其他传输形式的简单信息。eCTD 整体架构旨在规定共同商定的提交文件和使制造企业和监管机构受到最低程度限制的提交安排。

eCTD 的模块结构

在组织和导航方面，以电子方式提交文件的结构应与通用技术文档的模块结构相一致。这种设计原则的目的是规范 eCTD 通用部分的电子格式。

基于 XML 的 eCTD

XML eCTD DTD（文件类型定义）详细阐述了提交文件的整体结构。XML 主干有双重目的：（1）管理整个提交文件的元数据和提交申请中的每份文件（2）建立内容的全面目录，并提供相应的导航帮助。提交文件的元数据包含提交和接受组织、生产商、发行商、ID 和提交类型等信息以及相关数据项目。文件级元数据的的例子为版本信息、语言、描述性信息，例如，文件名和校验和。附录 6 对此有详细阐述。

任何提交文件的 XML 实例均应根据附录 8 所述 XML eCTD DTD 进行创建和验证。

XML eCTD DTD 根据由 ICH M4 专家工作组确定的 CTD 描述了分层结构。它包括基于 CTD 中所述具体模块的多个层级。实际提交的文件可以包含 CTD 中所述层级之下的更多层级。XML eCTD 实例涉及各层级的全部提交文件，并包括对每个独立文件的引用。

提交的文件应当包括一个支持 XML 实例呈现的样式表，根据目录进行导航，并提供对所有提交文件进行访问的路径。用于查看 eCTD 提交文件的标准样式表由 ICH M2 专家工作组确立并制定。通过接收方的其他样式表进行陈述和导航是有可能的。关于提交非 ICH 样式表是否可以被接受请咨询当地监管机构。

多区域支持

根据通用技术文档，每个注册申请文件的适用范围均是全球性的，这意味着，除了部分区域性文件外（如在质量模块），提交文件的模块 2 到模块 5 适用于所有区域。实质上，模块 1 是区域性管理要求。

ICH M2 专家工作组确定的 DTD 阐述了 eCTD 通用部分的结构，其主要集中阐述了模块 2 至模块 5。它可以链接到模块 1 中区域 XML 索引文件，各区域监管机构将对模块 1 进行单独制定。由于不同区域对注册文件的要求有着显著差异，因此，并不希望为不同区域构建和传送单独的全球性 eCTD 提交文件，然后由各地方监管机构忽略或删除其他区域的提交材料。

生命周期管理

申请人创建提交文件并保存在本地资料库。申请人向监管机构提交初始提交文件，该机构将此提交文件导入另一个本地资料库。当地资料库的性质和类型不在 eCTD 范围内。初始提交文件必须是独立的，即，其应当包含所有文件并且不会引用其他申请中的文件。如果需要引用其他提交文件，则应咨询区域指导原则。

继初始提交之后，申请人可以提交补充的更新资料，如修改和变更。更新资料可以提及先前提交的文件作为参考。更新的资料应设计为可以使其在加载到资料库后能够通过版本控制完全保留初始的或先前提交的文件。XML 主干应包括识别更新资料的元数据并为筛选不同的提交类型提供导航帮助。

通用技术文档首选通过电子方式提交，目前除了某些区域表格要求书面签名之外，整个提交文件均可以通过电子方式提交。区域性要求见附录 5。见附录 6 关于如何提交包含纸质文件和电子文件的 CTD 的说明。

附录 2：eCTD 提交

引言

本附录阐述了 eCTD 提交文件的技术信息内容。简言之，eCTD 提交是带有文档的目录结构，文档包括 XMLeCTD 实例、报告、数据和其他提交资料。eCTD 提交支持多语言和多区域提交。

eCTD 提交

- eCTD 提交文件是遵循 eCTD 规范的数据对象的集合。eCTD 提交的主要功能是进行数据交换。需要开发信息系统以处理 eCTD 提交文件。eCTD 最大优势是当 eCTD 提交文档载入信息系统时，系统可支持电子审评流程。但是，由于 eCTD 具有支持 Web 浏览特性，eCTD 提交文件也可以通过 Web 浏览器查看。

eCTD 提交由下列构成：

- 目录结构
- XML eCTD 实例
- 内容文件

目录结构

目录结构是目录和文件的结构。每个目录应当有合理最大数目的条目（目录和文件）。目录结构应遵循以下规则。这些文件可以为如下所示的几种格式。

文件和目录名称是标识符。它们应该很简短。文件名称不必表达元数据的内容，尽管一些名称的含义对了解元数据的内容有所帮助（即，无随机名称。）

附录 4 列出的目录结构推荐使用但不强制要求。被申请人添加到 eCTD 提交文件的任何目录名称和文件名称应为描述性的、符合逻辑并且简洁的。

XML eCTD 实例

实例在提交序号目录（见附录 6）。提交序号目录应至少包含两个文件和一个或多个目录。在提交序列目录中的一个文件应为一个实例，其他的应为该实例的 MD5 校验和。该实例是 XML 处理器进行处理的起始文件。

其目的是提供从实例的叶元素到 eCTD 提交文件中的文件的链接，而不是创建一个包含整个 eCTD 提交文件的单独的 XML 文件。实例还包含在叶元素层级上的元数据。

eCTD 模板

ICH 网站（http://estri.ich.org/eCTD）提供了空的 eCTD 文件夹模板作为 eCTD 提交文件文件夹结构示例。它展示了附录 4 所示模块 2-5 的全部可能的文件夹，可填充申请人的资料并进行适当的

修改（即增加子文件夹，或删除不必要的文件夹）。申请人还可以添加有关的区域模块 1 文件夹和内容，添加适当的所需文件夹和内容，并创建 XML 索引文件，以完成有效的 eCTD 提交。

格式

应监管流程需要，格式至少应该是可读。该程序可能会很长（例如，50 年）。这显示了中性格式的优势：正式的标准、行业标准、独立于供应商的、文本类。该格式应符合数据类型。附录 7 阐述了构建这些文件的方式。

商定的格式的列表将随着技术的发展和新的要求的提出而更新。XML 将是所有类型数据的首选格式。

通用格式

可以包含在 eCTD 提交文件的通用格式如下：

- 叙述性的：可携式文件格式（PDF）
- 结构式：可扩展的标记语言（XML）
- 图表的：可能的情况下尽量使用 PDF 格式。在适当的时候，或不能使用 PDF 时，使用联合图像专家组（JPEG）、便携式网络图像格式形（PNG），可伸缩矢量图形（SVG）和图形交换格式（GIF）。根据个案，在适当的情况下可以使用高分辨率的特殊格式。

其他格式的区域性使用

监管机构和申请人可以商定区域性地使用其它格式（即非通用格式或以与上述方式不同的方式使用通用格式）。不建议使用其他格式，此目的是为了尽可能使用统一的格式。使用其他格式的目的是为了转换。

有两种形式的转换：

- 遗留转换：从过去到现在（即旧的格式到目前的格式。）
- 未来转换：从现在到未来（即从目前的格式到新的格式。）新的格式通常为统一格式的候选格式。

链接

CTD 交叉引用可以在 eCTD 中通过使用超链接得到支持。在 eCTD 提交文件中的对象之间的超链接应是相对的。其目的是使 eCTD 提交文件独立。由申请人引入的所有参考文献应包含在提交文件中。

可以一直指向一个文件。指向一个文件中特定位置的能力取决于链接技术。不同的格式允许使用不同的链接技术。见附录 7。

显示

显示与格式密切相关。为了使样式表与一文件联系起来，通常必须使用链接技术。样式表（可以在一个单独的文件中）和一个数据文件之间的链接应该是相对的。此外，还有媒介的尺寸。一个文件可以有多个样式表，根据媒介确定采用哪一种样式表。例如，可以一个用于屏幕显示，另一个通过纸质显示。

校验和

eCTD 提交文件应包含针对每个单独文件的校验和，包括 eCTD XML 实例校验和。最初，MD5 信息摘要算法（MD5）应用于此目的。为每个独立的文件校验有很多好处，包括：

- 每个文件的完整性可以通过比较随文件一同提交的验证和与计算的校验和来进行验证。
- 校验和可以用来验证在监管机构历史档案中的文件尚未被改变。当文件被从一个存储媒介转移至另一个存储媒介时，此校验是特别有用的，例如备份到磁带存储器。

文件目录映射元素

建议遵循以下规则：

- 优先考虑以下文件和目录规则，
- 添加文件的相应扩展名，
- 如果合适，使用合理的缩写。

文件扩展名

所有文件应有一个且仅有一个文件扩展名。文件扩展名应该用来表示文件的格式。例如：

hello.pdf	PDF
hello.rtf	RTF

格式和扩展名的之间的映射如下：

IANA 系统命名法

text/css	css
text/html	html or htm
text/xml	xml
application/pdf	pdf
application/rtf	rtf
application/vnd.ms-excel	xls
image/jpeg	jpg
image/png	png
image/gif	gif

非 IANA 系统命名法

DTD	dtd
XPT (SAS)	xpt
XSL	xsl

eCTD 提交文件可以使用未在互联网编号分配委员会（IANA）注册的格式。

出现在此列表中列举的格式并不意味着该格式就是可以接受的格式。未在此列表中列举的格式被广泛用于各种格式和扩展名之间的映射。

未来的趋势：如果一个机制（例如，标准）可用，其将文件扩展名和格式联系在一起，则应将其视为符合本规范。

名称

名称是下列字符组成的标记：

- 字母“a”至“z”[U+0061 to U+007A].
- 数字“0”至“9”[U+0030 to U+0039].
- "-" [HYPHEN-MINUS, U+002D].

符号“U +”指的是统一的字符编码标准的[UNICODE]符号。

本规范没有规定在文件和文件夹名称中的日文字符。

正确名称（仅为不带扩展名的名称）的示例：

part-b
myfile
hello

不正确名称（仅为不带扩展名的名称）的示例：

part a （' '；不允许空格)
myfile. （'.'；不允许句号）
xml
hello:pd （':'；不允许冒号）
f
part_a （‘_’，不允许下划线）
Parta （不允许大写字母）

目录名称是一个名称。

文件名是指被“.”分开的名称前面的名称（句号, U+002E）。

正确文件名称（带扩展名)：

myfile.pdf
hello.cml

不正确文件名称（带扩展名)：

a part.pdf （' '; 不允许空格）

hello （缺少扩展名）

hello:xm （':'; 不允许冒号）

单一文件夹名或文件名称的最大长度为 64 个字符，包括扩展名。在所有文件和目录名中仅可以使用小写字母。该路径的最大长度为 230 个字符，包括文件名和扩展名。这使得可以在审查环境中添加 26 个字符到路径。关于最大路径长度的其他限制请咨询区域指导文件。如果路径超过 230 个字符限制或区域规定的限制，则由申请人创建的文件夹和文件名称应该缩写。如果仍需要进一步削减，则文件名称和文件夹名称应按照附录 4 的建议应进行缩写。此外，申请人应征询区域媒介格式要求和 M2 专家工作组就媒介对文件夹的限制的相关建议。

文档名是在文件名称中的第一个名称。例如，在文件名“docname.ext”中的“docname”。

字符编码

字符编码（字符集）的优先排列顺序是：

- Unicode UTF-8, Unicode 16 位[ISO-10646]。
- ISO -8859 -1（拉丁语-1）或有关的 ISO -8859- x；例如，希腊语 ISO - 8859-7。
- 有关的 SHIFT_JIS。
- 由区域监管机构和申请人商定的其他字符编码。

参考文献

[CML] *Chemical Markup Language*
http://cml.sourceforge.net

[CSS2] *Cascading Style Sheets, level 2*
http://www.w3.org/TR/REC-CSS2

[ECMAScript] *ECMAScript Language Specification*, 3rd edition. ECMA- 262
http://www.ecma-international.org/publications/standards/Ecma-262.htm

[EXCEL] Microsoft Excel
http://www.microsoft.com/office/excel/default.htm

[GIF] *Graphics Interchange Format*
http://tronche.com/computer-graphics/gif/gif89a.html

[HTML] *HTML 4.01 Specification*
http://www.w3.org/TR/html4

[IANA] Internet Assigned Numbers Authority
http://www.iana.org

[IMT] Internet Media Types
http://www.iana.org/assignments/media-types/

[ISO-10646] Information Technology -- Universal Multiple-Octet Coded Character Set (UCS) -- Part 1: Architecture and Basic Multilingual Plane, ISO/IEC 10646-1:1993

[ISO-639] *Codes for the representation of names of languages*
ISO 639:1988.
http://www.oasis-open.org/cover/iso639a.html

[JPEG] Joint Photographic Experts Group
http://www.jpeg.org/public/wg1n1807.txt

[MD5] *The MD5 Message-Digest Algorithm*
http://ietf.org/rfc/rfc1321.txt

[PDF] *Portable Document Format*
http://www.adobe.com/devnet/pdf/pdf_reference.html

[PNG] *PNG (Portable Network Graphics) Specification Version 1.0*
http://www.w3.org/TR/REC-png.html

[RTF] *Rich Text Format (RTF) Specification, version 1.6*
http://msdn.microsoft.com/library/specs/rtfspec.htm

[SVG] *Scalable Vector Graphics (SVG) 1.0 Specification* (work in progress)
http://www.w3.org/TR/1999/WD-SVG-19991203

[UNICODE] Unicode Consortium
http://www.unicode.org

[XHTML] *XHTML 1.0: The Extensible HyperText Markup Language*
http://www.w3.org/TR/WD-html-in-xml

[XML] *Extensible Markup Language (XML) 1.0 (Second Edition)*
http://www.w3.org/TR/REC-xml.html

[XSL] *Extensible Stylesheet Language (XSL)*
Version 1.0 W3C Recommendation 15 October 2001
http://www.w3.org/TR/WD-xsl

[XSLT] *XSL Transformations*
http://www.w3.org/TR/xslt.html

附录 3：CTD 模块总则

引言

在不同的模块中提供的文件应采取 ICH 通用技术文档中规定的格式。此外还应与提供导航帮助的方式一致。在每个文件内，应在目录表中为所有表格、图表、发表文献及其附录提供书签和超文本链接。

应在整个文件提供超文本链接，以便向未在同一页的注释、相关章节、发表文献、附录、表格，以及数字提供有效的导航。CTD 交叉引用可以通过使用超链接在 eCTD 中获得支持。如果文件末尾包含引用列表，则应该有超文本链接将其链接到适当的文件。

应从电子源文件生成文件，而不是从扫描材料生成，除非不能获得电子源文件或有签字要求。

文件夹和文件命名规则

建议，但不强制，采用列于本规范的文件夹和文件名称。这些名称可用于大多数情况，但申请人可以在适当的情况下修改本规范[1]，例如，当 eCTD 技术规范中没有适用的文件夹名称时，添加额外的文件夹用于信息参考，或在建议的文件夹不充足时为额外的文件组织添加文件夹，都是被普遍接受的。建议申请人保持本规范列出的文件夹名称。这不应解释为实际 eCTD XML DTD 应被以任何方式改变或更改。

单一文件夹或文件的名称的最大长度为 64 个字符，其中包括扩展名。文件夹或文件名称应该仅为小写形式。所有文件应该有一个且仅有一个文件扩展名。文件扩展名应该用来表明文件的格式。关于命名规范的更多详情在附录 2 中阐述，附录 4 中有示例。

在 eCTD 中提供的文件名是可选的。为了在几个类似的文件同时打开的情况下协助审评人员，可以适当考虑能够提供独有的、容易被理解的文件名的其他命名规范。文件命名的一般规定在本规范的附录 2 中阐述。

通常，文件的名称是申请人的内部编号或用于研究的命名规范。下表给出了文件如何命名的例子。

[1] 如对文件夹结构进行任何补充和修改，应根据区域指导文件通知监管机构。

表3-1

描述	文件名

研究报告1	*study-report-1.pdf*
研究报告2	*study-report-2.pdf*
…	…
研究报告n	*study-report-n.pdf*

截图和文件夹层次结构

在以下章节中规定了关于所有模块直至本附录中所述层级的截图。由于计算机操作系统的性质，模块 3 的表述采纳了字母顺序，因此不完全符合 CTD 的顺序。在 Web 浏览器中内容将以 CTD 目录顺序显示。

文件夹和文件的详细选项在附录 4 阐述，如果申请人选择提交更详细的文件。不强制使用完整的文件夹层次结构。空目录可以省略，但是，如果内容是根据预期需要提及的，则应根据区域指南说明找不到该内容的理由。

模块 1 行政文件和药品信息

模块 1 文件夹的名称应该是 m1。

本模块包含每个区域独一无二的管理信息。区域指南将规定如何提供管理表格及详细的处方信息的具体说明。制作模块 1 时请参阅附录 5。

模块 2 概要

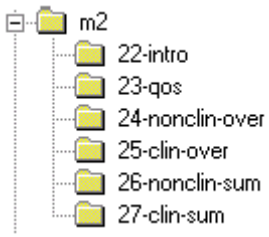
此模块中的文件应以 PDF 格式提供，嵌入图像除外。模块 2 的文件夹的名称应为 m2。在模块 2 中的文件夹应作如下命名，但可以进一步简化或省略，以尽量减少路径的长度。

表3-2

在 CTD 中的章节	描述	文件夹名
2.2	引言	*22-intro*
2.3	整体质量概述	*23-qos*
2.4	非临床综述	*24-nonclin-over*
2.5	临床综述	*25-clin-over*
2.6	非临床书面列表总结	*26-nonclin-sum*
2.7	临床概述	*27-clin-sum*

模块 2 的代表性文件夹层次结构在图 3-1 的截图中。

图 3-1 模块 2 文件夹结构的截图示例



模块 3 质量

模块 3 的文件夹的名称应为 *m3*。在模块 3 中的文件夹应作如下命名，但可以进一步简化或省略，以尽量减少路径的长度。

表3-3

CTD章节	描述	文件夹名称
3.2	数据主体	*32-body-data*
3.2.S	原料药	*32s-drug-sub*
3.2.S	原料药[原料药名称][生产商][2]	*substance-1-manufacturer-1*
3.2.S.1	基本信息（名称，生产商）	*32s1-gen-info*
3.2.S.2	生产（名称，生产商）	*32s2-manuf*
3.2.S.3	特性鉴定（名称，生产商）	*32s3-charac*
3.2.S.4	原料药质量控制（名称，生产商）	*32s4-contr-drug-sub*
3.2.S.4.1	质量标准（名称，生产商）	*32s41-spec*
3.2.S.4.2	分析方法（名称，生产商）	*32s42- analyt-proc*
3.2.S.4.3	分析方法验证（名称，生产商）	*32s43-val-analyt-proc*
3.2.S.4.4	批次分析（名称，生产商）	*32s44-batch-analys*
3.2.S.4.5	质量标准的制定依据（名称，剂型）	*32s45-justif-spec*
3.2.S.5	参考标准品或材料（名称，生产商）	*32s5-ref-stand*
3.2.S.6	容器密封系统（名称，生产商）	*32s6-cont-closure-sys*
3.2.S.7	稳定性（名称，生产商）	*32s7-stab*
3.2.P	制剂（名称，剂型）[3]	*32p-drug-prod*
3.2.P	制剂（名称，剂型） - *名称*	*product-1*
3.2.P.1	剂型及产品组成（名称，剂型）	*32p1-desc-comp*
3.2.P.2	产品开发（名称、剂型）	*32p2-pharm-dev*

[2] 每个原料药生产商组合应放置在一个单独的下级文件夹。按照下面章节确定的级别为包含在提交文件中的每个原料药生产商章节创建文件夹和文件。

[3] 每种制剂应放置在一个单独的下级文件夹中。按照下面章节确定的级别为包含在提交文件中的每个制剂章节创建文件夹和文件。应参阅区域指导以确定在一项申请中包含了多个产品是否适当。

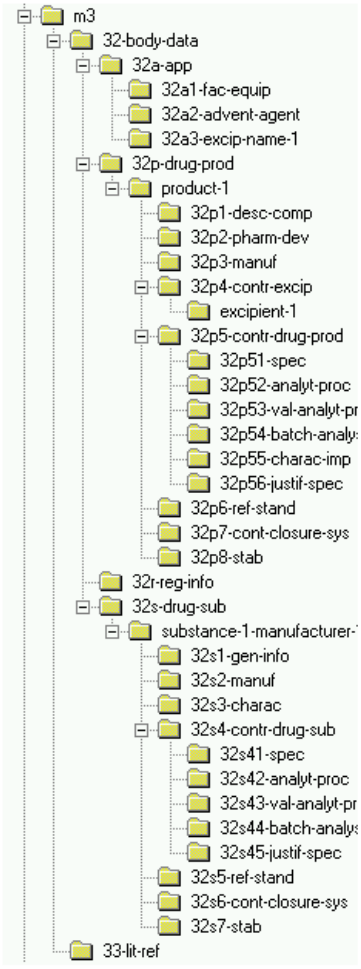
CTD章节	描述	文件夹名称
3.2.P.3	生产（名称，剂型）	*32p3-manuf*
3.2.P.4	辅料控制（名称、剂型）	*32p4-contr-excip*
3.2.P.4	辅料控制（名称、剂型） - *辅料1*	*excipient-1*
3.2.P.5	制剂控制（名称，剂型）	*32p5-contr-drug-prod*
3.2.P.5.1	质量标准（名称，剂型）	*32p51-spec*
3.2.P.5.2	分析方法（名称，剂型）	*32p52-analyt-proc*
3.2.P.5.3	分析方法验证（名称，剂型）	*32p53-val-analyt-proc*
3.2.P.5.4	批次分析（名称，剂型）	*32p54-batch-analys*

3.2.P.5.5	杂质鉴定（名称，剂型）	*32p55-charac-imp*
3.2.P.5.6	质量标准的制定依据（名称，剂型）	*32p56-justif-spec*
3.2.P.6	参考标准品或材料（名称，剂型）	*32p6-ref-stand*
3.2.P.7	容器密封系统（名称，剂型）	*32p7-cont-closure-sys*
3.2.P.8	稳定性（名称，剂型）	*32p8-stab*
3.2.A	附件	*32a-app*
3.2.A.1	设施和设备（名称，生产商）	*32a1-fac-equip*
3.2.A.2	外源性物质安全性评估（名称、剂型、生产商）	*32a2-advent-agent*
3.2.A.3	新型辅料-名称 [4]	*32a3-excip-name-1*
3.2.R	区域信息 [5]	*32r-reg-info*
3.3	参考文献	*33-lit-ref*

[4] 文件夹的名称应包括辅料名称，为保证长度在 64 个字符内，可做必要的缩减。
[5] 适于区域信息时应包括此文件夹。本章节应包含的信息类型应参考区域指导。

模块 3 的代表性文件夹层次结构在图 3-2 的截图中。

图 3-2 模块 3 文件夹结构的截图示例



模块 4 非临床研究报告

模块 4 的文件夹的名称应为 m4。在模块 4 中的文件夹应作如下命名，但可以进一步简化或省

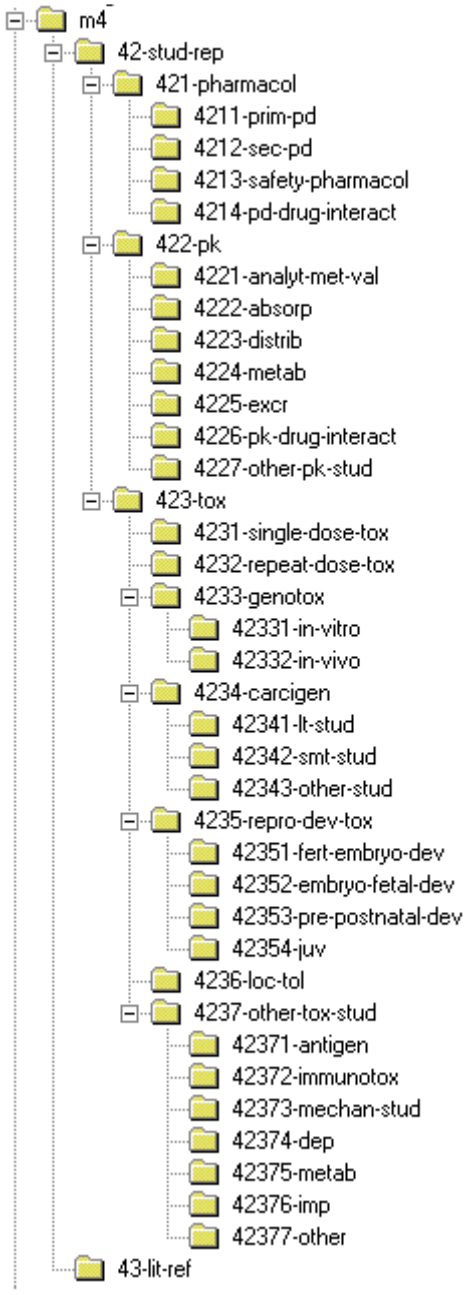
略，以尽量减少路径的长度。

表 3-4

CTD章节	描述	文件夹名称
4.2	研究报告	*42-stud-rep*
4.2.1	药理学	*421-pharmacol*
4.2.1.1	主要药效学	*4211-prim-pd*
4.2.1.2	次要药效学	*4212-sec-pd*
4.2.1.3	安全药理学	*4213-safety-pharmacol*
4.2.1.4	药效学药物相互作用	*4214-pd-drug-interact*
4.2.2	药代动力学	*422-pk*
4.2.2.1	分析方法和验证报告（如果存在单独报告）	*4221-analyt-met-val*
4.2.2.2	吸收	*4222-absorp*
4.2.2.3	分布	*4223-distrib*
4.2.2.4	代谢	*4224-metab*
4.2.2.5	排泄	*4225-excr*
4.2.2.6	药代动力学药物相互作用（非临床）	*4226-pk-drug-interact*
4.2.2.7	其他药代动力学研究	*4227-other-pk-stud*
4.2.3	毒理学	*423-tox*
4.2.3.1	单次给药毒性（按照种属、给药途径顺序）	*4231-single-dose-tox*
4.2.3.2	重复给药毒性（按照种属、给药、持续时间顺序，包括支持性的毒代动力学评价）	*4232-repeat-dose-tox*
4.2.3.3	遗传毒性	*4233-genotox*
4.2.3.3.1	体外	*42331-in-vitro*
4.2.3.3.2	体内（包括支持性的毒代动力学评价）	*42332-in-vivo*
4.2.3.4	致癌性（包括支持性的毒代动力学评价）	*4234-carcigen*
4.2.3.4.1	长期研究（按照种属顺序，包括不能恰当纳入重复给药毒性或药代动力学内的剂量范围探索研究）	*42341-lt-stud*
4.2.3.4.2	短期或中期研究（包括不能恰当纳入重复给药毒性或药代动力学内的剂量范围探索研究）	*42342-smt-stud*
4.2.3.4.3	其他研究	*42343-other-stud*
4.2.3.5	生殖与发育毒性（包括剂量范围探索研究和支持性的毒代动力学评价）	*4235-repro-dev-tox*
4.2.3.5.1	生育和早期胚胎发育	*42351-fert-embryo-dev*
4.2.3.5.2	胚胎及胎儿发育	*42352-embryo-fetal-dev*
4.2.3.5.3	产前和产后发育，包括母体功能	*42353-pre-postnatal-dev*
4.2.3.5.4	子代（动物幼仔）给药研究和/或进一步的评估	*42354-juv*
4.2.3.6	局部耐受性	*4236-loc-tol*
4.2.3.7	其他毒性研究（如适用）	*4237-other-tox-stud*
4.2.3.7.1	抗原性	*42371-antigen*
4.2.3.7.2	免疫毒性	*42372-immunotox*
4.2.3.7.3	机制研究（如未在他处纳入）	*42373-mechan-stud*
4.2.3.7.4	依赖性	*42374-dep*
4.2.3.7.5	代谢	*42375-metab*
4.2.3.7.6	杂质	*42376-imp*
4.2.3.7.7	其他	*42377-other*
4.3	参考文献	*43-lit-ref*

代表一个模块 4 的代表性文件夹层次结构在图 3-3 的截图中展示。

图 3-3 模块 4 文件夹结构的截图示例



模块 5 临床研究报告

模块 5 的文件夹的名称应为 m5。在模块 5 中的文件夹应作如下命名，但可以进一步简化或省略，以尽量减少路径的长度。

表 3-5

CTD章节	描述	文件夹名称
5.2	所有临床研究的行列表	*52-tab-list*

CTD章节	描述	文件夹名称
5.3	临床研究报告	*53-clin-stud-rep*
5.3.1	生物药学研究报告	*531-rep-biopharm-stud*
5.3.1.1	生物利用度（BA）研究报告	*5311-ba-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.1.2	比较性 BA 和生物等效性（BE）研究报告	*5312-compar-ba-be-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.1.3	体外 - 体内相关性研究报告	*5313-in-vitro-in-vivo-corr-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.1.4	人体研究的生物分析和分析方法报告	*5314-bioanalyt-analyt-met*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.2	使用人类生物材料的药代动力学研究报告	*532-rep-stud-pk-human-biomat*
5.3.2.1	血浆蛋白结合研究报告	*5321-plasma-prot-bind-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.2.2	肝脏代谢和药物相互作用研究报告	*5322-rep-hep-metab-interact-stud*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.2.3	使用其他人类生物材料的研究报告	*5323-stud-other-human-biomat*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.3	人体药代动力学（PK）研究	*533-rep-human-pk-stud*
5.3.3.1	健康受试者 PK 和初步耐受性研究报告	*5331-healthy-subj-pk-init-tol-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.3.2	患者PK和初步耐受性研究报告	*5332-patient-pk-init-tol-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.3.3	内在因素 PK 研究报告	*5333-intrin-factor-pk-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.3.4	外在因素PK研究报告	*5334-extrin-factor-pk-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.3.5	群体 PK 研究报告	*5335-popul-pk-stud-rep*
	“研究报告1”	*study-report-1*

CTD章节	描述	文件夹名称
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.4	人体药效学（PD）研究报告	*534-rep-human-pd-stud*
5.3.4.1	健康受试者 PD 和 PK /PD 研究报告	*5341-healthy-subj-pd-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.4.2	患者PD和PK/PD研究报告	*5342-patient-pd-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.5	有效性和安全性研究报告	*535-rep-effic-safety-stud*
5.3.5	有效性和安全性研究报告 – 适应症名称	*indication-1*
5.3.5.1	与声明适应症相关的对照临床研究的研究报告	*5351-stud-rep-contr*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.5.2	非对照临床研究报告	*5352-stud-rep-uncontr*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.5.3	多项研究数据的分析报告	*5353-rep-analys-data-more-one-stud*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.5.4	其他研究报告	*5354-other-stud-rep*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.3.6	上市后经验报告	*536-postmark-exp*
5.3.7	病例报告表和个体患者列表 [6]	*537-crf-ipl*
	“研究报告1”	*study-report-1*
	“研究报告2”	*study-report-2*
	“研究报告3”	*study-report-3*
5.4	参考文献	*54-lit-ref*

CTD 组织规定了模块 5.3.7 中的病例报告表和个体患者数据列表以及模块 5.4 中的参考文献的位置。

在 eCTD 中，发表文献和参考文献的文件应位于模块 5.4 的文件夹中。然而，在 index.xml 文件中，这些发表文献和参考文献的叶元素应与通过使用研究标记文件的方式包含额外信息的其他研究报告文件位于同一标题下（如适用于该区域）。此外叶元素重复应置于模块 5.4 参考文献的标题下。

[6] 文件夹的内容应遵循区域指导规定。

病例报告表，数据集和个体患者数据列表应根据区域指导进行组织。

模块 5 的代表性文件夹层次结构可参见图 3-4。

图 3-4 模块 5 文件夹结构的截图示例

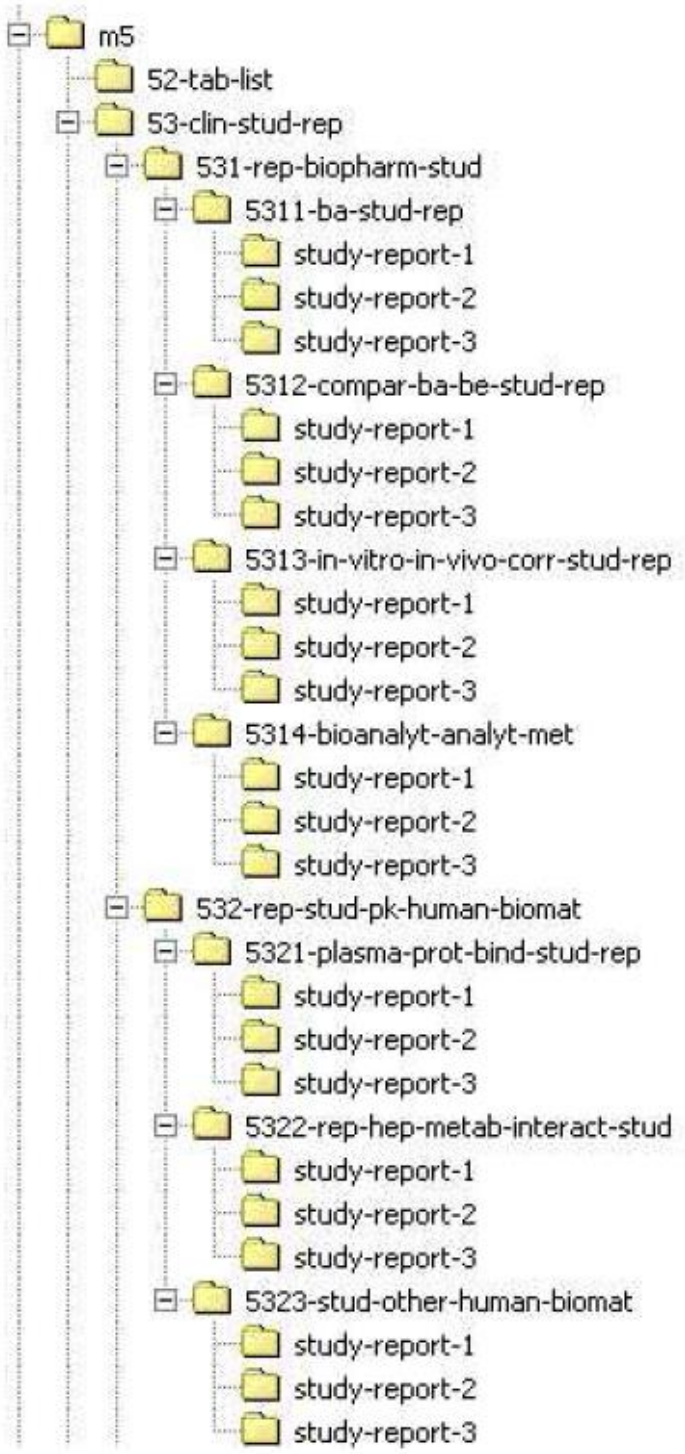


图 3-4 模块 5 文件夹结构的截图示例（续）

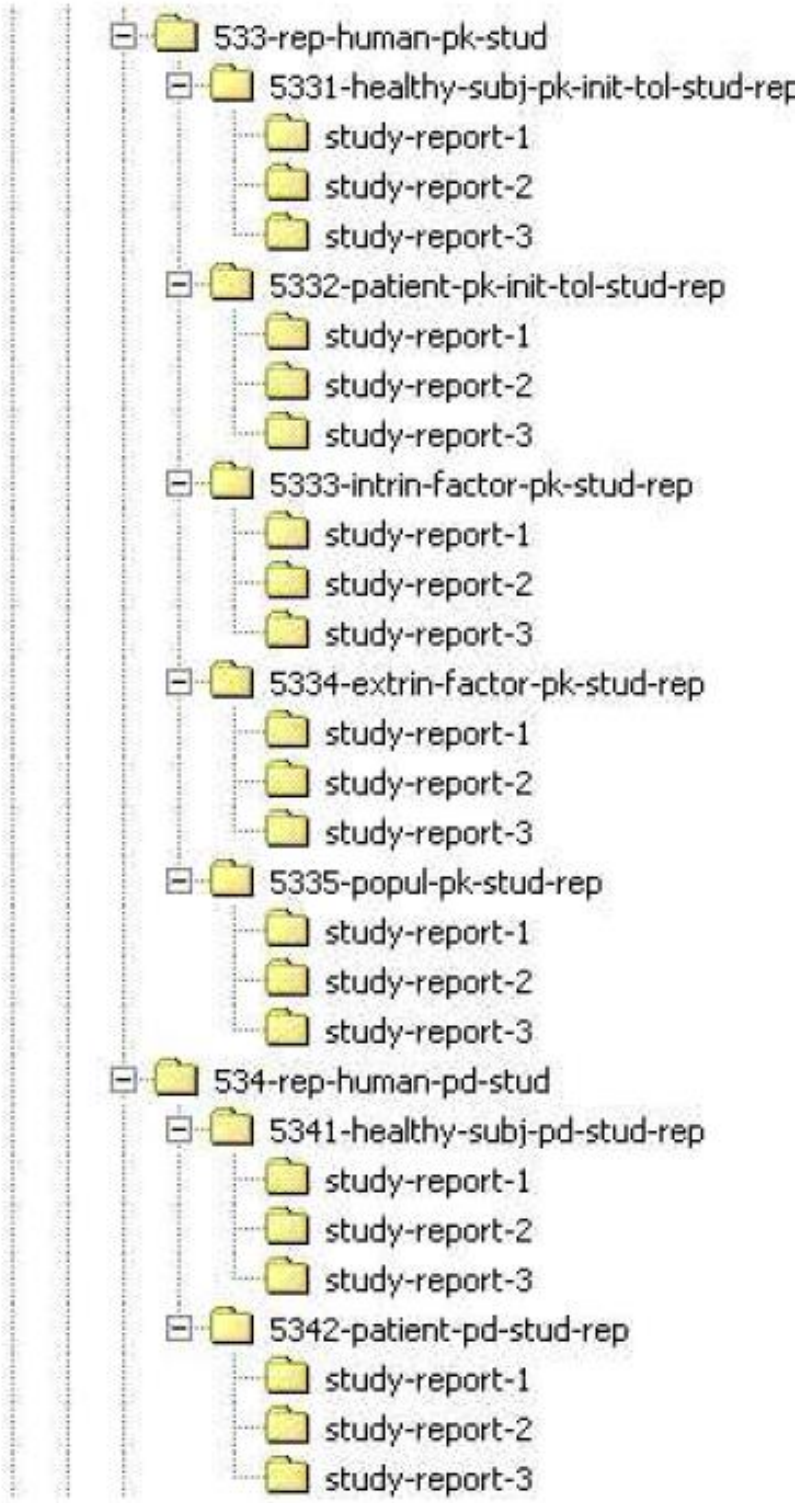
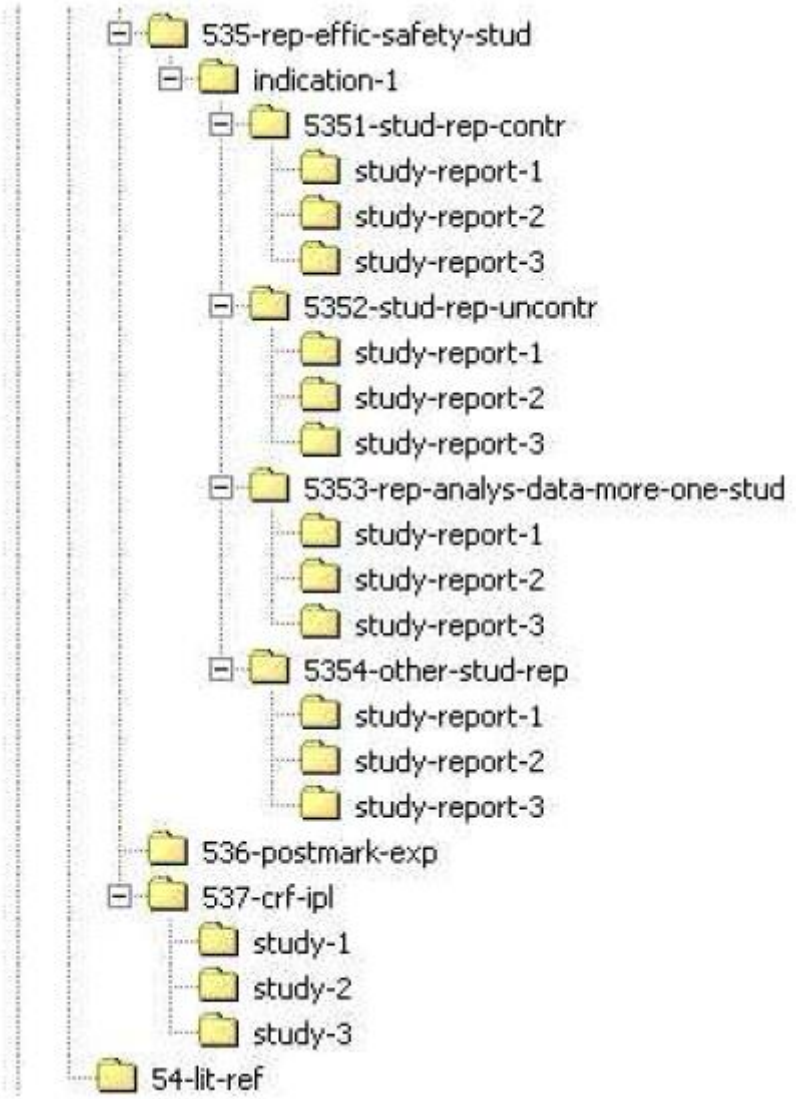


图 3-4 模块 5 文件夹结构的截图示例（续）


535-rep-effic-safety-stud
indication-1
5351-stud-rep-contr
study-report-1
study-report-2
study-report-3
5352-stud-rep-uncontr
study-report-1
study-report-2
study-report-3
5353-rep-analys-data-more-one-stud
study-report-1
study-report-2
study-report-3
5354-other-stud-rep
study-report-1
study-report-2
study-report-3
536-postmark-exp
537-crf-ipl
study-1
study-2
study-3
54-lit-ref

附录 4：eCTD 文件组织结构

本附录所列文件组织表中的每个项目包括下述信息：

Sequential number		Each item in the table has a unique sequentially assigned reference number. These reference numbers can change with each version of this appendix.
	Number	CTD section number
	Title	CTD title
	Element	Element name in the Backbone
	File/Directory	Relative path of the File/Directory. The file extension corresponds to the file type; i.e., the “pdf” extension is only illustrative. Refer to Table 6.1, Appendix 6, for details for the head of the path name
	Comment	Comments

文件组织表包含构成主干的文件，以及附加文件，从而使提交文件完整、可读并可处理。模块 2-5 所示文件和文件夹名称不是强制性的，但建议予以使用，可以进一步缩减或省略以避免路径长度超过规定长度。适用多个文档/文件的 eCTD 的各章节或次章节的相关信息，请参阅 M4 组织文件：“关于注册人用药品的通用技术文档的组织”的 ICH 指导中粒度附件。该文件说明了什么被认为是 CTD 各章节以及 eCTD 的适当的组成部分。凡在此组织文件中未说明的，申请人可以自由构建其认为与粒度文件匹配的档案资料。

凡文件和文件夹名称为斜体的，申请人应根据其自己的命名规范以合适的文件名替代这些名称。

表 4-1

1	Number	
	Title	
	Element	
	File	index.xml
	Comment	This is the Backbone
2	Number	
	Title	
	Element	
	File	index-md5.txt
	Comment	The MD5 of the Backbone
3	Number	1
	Title	Administrative Information and Prescribing Information
	Element	m1-administrative-information-and-prescribing-information
	Directory	m1
	Comment	Only one of the regional directories is needed
4	Number	
	Title	
	Element	
	Directory	m1/eu
	Comment	EU directory: In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
5	Number	
	Title	

	Element	
	Directory	m1/jp
	Comment	Japan directory: In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
6	Number	
	Title	
	Element	
	Directory	m1/us
	Comment	US directory: In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
7	Number	
	Title	
	Element	
	Directory	m1/xx
	Comment	xx directory; where xx is a two character country code from ISO-3166-1. In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
8	Number	2
	Title	Common Technical Document Summaries
	Element	m2-common-technical-document-summaries
	Directory	m2
	Comment	
9	Number	2.2
	Title	Introduction
	Element	m2-2-introduction
	Directory	m2/22-intro
	Commen	

	t	
10	Number	2.2
	Title	Introduction
	Element	m2-2-introduction
	File	m2/22-intro/introduction.pdf
	Comment	
11	Number	2.3
	Title	Quality Overall Summary
	Element	m2-3-quality-overall-summary
	Directory	m2/23-qos
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for the Quality Overall Summary
12	Number	2.3
	Title	Introduction
	Element	m2-3-introduction
	File	m2/23-qos/introduction.pdf
	Comment	
13	Number	2.3.S
	Title	Drug Substance - *Name* - *Manufacturer*
	Element	m2-3-s-drug-substance
	File	m2/23-qos/drug-substance.pdf
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for the Quality Overall Summary Where there are more than one drug substance and/or manufacturer, separate files can be provided for each.
14	Number	2.3.P

	Title	Drug Product -*Name*
	Element	m2-3-p-drug-product
	File	m2/23-qos/drug-product-*name*.pdf
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for the Quality Overall Summary Refer to regional guidance for definition of what constitutes a drug product and the acceptability of more than one drug product in an application. Where more than one drug product is acceptable in an application, a separate file can be provided for each drug product.
15	Number	2.3.A
	Title	Appendices
	Element	m2-3-a-appendices
	File	m2/23-qos/appendices.pdf
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for the Quality Overall Summary
16	Number	2.3.R
	Title	Regional Information
	Element	m2-3-r-regional-information
	File	m2/23-qos/regional-information.pdf
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for the Quality Overall Summary
17	Number	2.4
	Title	Nonclinical Overview
	Element	m2-4-nonclinical-overview
	Directory	m2/24-nonclin-over
	Comment	
18	Number	2.4
	Title	Nonclinical Overview

	Element	m2-4-nonclinical-overview
	File	m2/24-nonclin-over/nonclinical-overview.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
19	Number	2.5
	Title	Clinical Overview
	Element	m2-5-clinical-overview
	Directory	m2/25-clin-over
	Comment	
20	Number	2.5
	Title	Clinical Overview
	Element	m2-5-clinical-overview
	File	m2/25-clin-over/clinical-overview.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
21	Number	2.6
	Title	Nonclinical Written and Tabulated Summaries
	Element	m2-6-nonclinical-written-and-tabulated-summaries
	Directory	m2/26-nonclin-sum
	Comment	
22	Number	2.6.1
	Title	Introduction
	Element	m2-6-1-introduction
	File	m2/26-nonclin-sum/introduction.pdf
	Commen	

	t	
23	Number	2.6.2
	Title	Pharmacology Written Summary
	Element	m2-6-2-pharmacology-written-summary
	File	m2/26-nonclin-sum/pharmacol-written-summary.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
24	Number	2.6.3
	Title	Pharmacology Tabulated Summary
	Element	m2-6-3-pharmacology-tabulated-summary
	File	m2/26-nonclin-sum/pharmacol-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
25	Number	2.6.4
	Title	Pharmacokinetics Written Summary
	Element	m2-6-4-pharmacokinetics-written-summary
	File	m2/26-nonclin-sum/pharmkin-written-summary.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
26	Number	2.6.5
	Title	Pharmacokinetics Tabulated Summary
	Element	m2-6-5-pharmacokinetics-tabulated-summary
	File	m2/26-nonclin-sum/pharmkin-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
27	Number	2.6.6
	Title	Toxicology Written Summary

	Element	m2-6-6-toxicology-written-summary
	File	m2/26-nonclin-sum/toxicology-written-summary.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
28	Number	2.6.7
	Title	Toxicology Tabulated Summary
	Element	m2-6-7-toxicology-tabulated-summary
	File	m2/26-nonclin-sum/toxicology-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
29	Number	2.7
	Title	Clinical Summary
	Element	m2-7-clinical-summary
	Directory	m2/27-clin-sum
	Comment	
30	Number	2.7.1
	Title	Summary of Biopharmaceutic Studies and Associated Analytical Methods
	Element	m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods
	File	m2/27-clin-sum/summary-biopharm.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
31	Number	2.7.2
	Title	Summary of Clinical Pharmacology Studies
	Element	m2-7-2-summary-of-clinical-pharmacology-studies
	File	m2/27-clin-sum/summary-clin-pharm.pdf

	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
32	Number	2.7.3
	Title	Summary of Clinical Efficacy – *Indication*
	Element	m2-7-3-summary-of-clinical-efficacy
	File	m2/27-clin-sum/summary-clin-efficacy-*indication.pdf*
	Comment	The file name should always include the indication being claimed (abbreviated if appropriate) e.g., 'summary-clin-efficacy-asthma.pdf'. Where there is more than one indication (e.g., asthma & migraine) then the first indication has a file name 'summary-clin-efficacyasthma.pdf' and the second 'summary-clin-efficacy-migraine.pdf'. Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings. The 'indication' attribute in the backbone should be consistent with that used in the filename but can be different. For example, an 'indication' attribute value of 'Non-Small Cell Lung Cancer' could be expressed as 'NSCLC' in the filename for that document (i.e., summclineff-nsclc.pdf). There is currently no standard terminology list for 'indication' and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
33	Number	2.7.4
	Title	Summary of Clinical Safety
	Element	m2-7-4-summary-of-clinical-safety
	File	m2/27-clin-sum/summary-clin-safety.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
34	Number	2.7.5
	Title	Literature References
	Element	m2-7-5-literature-references
	File	m2/27-clin-sum/literature-references.pdf

	Comment	
35	Number	2.7.6
	Title	Synopses of Individual Studies
	Element	m2-7-6-synopses-of-individual-studies
	File	m2/27-clin-sum/synopses-indiv-studies.pdf
	Comment	These synopses should already be located in the Clinical Study Reports in Module 5 and should not, therefore, be repeated in Module 2. It is considered sufficient to provide hyperlinks from the listing of the studies, located here, to the locations of the synopses in Module 5.
36	Number	3
	Title	Quality
	Element	m3-quality
	Directory	m3
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for Module 3
37	Number	3.2
	Title	Body of Data
	Element	m3-2-body-of-data
	Directory	m3/32-body-data
	Comment	
38	Number	3.2.S
	Title	Drug Substance
	Element	m3-2-s-drug-substance
	Directory	m3/32-body-data/32s-drug-sub
	Comment	
39	Number	3.2.S
	Title	Drug Substance - *Drug Substance Name - Manufacturer*
	Element	m3-2-s-drug-substance
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*

	Comment	In this section, it can be helpful if the folder name includes the name of the drug substance and manufacturer. This applies particularly when there are multiple drug substances and/or manufacturers. When naming folders, attention should be paid to the length of the name of the folder on the overall length of the full path. Abbreviations can help control the length of the path. The 'substance' and 'manufacturer' attribute values in the backbone should be consistent with that used in the folder name but can be different. For example, a 'manufacturer' attribute value of 'Company XXX, City Name, Country Name' could be expressed as 'xxx' in the folder name. There is currently no standard terminology list for these attributes and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
40	Number	3.2.S.1
	Title	General Information (name, manufacturer)
	Element	m3-2-s-1-general-information
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info
	Comment	
41	Number	3.2.S.1.1
	Title	Nomenclature (name, manufacturer)
	Element	m3-2-s-1-1-nomenclature
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info/nomenclature.pdf
	Comment	
42	Number	3.2.S.1.2
	Title	Structure (name, manufacturer)
	Element	m3-2-s-1-2-structure
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info/structure.pdf
	Commen	

	t	
43	Number	3.2.S.1.3
	Title	General Properties (name, manufacturer)
	Element	m3-2-s-1-3-general-properties
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info/general-properties.pdf
	Comment	
44	Number	3.2.S.2
	Title	Manufacture (name, manufacturer)
	Element	m3-2-s-2-manufacture
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf
	Comment	
45	Number	3.2.S.2.1
	Title	Manufacturer(s) (name, manufacturer)
	Element	m3-2-s-2-1-manufacturer
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/manufacturer.pdf
	Comment	For this document there should be only information regarding one manufacturer
46	Number	3.2.S.2.2
	Title	Description of Manufacturing Process and Process Controls (name, manufacturer)
	Element	m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/manuf-process-and-controls.pdf
	Comment	
47	Number	3.2.S.2.3
	Title	Control of Materials (name, manufacturer)

	Element	m3-2-s-2-3-control-of-materials
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/control-of-materials.pdf
	Comment	
48	Number	3.2.S.2.4
	Title	Controls of Critical Steps and Intermediates (name, manufacturer)
	Element	m3-2-s-2-4-controls-of-critical-steps-and-intermediates
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/control-critical-steps.pdf
	Comment	
49	Number	3.2.S.2.5
	Title	Process Validation and/or Evaluation (name, manufacturer)
	Element	m3-2-s-2-5-process-validation-and-or-evaluation
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/process-validation.pdf
	Comment	
50	Number	3.2.S.2.6
	Title	Manufacturing Process Development (name, manufacturer)
	Element	m3-2-s-2-6-manufacturing-process-development
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/manuf-process-development.pdf
	Comment	
51	Number	3.2.S.3
	Title	Characterisation (name, manufacturer)
	Element	m3-2-s-3-characterisation
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s3-charac
	Commen	

	t	
52	Number	3.2.S.3.1
	Title	Elucidation of Structure and Other Characteristics (name, manufacturer)
	Element	m3-2-s-3-1-elucidation-of-structure-and-other-characteristics
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s3-charac/elucidation-of-structure.pdf
	Comment	
53	Number	3.2.S.3.2
	Title	Impurities (name, manufacturer)
	Element	m3-2-s-3-2-impurities
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s3-charac/impurities.pdf
	Comment	
54	Number	3.2.S.4
	Title	Control of Drug Substance (name, manufacturer)
	Element	m3-2-s-4-control-of-drug-substance
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub
	Comment	
55	Number	3.2.S.4.1
	Title	Specification (name, manufacturer)
	Element	m3-2-s-4-1-specification
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s41-spec
	Comment	
56	Number	3.2.S.4.1
	Title	Specification (name, manufacturer)

	Element	m3-2-s-4-1-specification
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s41-spec/specification.pdf
	Comment	
57	Number	3.2.S.4.2
	Title	Analytical Procedures (name, manufacturer)
	Element	m3-2-s-4-2-analytical-procedures
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, can be organized. CTD numbering is not defined below this level (e.g., 3.2.S.4.2.1).
58	Number	
	Title	*Analytical Procedure-1*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-1.pdf*
	Comment	
59	Number	
	Title	*Analytical Procedure-2*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-2.pdf*
	Comment	
60	Number	
	Title	*Analytical Procedure-3*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-3.pdf*
	Commen	

	t	
61	Number	3.2.S.4.3
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures (name, manufacturer)
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, can be organized. CTD numbering is not defined below this level (e.g., 3.2.S.4.3.1).
62	Number	
	Title	*Validation of Analytical Procedure-1*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-1.pdf*
	Comment	
63	Number	
	Title	*Validation of Analytical Procedure-2*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-2.pdf*
	Comment	
64	Number	
	Title	*Validation of Analytical Procedure-3*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-3.pdf*
	Commen	

	t	
65	Number	3.2.S.4.4
	Title	Batch Analyses (name, manufacturer)
	Element	m3-2-s-4-4-batch-analyses
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s44-batch-analys
	Comment	
66	Number	3.2.S.4.4
	Title	Batch Analyses (name, manufacturer)
	Element	m3-2-s-4-4-batch-analyses
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s44-batch-analys/batch-analyses.pdf
	Comment	
67	Number	3.2.S.4.5
	Title	Justification of Specification (name, manufacturer)
	Element	m3-2-s-4-5-justification-of-specification
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s45-justif-spec
	Comment	
68	Number	3.2.S.4.5
	Title	Justification of Specification (name, manufacturer)
	Element	m3-2-s-4-5-justification-of-specification
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s45-justif-spec/justification-of-specification.pdf
	Comment	
69	Number	3.2.S.5
	Title	Reference Standards or Materials (name, manufacturer)
	Element	m3-2-s-5-reference-standards-or-materials
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s5-ref-stand
	Comment	

70	Number	3.2.S.5
	Title	Reference Standards or Materials (name, manufacturer)
	Element	m3-2-s-5-reference-standards-or-materials
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s5-ref-stand/reference-standards.pdf
	Comment	Where a multiple file approach is taken for this section, the file names should indicate which reference standard is covered in the document.
71	Number	3.2.S.6
	Title	Container Closure System (name, manufacturer)
	Element	m3-2-s-6-container-closure-system
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s6-cont-closure-sys
	Comment	
72	Number	3.2.S.6
	Title	Container Closure System (name, manufacturer)
	Element	m3-2-s-6-container-closure-system
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s6-cont-closure-sys/container-closure-system.pdf
	Comment	
73	Number	3.2.S.7
	Title	Stability (name, manufacturer)
	Element	m3-2-s-7-stability
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab
	Comment	
74	Number	3.2.S.7.1
	Title	Stability Summary and Conclusions (name, manufacturer)
	Element	m3-2-s-7-1-stability-summary-and-conclusions
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab/stability-summary.pdf
	Commen	

	t	
75	Number	3.2.S.7.2
	Title	Post-approval Stability Protocol and Stability Commitment (name, manufacturer)
	Element	m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab/postapproval-stability.pdf
	Comment	
76	Number	3.2.S.7.3
	Title	Stability Data (name, manufacturer)
	Element	m3-2-s-7-3-stability-data
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab/stability-data.pdf
	Comment	
77	Number	3.2.P
	Title	Drug Product (name, dosage form)
	Element	m3-2-p-drug-product
	Directory	m3/32-body-data/32p-drug-prod
	Comment	
78	Number	3.2.P
	Title	Drug Product (name, dosage form) – *Name*
	Element	m3-2-p-drug-product
	Directory	m3/32-body-data/32p-drug-prod/*product-1*
	Comment	In this section, it can be helpful if the folder name includes the name of the drug product. This applies particularly where there is more than one drug product (e.g., powder for reconstitution and diluent); the first drug product would have a folder 'powder-for-reconstitution' and the second, 'diluent'. Refer to regional guidance for definition of what constitutes a drug product and the acceptability of more than one drug product in an

		application. The 'product-name' attribute value in the backbone should be consistent with that used in the folder name but can be different. For example, a 'product-name' attribute value of 'Lyophilized Powder for Reconstitution' could be expressed as 'powder' in the folder name. There is currently no standard terminology list for these attributes and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
79	Number	3.2.P.1
	Title	Description and Composition of the Drug Product (name, dosage form)
	Element	m3-2-p-1-description-and-composition-of-the-drug-product
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p1-desc-comp
	Comment	
80	Number	3.2.P.1
	Title	Description and Composition of the Drug Product (name, dosage form)
	Element	m3-2-p-1-description-and-composition-of-the-drug-product
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p1-desc-comp/description-and-composition.pdf
	Comment	
81	Number	3.2.P.2
	Title	Pharmaceutical Development (name, dosage form)
	Element	m3-2-p-2-pharmaceutical-development
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p2-pharm-dev
	Comment	Refer to the M4 Organisation Document: Granularity Annex for guidance on the flexibility of multiple documents for the Pharmaceutical Development section.
82	Number	3.2.P.2
	Title	Pharmaceutical Development (name, dosage form)

	Element	m3-2-p-2-pharmaceutical-development
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p2-pharm-dev/pharmaceutical-development.pdf
	Comment	Refer to the M4 Organisation Document: Granularity Annex for guidance on the flexibility of multiple documents for the Pharmaceutical Development section.
83	Number	3.2.P.3
	Title	Manufacture (name, dosage form)
	Element	m3-2-p-3-manufacture
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf
	Comment	
84	Number	3.2.P.3.1
	Title	Manufacturer(s) (name, dosage form)
	Element	m3-2-p-3-1-manufacturers
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/manufacturers.pdf
	Comment	
85	Number	3.2.P.3.2
	Title	Batch Formula (name, dosage form)
	Element	m3-2-p-3-2-batch-formula
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/batch-formula.pdf
	Comment	
86	Number	3.2.P.3.3
	Title	Description of Manufacturing Process and Process Controls (name, dosage form)
	Element	m3-2-p-3-3-description-of-manufacturing-process-and-process-controls
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/manuf-process-and-controls.pdf
	Commen	

	t	
87	Number	3.2.P.3.4
	Title	Controls of Critical Steps and Intermediates (name, dosage form)
	Element	m3-2-p-3-4-controls-of-critical-steps-and-intermediates
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/control-critical-steps.pdf
	Comment	
88	Number	3.2.P.3.5
	Title	Process Validation and/or Evaluation (name, dosage form)
	Element	m3-2-p-3-5-process-validation-and-or-evaluation
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/process-validation.pdf
	Comment	The applicant has the option to submit one or multiple files, one for each validation or evaluation.
89	Number	3.2.P.4
	Title	Control of Excipients (name, dosage form)
	Element	m3-2-p-4-control-of-excipients
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip
	Comment	
90	Number	3.2.P.4
	Title	Control of Excipients (name, dosage form) – *Excipient*
	Element	m3-2-p-4-control-of-excipients
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*

	Comment	For a drug product containing more than one excipient, the information requested for sections 3.2.P.4.1 – 3.2.P.4.4 should be provided in its entirety for each excipient. Refer to the ICH eCTD QA and Change Requests document, Q&A No.4 for additional suggestions on structuring this section. For compendial excipient(s) without additional specification tests, it is appropriate to have all information in one file, making sure to introduce a folder for each of new documents to avoid mixing files and folders at the same level. Non-compendial excipients should follow the structure outlined below. The 'excipient' attribute value in the backbone should be consistent with that used in the folder name but can be different. There is currently no standard terminology list for these attributes and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
91	Number	3.2.P.4.1
	Title	Specifications (name, dosage form)
	Element	m3-2-p-4-1-specifications
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/specifications.pdf
	Comment	See comment under 3.2.P.4.
92	Number	3.2.P.4.2
	Title	Analytical Procedures (name, dosage form)
	Element	m3-2-p-4-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/analytical-procedures.pdf
	Comment	See comment under 3.2.P.4.
93	Number	3.2.P.4.3
	Title	Validation of Analytical Procedures (name, dosage form)
	Element	m3-2-p-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/validation-analyt-procedures.pdf
	Comment	See comment under 3.2.P.4.
94	Number	3.2.P.4.4
	Title	Justification of Specifications (name, dosage form)

	Element	m3-2-p-4-4-justification-of-specifications
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/justification-of-specifications.pdf
	Comment	See comment under 3.2.P.4.
95	Number	3.2.P.4.5
	Title	Excipients of Human or Animal Origin (name, dosage form)
	Element	m3-2-p-4-5-excipients-of-human-or-animal-origin
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/excipients-human-animal.pdf
	Comment	
96	Number	3.2.P.4.6
	Title	Novel Excipients (name, dosage form)
	Element	m3-2-p-4-6-novel-excipients
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/novel-excipients.pdf
	Comment	
97	Number	3.2.P.5
	Title	Control of Drug Product (name, dosage form)
	Element	m3-2-p-5-control-of-drug-product
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod
	Comment	
98	Number	3.2.P.5.1
	Title	Specification(s) (name, dosage form)
	Element	m3-2-p-5-1-specifications
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p51-spec
	Comment	
99	Number	3.2.P.5.1
	Title	Specification(s) (name, dosage form)
	Element	m3-2-p-5-1-specifications

	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p51-spec/specifications.pdf
	Comment	
100	Number	3.2.P.5.2
	Title	Analytical Procedures (name, dosage form)
	Element	m3-2-p-5-2-analytical-procedures
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, may be organized. CTD numbering is not defined below this level (e.g., 3.2.P.5.2.1).
101	Number	
	Title	*Analytical Procedure – 1*
	Element	m3-2-p-5-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc/*analytical-procedure-1.pdf*
	Comment	
102	Number	
	Title	*Analytical Procedure – 2*
	Element	m3-2-p-5-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc/*analytical-procedure-2.pdf*
	Comment	
103	Number	
	Title	*Analytical Procedure – 3*
	Element	m3-2-p-5-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc/*analytical-procedure-3.pdf*
	Comment	
104	Number	3.2.P.5.3
	Title	Validation of Analytical Procedures (name, dosage form)
	Element	m3-2-p-5-3-validation-of-analytical-procedures

	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p53-val-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, may be organized. CTD numbering is not defined below this level (e.g., 3.2.P.5.3.1).
105	Number	
	Title	*Validation of Analytical Procedures – 1*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p53-val-analyt-proc/*validation-analytical-procedures-1.pdf*
	Comment	
106	Number	
	Title	*Validation of Analytical Procedures – 2*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p53-val-analyt-proc/*validation-analytical-procedures-2.pdf*
	Comment	
107	Number	
	Title	*Validation of Analytical Procedures – 3*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p53-val-analyt-proc/*validation-analytical-procedures-3.pdf*
	Comment	
108	Number	3.2.P.5.4
	Title	Batch Analyses (name, dosage form)
	Element	m3-2-p-5-4-batch-analyses
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p54-batch-analys
	Comment	
109	Number	3.2.P.5.4
	Title	Batch Analyses (name, dosage form)
	Element	m3-2-p-5-4-batch-analyses

	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p54-batch-analys/batch-analyses.pdf
	Comment	
110	Number	3.2.P.5.5
	Title	Characterisation of Impurities (name, dosage form)
	Element	m3-2-p-5-5-characterisation-of-impurities
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p55-charac-imp
	Comment	
111	Number	3.2.P.5.5
	Title	Characterisation of Impurities (name, dosage form)
	Element	m3-2-p-5-5-characterisation-of-impurities
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p55-charac-imp/characterisation-impurities.pdf
	Comment	
112	Number	3.2.P.5.6
	Title	Justification of Specifications (name, dosage form)
	Element	m3-2-p-5-6-justification-of-specifications
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p56-justif-spec
	Comment	
113	Number	3.2.P.5.6
	Title	Justification of Specifications (name, dosage form)
	Element	m3-2-p-5-6-justification-of-specifications
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p56-justif-spec/justification-of-specifications.pdf
	Comment	
114	Number	3.2.P.6
	Title	Reference Standards or Materials (name, dosage form)
	Element	m3-2-p-6-reference-standards-or-materials
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p6-ref-stand

	Comment	
115	Number	3.2.P.6
	Title	Reference Standards or Materials (name, dosage form)
	Element	m3-2-p-6-reference-standards-or-materials
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p6-ref-stand/reference-standards.pdf
	Comment	When a multiple file approach is taken for this section, the file names should indicate which reference standard is covered in the document.
116	Number	3.2.P.7
	Title	Container Closure System (name, dosage form)
	Element	m3-2-p-7-container-closure-system
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p7-cont-closure-sys
	Comment	
117	Number	3.2.P.7
	Title	Container Closure System (name, dosage form)
	Element	m3-2-p-7-container-closure-system
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p7-cont-closure-sys/container-closure-system.pdf
	Comment	
118	Number	3.2.P.8
	Title	Stability (name, dosage form)
	Element	m3-2-p-8-stability
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p8-stab
	Comment	
119	Number	3.2.P.8.1
	Title	Stability Summary and Conclusion (name, dosage form)
	Element	m3-2-p-8-1-stability-summary-and-conclusion
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p8-stab/stability-summary.pdf
	Comment	

120	Number	3.2.P.8.2
	Title	Post-approval Stability Protocol and Stability Commitment (name, dosage form)
	Element	m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p8-stab/postapproval-stability.pdf
	Comment	
121	Number	3.2.P.8.3
	Title	Stability Data (name, dosage form)
	Element	m3-2-p-8-3-stability-data
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p8-stab/stability-data.pdf
	Comment	
122	Number	3.2.A
	Title	Appendices
	Element	m3-2-a-appendices
	Directory	m3/32-body-data/32a-app
	Comment	
123	Number	3.2.A.1
	Title	Facilities and Equipment (name, manufacturer)
	Element	m3-2-a-1-facilities-and-equipment
	Directory	m3/32-body-data/32a-app/32a1-fac-equip
	Comment	Several reports are likely to be included in this appendix. The organisation is left to the applicant to define. However, where there is more than one manufacturer a folder should be created for each manufacturer and the identity of the manufacturer included in the directory name. CTD numbering is not defined below this level (e.g., 3.2.A.1.1).
124	Number	
	Title	*Facilities and Equipment Report 1*
	Element	m3-2-a-1-facilities-and-equipment
	File	m3/32-body-data/32a-app/32a1-fac-equip*/facilities-and-equipment-report-1.pdf*
	Comment	

125	Number	
	Title	*Facilities and Equipment Report 2*
	Element	m3-2-a-1-facilities-and-equipment
	File	m3/32-body-data/32a-app/32a1-fac-equip/*facilities-and-equipment-report-2.pdf*
	Comment	
126	Number	
	Title	*Facilities and Equipment Report 3*
	Element	m3-2-a-1-facilities-and-equipment
	File	m3/32-body-data/32a-app/32a1-fac-equip/*facilities-and-equipment-report-3.pdf*
	Comment	
127	Number	3.2.A.2
	Title	Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	Directory	m3/32-body-data/32a-app/32a2-advent-agent
	Comment	Nonviral adventitious agents reports should be placed in this folder. For viral adventitious agents the following sub-folder structure should be used. However, where there is more than one drug substance, drug product, manufacturer etc., a directory should be created for each option and its identity included in the directory name. CTD numbering is not defined below this level (e.g., 3.2.A.2.1).
128	Number	
	Title	*Adventitious Agents Safety Evaluation Report 1*
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	File	m3/32-body-data/32a-app/32a2-advent-agent/*adventitious-agents-report-1.pdf*
	Comment	
129	Number	
	Title	*Adventitious Agents Safety Evaluation Report 2*
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	File	m3/32-body-data/32a-app/32a2-advent-agent/*adventitious-agents-report-2.pdf*
	Comment	

130	Number	
	Title	*Adventitious Agents Safety Evaluation Report 3*
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	File	m3/32-body-data/32a-app/32a2-advent-agent/*adventitious-agents-report-3.pdf*
	Comment	
131	Number	3.2.A.3
	Title	Excipients – *Name*
	Element	m3-2-a-3-excipients
	Directory	m3/32-body-data/32a-app/32a3-excip-*name-1*
	Comment	The name of any novel excipient should be included in the folder name. If there is more than one novel excipient then each folder should have unique identification through the use of different names e.g., '32a3-excip-*name-1'* and '32a3-excip-*name-2'*. The directory/file structure would typically follow that of the drug substance section in Module 3.2.S. Refer to regional guidances for the need for such information to be included in the submission directly as opposed to its inclusion in a Drug Master File.
132	Number	3.2.R
	Title	Regional Information
	Element	m3-2-r-regional-information
	Directory	m3/32-body-data/32r-reg-info
	Comment	Refer to the M4 Organisation Document: Granularity Annex for the approach to take with this section.
133	Number	3.3
	Title	Literature References
	Element	m3-3-literature-references
	Directory	m3/33-lit-ref
	Comment	Copies of literature references should ordinarily be submitted as individual files (i.e., one for each reference). CTD numbering is not defined below this level (e.g., 3.3.1).
134	Number	
	Title	*Reference 1*

	Element	m3-3-literature-references
	File	m3/33-lit-ref/*reference-1.pdf*
	Comment	
135	Number	
	Title	*Reference 2*
	Element	m3-3-literature-references
	File	m3/33-lit-ref/*reference-2.pdf*
	Comment	
136	Number	
	Title	*Reference 3*
	Element	m3-3-literature-references
	File	m3/33-lit-ref/*reference-3.pdf*
	Comment	
137	Number	4
	Title	Nonclinical Study Reports
	Element	m4-nonclinical-study-reports
	Directory	m4
	Comment	
138	Number	4.2
	Title	Study Reports
	Element	m4-2-study-reports
	Directory	m4/42-stud-rep
	Comment	
139	Number	4.2.1
	Title	Pharmacology
	Element	m4-2-1-pharmacology

	Directory	m4/42-stud-rep/421-pharmacol
	Comment	
140	Number	4.2.1.1
	Title	Primary Pharmacodynamics
	Element	m4-2-1-1-primary-pharmacodynamics
	Directory	m4/42-stud-rep/421-pharmacol/4211-prim-pd
	Comment	
141	Number	
	Title	*Study Report 1*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	m4/42-stud-rep/421-pharmacol/4211-prim-pd/*study-report-1.pdf*
	Comment	This comment is applicable to all study reports in Module 4. A single file can be provided for each study report document in Module 4. However, where the study report is large (e.g., a carcinogenicity study) the applicant can choose to submit the report as more than one file. In this case the text portion of the report should be one file and the appendices can be one or more files. In choosing the level of granularity for these reports, the applicant should consider that, when relevant information is changed at any point in the product's life cycle, replacements of complete files should be provided. Where submission as a collection of multiple files is used it is recommended that a directory is created at the study report level and the relevant files included within the directory. It is possible to have the additional graphical file(s) inserted directly into the PDF file, thus making management of the file easier. Alternatively, the applicant can choose to manage graphical files independently. Individual studies and files do not have specific CTD numbers.
142	Number	
	Title	*Study Report 2*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	m4/42-stud-rep/421-pharmacol/4211-prim-pd/*study-report-2.pdf*

	Comment	
143	Number	
	Title	*Study Report 3*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	m4/42-stud-rep/421-pharmacol/4211-prim-pd/*study-report-3.pdf*
	Comment	
144	Number	4.2.1.2
	Title	Secondary Pharmacodynamics
	Element	m4-2-1-2-secondary-pharmacodynamics
	Directory	m4/42-stud-rep/421-pharmacol/4212-sec-pd
	Comment	
145	Number	
	Title	*Study Report 1*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	m4/42-stud-rep/421-pharmacol/4212-sec-pd/*study-report-1.pdf*
	Comment	
146	Number	
	Title	*Study Report 2*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	m4/42-stud-rep/421-pharmacol/4212-sec-pd/*study-report-2.pdf*
	Comment	
147	Number	
	Title	*Study Report 3*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	m4/42-stud-rep/421-pharmacol/4212-sec-pd/*study-report-3.pdf*
	Comment	

148	Number	4.2.1.3
	Title	Safety Pharmacology
	Element	m4-2-1-3-safety-pharmacology
	Directory	m4/42-stud-rep/421-pharmacol/4213-safety-pharmacol
	Comment	
149	Number	
	Title	*Study Report 1*
	Element	m4-2-1-3-safety-pharmacology
	File	m4/42-stud-rep/421-pharmacol/4213-safety-pharmacol/*study-report-1.pdf*
	Comment	
150	Number	
	Title	*Study Report 2*
	Element	m4-2-1-3-safety-pharmacology
	File	m4/42-stud-rep/421-pharmacol/4213-safety-pharmacol/*study-report-2.pdf*
	Comment	
151	Number	
	Title	*Study Report 3*
	Element	m4-2-1-3-safety-pharmacology
	File	m4/42-stud-rep/421-pharmacol/4213-safety-pharmacol/*study-report-3.pdf*
	Comment	
152	Number	4.2.1.4
	Title	Pharmacodynamic Drug Interactions
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	Directory	m4/42-stud-rep/421-pharmacol/4214-pd-drug-interact
	Comment	
153	Number	

	Title	*Study Report 1*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	m4/42-stud-rep/421-pharmacol/4214-pd-drug-interact/*study-report-1.pdf*
	Comment	
154	Number	
	Title	*Study Report 2*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	m4/42-stud-rep/421-pharmacol/4214-pd-drug-interact/*study-report-2.pdf*
	Comment	
155	Number	
	Title	*Study Report 3*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	m4/42-stud-rep/421-pharmacol/4214-pd-drug-interact/*study-report-3.pdf*
	Comment	
156	Number	4.2.2
	Title	Pharmacokinetics
	Element	m4-2-2-pharmacokinetics
	Directory	m4/42-stud-rep/422-pk
	Comment	
157	Number	4.2.2.1
	Title	Analytical Methods and Validation Reports (if separate reports are available)
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	Directory	m4/42-stud-rep/422-pk/4221-analyt-met-val
	Comment	
158	Number	
	Title	*Study Report 1*

	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	m4/42-stud-rep/422-pk/4221-analyt-met-val/*study-report-1.pdf*
	Comment	
159	Number	
	Title	*Study Report 2*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	m4/42-stud-rep/422-pk/4221-analyt-met-val/*study-report-2.pdf*
	Comment	
160	Number	
	Title	*Study Report 3*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	m4/42-stud-rep/422-pk/4221-analyt-met-val/*study-report-3.pdf*
	Comment	
161	Number	4.2.2.2
	Title	Absorption
	Element	m4-2-2-2-absorption
	Directory	m4/42-stud-rep/422-pk/4222-absorp
	Comment	
162	Number	
	Title	*Study Report 1*
	Element	m4-2-2-2-absorption
	File	m4/42-stud-rep/422-pk/4222-absorp/*study-report-1.pdf*
	Comment	
163	Number	
	Title	*Study Report 2*
	Element	m4-2-2-2-absorption

	File	m4/42-stud-rep/422-pk/4222-absorp/*study-report-2.pdf*
	Comment	
164	Number	
	Title	*Study Report 3*
	Element	m4-2-2-2-absorption
	File	m4/42-stud-rep/422-pk/4222-absorp/*study-report-3.pdf*
	Comment	
165	Number	4.2.2.3
	Title	Distribution
	Element	m4-2-2-3-distribution
	Directory	m4/42-stud-rep/422-pk/4223-distrib
	Comment	
166	Number	
	Title	*Study Report 1*
	Element	m4-2-2-3-distribution
	File	m4/42-stud-rep/422-pk/4223-distrib/*study-report-1.pdf*
	Comment	
167	Number	
	Title	*Study Report 2*
	Element	m4-2-2-3-distribution
	File	m4/42-stud-rep/422-pk/4223-distrib/*study-report-2.pdf*
	Comment	
168	Number	
	Title	*Study Report 3*
	Element	m4-2-2-3-distribution
	File	m4/42-stud-rep/422-pk/4223-distrib/*study-report-3.pdf*

	Comment	
169	Number	4.2.2.4
	Title	Metabolism
	Element	m4-2-2-4-metabolism
	Directory	m4/42-stud-rep/422-pk/4224-metab
	Comment	
170	Number	
	Title	*Study Report 1*
	Element	m4-2-2-4-metabolism
	File	m4/42-stud-rep/422-pk/4224-metab/*study-report-1.pdf*
	Comment	
171	Number	
	Title	*Study Report 2*
	Element	m4-2-2-4-metabolism
	File	m4/42-stud-rep/422-pk/4224-metab/*study-report-2.pdf*
	Comment	
172	Number	
	Title	*Study Report 3*
	Element	m4-2-2-4-metabolism
	File	m4/42-stud-rep/422-pk/4224-metab/*study-report-3.pdf*
	Comment	
173	Number	4.2.2.5
	Title	Excretion
	Element	m4-2-2-5-excretion
	Directory	m4/42-stud-rep/422-pk/4225-excr
	Comment	

174	Number	
	Title	*Study Report 1*
	Element	m4-2-2-5-excretion
	File	m4/42-stud-rep/422-pk/4225-excr/*study-report-1.pdf*
	Comment	
175	Number	
	Title	*Study Report 2*
	Element	m4-2-2-5-excretion
	File	m4/42-stud-rep/422-pk/4225-excr/*study-report-2.pdf*
	Comment	
176	Number	
	Title	*Study Report 3*
	Element	m4-2-2-5-excretion
	File	m4/42-stud-rep/422-pk/4225-excr/*study-report-3.pdf*
	Comment	
177	Number	4.2.2.6
	Title	Pharmacokinetic Drug Interactions (nonclinical)
	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	Directory	m4/42-stud-rep/422-pk/4226-pk-drug-interact
	Comment	
178	Number	
	Title	*Study Report 1*
	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	m4/42-stud-rep/422-pk/4226-pk-drug-interact/*study-report-1.pdf*
	Comment	
179	Number	

	Title	*Study Report 2*
	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	m4/42-stud-rep/422-pk/4226-pk-drug-interact/*study-report-2.pdf*
	Comment	
180	Number	
	Title	*Study Report 3*
	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	m4/42-stud-rep/422-pk/4226-pk-drug-interact/*study-report-3.pdf*
	Comment	
181	Number	4.2.2.7
	Title	Other Pharmacokinetic Studies
	Element	m4-2-2-7-other-pharmacokinetic-studies
	Directory	m4/42-stud-rep/422-pk/4227-other-pk-stud
	Comment	
182	Number	
	Title	*Study Report 1*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	m4/42-stud-rep/422-pk/4227-other-pk-stud/*study-report-1.pdf*
	Comment	
183	Number	
	Title	*Study Report 2*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	m4/42-stud-rep/422-pk/4227-other-pk-stud/*study-report-2.pdf*
	Comment	
184	Number	
	Title	*Study Report 3*

	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	m4/42-stud-rep/422-pk/4227-other-pk-stud/*study-report-3.pdf*
	Comment	
185	Number	4.2.3
	Title	Toxicology
	Element	m4-2-3-toxicology
	Directory	m4/42-stud-rep/423-tox
	Comment	
186	Number	4.2.3.1
	Title	Single-Dose Toxicity (in order by species, by route)
	Element	m4-2-3-1-single-dose-toxicity
	Directory	m4/42-stud-rep/423-tox/4231-single-dose-tox
	Comment	
187	Number	
	Title	*Study Report 1*
	Element	m4-2-3-1-single-dose-toxicity
	File	m4/42-stud-rep/423-tox/4231-single-dose-tox/*study-report-1.pdf*
	Comment	
188	Number	
	Title	*Study Report 2*
	Element	m4-2-3-1-single-dose-toxicity
	File	m4/42-stud-rep/423-tox/4231-single-dose-tox/*study-report-2.pdf*
	Comment	
189	Number	
	Title	*Study Report 3*
	Element	m4-2-3-1-single-dose-toxicity

	File	m4/42-stud-rep/423-tox/4231-single-dose-tox/*study-report-3.pdf*
	Comment	
190	Number	4.2.3.2
	Title	Repeat-Dose Toxicity (in order by species, by route, by duration, including supportive toxicokinetics evaluations)
	Element	m4-2-3-2-repeat-dose-toxicity
	Directory	m4/42-stud-rep/423-tox/4232-repeat-dose-tox
	Comment	
191	Number	
	Title	*Study Report 1*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	m4/42-stud-rep/423-tox/4232-repeat-dose-tox/*study-report-1.pdf*
	Comment	
192	Number	
	Title	*Study Report 2*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	m4/42-stud-rep/423-tox/4232-repeat-dose-tox/*study-report-2.pdf*
	Comment	
193	Number	
	Title	*Study Report 3*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	m4/42-stud-rep/423-tox/4232-repeat-dose-tox/*study-report-3.pdf*
	Comment	
194	Number	4.2.3.3
	Title	Genotoxicity
	Element	m4-2-3-3-genotoxicity
	Directory	m4/42-stud-rep/423-tox/4233-genotox

	Comment	
195	Number	4.2.3.3.1
	Title	In vitro
	Element	m4-2-3-3-1-in-vitro
	Directory	m4/42-stud-rep/423-tox/4233-genotox/42331-in-vitro
	Comment	
196	Number	
	Title	*Study Report 1*
	Element	m4-2-3-3-1-in-vitro
	File	m4/42-stud-rep/423-tox/4233-genotox/42331-in-vitro/*study-report-1.pdf*
	Comment	
197	Number	
	Title	*Study Report 2*
	Element	m4-2-3-3-1-in-vitro
	File	m4/42-stud-rep/423-tox/4233-genotox/42331-in-vitro/*study-report-2.pdf*
	Comment	
198	Number	
	Title	*Study Report 3*
	Element	m4-2-3-3-1-in-vitro
	File	m4/42-stud-rep/423-tox/4233-genotox/42331-in-vitro/*study-report-3.pdf*
	Comment	
199	Number	4.2.3.3.2
	Title	In vivo (including supportive toxicokinetics evaluations)
	Element	m4-2-3-3-2-in-vivo
	Directory	m4/42-stud-rep/423-tox/4233-genotox/42332-in-vivo
	Comment	

200	Number	
	Title	*Study Report 1*
	Element	m4-2-3-3-2-in-vivo
	File	m4/42-stud-rep/423-tox/4233-genotox/42332-in-vivo/*study-report-1.pdf*
	Comment	
201	Number	
	Title	*Study Report 2*
	Element	m4-2-3-3-2-in-vivo
	File	m4/42-stud-rep/423-tox/4233-genotox/42332-in-vivo/*study-report-2.pdf*
	Comment	
202	Number	
	Title	*Study Report 3*
	Element	m4-2-3-3-2-in-vivo
	File	m4/42-stud-rep/423-tox/4233-genotox/42332-in-vivo/*study-report-3.pdf*
	Comment	
203	Number	4.2.3.4
	Title	Carcinogenicity (including supportive toxicokinetics evaluations)
	Element	m4-2-3-4-carcinogenicity
	Directory	m4/42-stud-rep/423-tox/4234-carcigen
	Comment	
204	Number	4.2.3.4.1
	Title	Long-term studies (in order by species, including range-finding studies that cannot be appropriately included under repeat-dose toxicity or pharmacokinetics)
	Element	m4-2-3-4-1-long-term-studies
	Directory	m4/42-stud-rep/423-tox/4234-carcigen/42341-lt-stud
	Comment	
205	Number	

	Title	*Study Report 1*
	Element	m4-2-3-4-1-long-term-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42341-lt-stud/*study-report-1.pdf*
	Comment	
206	Number	
	Title	*Study Report 2*
	Element	m4-2-3-4-1-long-term-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42341-lt-stud/*study-report-2.pdf*
	Comment	
207	Number	
	Title	*Study Report 3*
	Element	m4-2-3-4-1-long-term-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42341-lt-stud/*study-report-3.pdf*
	Comment	
208	Number	4.2.3.4.2
	Title	Short- or medium-term studies (including range-finding studies that cannot be appropriately included under repeat-dose toxicity or pharmacokinetics)
	Element	m4-2-3-4-2-short-or-medium-term-studies
	Directory	m4/42-stud-rep/423-tox/4234-carcigen/42342-smt-stud
	Comment	
209	Number	
	Title	*Study Report 1*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42342-smt-stud/*study-report-1.pdf*
	Comment	
210	Number	
	Title	*Study Report 2*

	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42342-smt-stud/*study-report-2.pdf*
	Comment	
211	Number	
	Title	*Study Report 3*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42342-smt-stud/*study-report-3.pdf*
	Comment	
212	Number	4.2.3.4.3
	Title	Other studies
	Element	m4-2-3-4-3-other-studies
	Directory	m4/42-stud-rep/423-tox/4234-carcigen/42343-other-stud
	Comment	
213	Number	
	Title	*Study Report 1*
	Element	m4-2-3-4-3-other-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42343-other-stud/*study-report-1.pdf*
	Comment	
214	Number	
	Title	*Study Report 2*
	Element	m4-2-3-4-3-other-studies
	File	m4/42-stud-rep/423-tox/4234-carcigen/42343-other-stud/*study-report-2.pdf*
	Comment	
215	Number	
	Title	*Study Report 3*
	Element	m4-2-3-4-3-other-studies

	File	m4/42-stud-rep/423-tox/4234-carcigen/42343-other-stud/*study-report-3.pdf*
	Comment	
216	Number	4.2.3.5
	Title	Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly)
	Element	m4-2-3-5-reproductive-and-developmental-toxicity
	Directory	m4/42-stud-rep/423-tox/4235-repro-dev-tox
	Comment	
217	Number	4.2.3.5.1
	Title	Fertility and early embryonic development
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	Directory	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42351-fert-embryo-dev
	Comment	
218	Number	
	Title	*Study Report 1*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42351-fert-embryo-dev/*study-report-1.pdf*
	Comment	
219	Number	
	Title	*Study Report 2*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42351-fert-embryo-dev/*study-report-2.pdf*
	Comment	
220	Number	
	Title	*Study Report 3*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42351-fert-embryo-dev/*study-report-3.pdf*

	Comment	
221	Number	4.2.3.5.2
	Title	Embryo-fetal development
	Element	m4-2-3-5-2-embryo-fetal-development
	Directory	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42352-embryo-fetal-dev
	Comment	
222	Number	
	Title	*Study Report 1*
	Element	m4-2-3-5-2-embryo-fetal-development
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42352-embryo-fetal-dev/*study-report-1.pdf*
	Comment	
223	Number	
	Title	*Study Report 2*
	Element	m4-2-3-5-2-embryo-fetal-development
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42352-embryo-fetal-dev/*study-report-2.pdf*
	Comment	
224	Number	
	Title	*Study Report 3*
	Element	m4-2-3-5-2-embryo-fetal-development
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42352-embryo-fetal-dev/*study-report-3.pdf*
	Comment	
225	Number	4.2.3.5.3
	Title	Prenatal and postnatal development, including maternal function
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	Directory	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42353-pre-postnatal-dev
	Comment	

226	Number	
	Title	*Study Report 1*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42353-pre-postnatal-dev/*study-report-1.pdf*
	Comment	
227	Number	
	Title	*Study Report 2*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42353-pre-postnatal-dev/*study-report-2.pdf*
	Comment	
228	Number	
	Title	*Study Report 3*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42353-pre-postnatal-dev/*study-report-3.pdf*
	Comment	
229	Number	4.2.3.5.4
	Title	Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	Directory	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42354-juv
	Comment	
230	Number	
	Title	*Study Report 1*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42354-juv/*study-report-1.pdf*
	Comment	
231	Number	

	Title	*Study Report 2*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42354-juv/*study-report-2.pdf*
	Comment	
232	Number	
	Title	*Study Report 3*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	m4/42-stud-rep/423-tox/4235-repro-dev-tox/42354-juv/*study-report-3.pdf*
	Comment	
233	Number	4.2.3.6
	Title	Local Tolerance
	Element	m4-2-3-6-local-tolerance
	Directory	m4/42-stud-rep/423-tox/4236-loc-tol
	Comment	
234	Number	
	Title	*Study Report 1*
	Element	m4-2-3-6-local-tolerance
	File	m4/42-stud-rep/423-tox/4236-loc-tol/*study-report-1.pdf*
	Comment	
235	Number	
	Title	*Study Report 2*
	Element	m4-2-3-6-local-tolerance
	File	m4/42-stud-rep/423-tox/4236-loc-tol/*study-report-2.pdf*
	Comment	
236	Number	
	Title	*Study Report 3*

	Element	m4-2-3-6-local-tolerance
	File	m4/42-stud-rep/423-tox/4236-loc-tol/*study-report-3.pdf*
	Comment	
237	Number	4.2.3.7
	Title	Other Toxicity Studies (if available)
	Element	m4-2-3-7-other-toxicity-studies
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud
	Comment	
238	Number	4.2.3.7.1
	Title	Antigenicity
	Element	m4-2-3-7-1-antigenicity
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42371-antigen
	Comment	
239	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-1-antigenicity
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42371-antigen/*study-report-1.pdf*
	Comment	
240	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-1-antigenicity
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42371-antigen/*study-report-2.pdf*
	Comment	
241	Number	
	Title	*Study Report 3*
	Element	m4-2-3-7-1-antigenicity

	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42371-antigen/*study-report-3.pdf*
	Comment	
242	Number	4.2.3.7.2
	Title	Immunotoxicity
	Element	m4-2-3-7-2-immunotoxicity
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42372-immunotox
	Comment	
243	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-2-immunotoxicity
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42372-immunotox/*study-report-1.pdf*
	Comment	
244	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-2-immunotoxicity
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42372-immunotox/*study-report-2.pdf*
	Comment	
245	Number	
	Title	*Study Report 3*
	Element	m4-2-3-7-2-immunotoxicity
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42372-immunotox/*study-report-3.pdf*
	Comment	
246	Number	4.2.3.7.3
	Title	Mechanistic studies (if not included elsewhere)
	Element	m4-2-3-7-3-mechanistic-studies
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42373-mechan-stud

	Comment	
247	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-3-mechanistic-studies
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42373-mechan-stud/*study-report-1.pdf*
	Comment	
248	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-3-mechanistic-studies
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42373-mechan-stud/*study-report-2.pdf*
	Comment	
249	Number	
	Title	*Study Report 3*
	Element	m4-2-3-7-3-mechanistic-studies
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42373-mechan-stud/*study-report-3.pdf*
	Comment	
250	Number	4.2.3.7.4
	Title	Dependence
	Element	m4-2-3-7-4-dependence
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42374-dep
	Comment	
251	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-4-dependence
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42374-dep/*study-report-1.pdf*
	Comment	

252	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-4-dependence
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42374-dep/*study-report-2.pdf*
	Comment	
253	Number	
	Title	*Study Report 3*
	Element	m4-2-3-7-4-dependence
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42374-dep/*study-report-3.pdf*
	Comment	
254	Number	4.2.3.7.5
	Title	Metabolites
	Element	m4-2-3-7-5-metabolites
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42375-metab
	Comment	
255	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-5-metabolites
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42375-metab/*study-report-1.pdf*
	Comment	
256	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-5-metabolites
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42375-metab/*study-report-2.pdf*
	Comment	
257	Number	

	Title	*Study Report 3*
	Element	m4-2-3-7-5-metabolites
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42375-metab/*study-report-3.pdf*
	Comment	
258	Number	4.2.3.7.6
	Title	Impurities
	Element	m4-2-3-7-6-impurities
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42376-imp
	Comment	
259	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-6-impurities
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42376-imp/*study-report-1.pdf*
	Comment	
260	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-6-impurities
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42376-imp/*study-report-2.pdf*
	Comment	
261	Number	
	Title	*Study Report 3*
	Element	m4-2-3-7-6-impurities
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42376-imp/*study-report-3.pdf*
	Comment	
262	Number	4.2.3.7.7
	Title	Other

	Element	m4-2-3-7-7-other
	Directory	m4/42-stud-rep/423-tox/4237-other-tox-stud/42377-other
	Comment	
263	Number	
	Title	*Study Report 1*
	Element	m4-2-3-7-7-other
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42377-other/*study-report-1.pdf*
	Comment	
264	Number	
	Title	*Study Report 2*
	Element	m4-2-3-7-7-other
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42377-other/*study-report-2.pdf*
	Comment	
265	Number	
	Title	*Study Report 3*
	Element	m4-2-3-7-7-other
	File	m4/42-stud-rep/423-tox/4237-other-tox-stud/42377-other/*study-report-3.pdf*
	Comment	
266	Number	4.3
	Title	Literature References
	Element	m4-3-literature-references
	Directory	m4/43-lit-ref
	Comment	Copies of literature references should ordinarily be submitted as individual files (i.e., one for each reference).
267	Number	
	Title	*Reference 1*
	Element	m4-3-literature-references

	File	m4/43-lit-ref/*reference-1.pdf*
	Comment	
268	Number	
	Title	*Reference 2*
	Element	m4-3-literature-references
	File	m4/43-lit-ref/*reference-2.pdf*
	Comment	
269	Number	
	Title	*Reference 3*
	Element	m4-3-literature-references
	File	m4/43-lit-ref/*reference-3.pdf*
	Comment	
270	Number	5
	Title	Clinical Study Reports
	Element	m5-clinical-study-reports
	Directory	m5
	Comment	
271	Number	5.2
	Title	Tabular Listing of all Clinical Studies
	Element	m5-2-tabular-listing-of-all-clinical-studies
	Directory	m5/52-tab-list
	Comment	
272	Number	5.2
	Title	Tabular Listing of all Clinical Studies
	Element	m5-2-tabular-listing-of-all-clinical-studies
	File	m5/52-tab-list/tabular-listing.pdf

	Comment	
273	Number	5.3
	Title	Clinical Study Reports
	Element	m5-3-clinical-study-reports
	Directory	m5/53-clin-stud-rep
	Comment	
274	Number	5.3.1
	Title	Reports of Biopharmaceutic Studies
	Element	m5-3-1-reports-of-biopharmaceutic-studies
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud
	Comment	
275	Number	5.3.1.1
	Title	Bioavailability (BA) Study Reports
	Element	m5-3-1-1-bioavailability-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5311-ba-stud-rep
	Comment	
276	Number	
	Title	*Study Report 1*
	Element	m5-3-1-1-bioavailability-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5311-ba-stud-rep/*study-report-1*
	Comment	This comment is applicable to all study reports in Module 5. The applicants should ordinarily provide the study reports as multiple files (a synopsis, a main body and appropriate appendices). Appendices should be organized in accordance with the ICH E3 guideline, which describes the content and format of the clinical study report. In choosing the level of granularity for reports the applicant should consider that, when relevant information is changed at any point in the product's life cycle, replacements of complete files should be provided. A directory should be created for each study and the files associated with the study report should be organized within the directory.

		Individual studies and files do not have specific CTD numbers.
277	Number	
	Title	*Study Report 2*
	Element	m5-3-1-1-bioavailability-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5311-ba-stud-rep/*study-report-2*
	Comment	
278	Number	
	Title	*Study Report 3*
	Element	m5-3-1-1-bioavailability-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5311-ba-stud-rep/*study-report-3*
	Comment	
279	Number	5.3.1.2
	Title	Comparative BA and Bioequivalence (BE) Study Reports
	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep
	Comment	
280	Number	
	Title	*Study Report 1*
	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/*study-report-1*
	Comment	
281	Number	

	Title	*Study Report 2*
	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/*study-report-2*
	Comment	
282	Number	
	Title	*Study Report 3*
	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/*study-report-3*
	Comment	
283	Number	5.3.1.3
	Title	In vitro – In vivo Correlation Study Reports
	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5313-in-vitro-in-vivo-corr-stud-rep
	Comment	
284	Number	
	Title	*Study Report 1*
	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5313-in-vitro-in-vivo-corr-stud-rep/*study-report-1*
	Comment	
285	Number	
	Title	*Study Report 2*
	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5313-in-vitro-in-vivo-corr-stud-rep/*study-report-2*
	Comment	
286	Number	
	Title	*Study Report 3*

	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5313-in-vitro-in-vivo-corr-stud-rep/*study-report-3*
	Comment	
287	Number	5.3.1.4
	Title	Reports of Bioanalytical and Analytical Methods for Human Studies
	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met
	Comment	
288	Number	
	Title	*Study Report 1*
	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/*study-report-1*
	Comment	
289	Number	
	Title	*Study Report 2*
	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/*study-report-2*
	Comment	
290	Number	
	Title	*Study Report 3*
	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	Directory	m5/53-clin-stud-rep/531-rep-biopharm-stud/5314-bioanalyt-analyt-met/*study-report-3*
	Comment	
291	Number	5.3.2
	Title	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
	Element	m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials

	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat
	Comment	
292	Number	5.3.2.1
	Title	Plasma Protein Binding Study Reports
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5321-plasma-prot-bind-stud-rep
	Comment	
293	Number	
	Title	*Study Report 1*
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5321-plasma-prot-bind-stud-rep/*study-report-1*
	Comment	
294	Number	
	Title	*Study Report 2*
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5321-plasma-prot-bind-stud-rep/*study-report-2*
	Comment	
295	Number	
	Title	*Study Report 3*
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5321-plasma-prot-bind-stud-rep/*study-report-3*
	Comment	
296	Number	5.3.2.2
	Title	Reports of Hepatic Metabolism and Drug Interaction Studies
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud

	Comment	
297	Number	
	Title	*Study Report 1*
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud/*study-report-1*
	Comment	
298	Number	
	Title	*Study Report 2*
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud/*study-report-2*
	Comment	
299	Number	
	Title	*Study Report 3*
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud/*study-report-3*
	Comment	
300	Number	5.3.2.3
	Title	Reports of Studies Using Other Human Biomaterials
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5323-stud-other-human-biomat
	Comment	
301	Number	
	Title	*Study Report 1*
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5323-stud-other-human-biomat/*study-report-1*
	Comment	

302	Number	
	Title	*Study Report 2*
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5323-stud-other-human-biomat/*study-report-2*
	Comment	
303	Number	
	Title	*Study Report 3*
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	Directory	m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5323-stud-other-human-biomat/*study-report-3*
	Comment	
304	Number	5.3.3
	Title	Reports of Human Pharmacokinetic (PK) Studies
	Element	m5-3-3-reports-of-human-pharmacokinetics-pk-studies
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud
	Comment	
305	Number	5.3.3.1
	Title	Healthy Subject PK and Initial Tolerability Study Reports
	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5331-healthy-subj-pk-init-tol-stud-rep
	Comment	
306	Number	
	Title	*Study Report 1*
	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5331-healthy-subj-pk-init-tol-stud-rep/*study-report-1*
	Comment	
307	Number	

	Title	*Study Report 2*
	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5331-healthy-subj-pk-init-tol-stud-rep/*study-report-2*
	Comment	
308	Number	
	Title	*Study Report 3*
	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5331-healthy-subj-pk-init-tol-stud-rep/*study-report-3*
	Comment	
309	Number	5.3.3.2
	Title	Patient PK and Initial Tolerability Study Reports
	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5332-patient-pk-init-tol-stud-rep
	Comment	
310	Number	
	Title	*Study Report 1*
	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5332-patient-pk-init-tol-stud-rep/*study-report-1*
	Comment	
311	Number	
	Title	*Study Report 2*
	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5332-patient-pk-init-tol-stud-rep/*study-report-2*
	Comment	
312	Number	
	Title	*Study Report 3*

	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5332-patient-pk-init-tol-stud-rep/*study-report-3*
	Comment	
313	Number	5.3.3.3
	Title	Intrinsic Factor PK Study Reports
	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5333-intrin-factor-pk-stud-rep
	Comment	
314	Number	
	Title	*Study Report 1*
	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5333-intrin-factor-pk-stud-rep/*study-report-1*
	Comment	
315	Number	
	Title	*Study Report 2*
	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5333-intrin-factor-pk-stud-rep/*study-report-2*
	Comment	
316	Number	
	Title	*Study Report 3*
	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5333-intrin-factor-pk-stud-rep/*study-report-3*
	Comment	
317	Number	5.3.3.4
	Title	Extrinsic Factor PK Study Reports
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports

	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5334-extrin-factor-pk-stud-rep
	Comment	
318	Number	
	Title	*Study Report 1*
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5334-extrin-factor-pk-stud-rep/*study-report-1*
	Comment	
319	Number	
	Title	*Study Report 2*
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5334-extrin-factor-pk-stud-rep/*study-report-2*
	Comment	
320	Number	
	Title	*Study Report 3*
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5334-extrin-factor-pk-stud-rep/*study-report-3*
	Comment	
321	Number	5.3.3.5
	Title	Population PK Study Reports
	Element	m5-3-3-5-population-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5335-popul-pk-stud-rep
	Comment	
322	Number	
	Title	*Study Report 1*
	Element	m5-3-3-5-population-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5335-popul-pk-stud-rep/*study-report-1*

	Comment	
323	Number	
	Title	*Study Report 2*
	Element	m5-3-3-5-population-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5335-popul-pk-stud-rep/*study-report-2*
	Comment	
324	Number	
	Title	*Study Report 3*
	Element	m5-3-3-5-population-pk-study-reports
	Directory	m5/53-clin-stud-rep/533-rep-human-pk-stud/5335-popul-pk-stud-rep/*study-report-3*
	Comment	
325	Number	5.3.4
	Title	Reports of Human Pharmacodynamic (PD) Studies
	Element	m5-3-4-reports-of-human-pharmacodynamics-pd-studies
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud
	Comment	
326	Number	5.3.4.1
	Title	Healthy Subject PD and PK/PD Study Reports
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5341-healthy-subj-pd-stud-rep
	Comment	
327	Number	
	Title	*Study Report 1*
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5341-healthy-subj-pd-stud-rep/*study-report-1*
	Comment	

328	Number	
	Title	*Study Report 2*
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5341-healthy-subj-pd-stud-rep/*study-report-2*
	Comment	
329	Number	
	Title	*Study Report 3*
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5341-healthy-subj-pd-stud-rep/*study-report-3*
	Comment	
330	Number	5.3.4.2
	Title	Patient PD and PK/PD Study Reports
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5342-patient-pd-stud-rep
	Comment	
331	Number	
	Title	*Study Report 1*
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5342-patient-pd-stud-rep/*study-report-1*
	Comment	
332	Number	
	Title	*Study Report 2*
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5342-patient-pd-stud-rep/*study-report-2*
	Comment	
333	Number	

	Title	*Study Report 3*
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	Directory	m5/53-clin-stud-rep/534-rep-human-pd-stud/5342-patient-pd-stud-rep/*study-report-3*
	Comment	
334	Number	5.3.5
	Title	Reports of Efficacy and Safety Studies
	Element	m5-3-5-reports-of-efficacy-and-safety-studies
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud
	Comment	
335	Number	5.3.5
	Title	Reports of Efficacy and Safety Studies - *Indication Name*
	Element	m5-3-5-reports-of-efficacy-and-safety-studies
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*
	Comment	The folder name should always include the indication being claimed, for example, 'asthma' (abbreviated if appropriate). Where there is more than one indication (e.g., asthma and migraine), then the first indication has a folder 'asthma' and the second 'migraine'. The 'indication' attribute in the backbone should be consistent with that used in the folder name but can be different. For example, an 'indication' attribute value of 'Non-Small Cell Lung Cancer' could be expressed as 'NSCLC' in the folder name. There is currently no standard terminology list for 'indication' and applicants should choose the 'indication' attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
336	Number	5.3.5.1
	Title	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5351-stud-rep-contr
	Comment	

337	Number	
	Title	*Study Report 1*
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5351-stud-rep-contr/*study-report-1*
	Comment	
338	Number	
	Title	*Study Report 2*
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5351-stud-rep-contr/*study-report-2*
	Comment	
339	Number	
	Title	*Study Report 3*
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5351-stud-rep-contr/*study-report-3*
	Comment	
340	Number	5.3.5.2
	Title	Study Reports of Uncontrolled Clinical Studies
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5352-stud-rep-uncontr
	Comment	
341	Number	
	Title	*Study Report 1*
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5352-stud-rep-uncontr/*study-report-1*
	Comment	
342	Number	

	Title	*Study Report 2*
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5352-stud-rep-uncontr/*study-report-2*
	Comment	
343	Number	
	Title	*Study Report 3*
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5352-stud-rep-uncontr/*study-report-3*
	Comment	
344	Number	5.3.5.3
	Title	Reports of Analyses of Data from More than One Study
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5353-rep-analys-data-more-one-stud
	Comment	
345	Number	
	Title	*Study Report 1*
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5353-rep-analys-data-more-one-stud/*study-report-1*
	Comment	
346	Number	
	Title	*Study Report 2*
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5353-rep-analys-data-more-one-stud/*study-report-2*
	Comment	
347	Number	
	Title	*Study Report 3*

	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5353-rep-analys-data-more-one-stud/*study-report-3*
	Comment	
348	Number	5.3.5.4
	Title	Other Study Reports
	Element	m5-3-5-4-other-study-reports
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5354-other-stud-rep
	Comment	
349	Number	
	Title	*Study Report 1*
	Element	m5-3-5-4-other-study-reports
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5354-other-stud-rep/*study-report-1*
	Comment	
350	Number	
	Title	*Study Report 2*
	Element	m5-3-5-4-other-study-reports
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5354-other-stud-rep/*study-report-2*
	Comment	
351	Number	
	Title	*Study Report 3*
	Element	m5-3-5-4-other-study-reports
	Directory	m5/53-clin-stud-rep/535-rep-effic-safety-stud/*indication-1*/5354-other-stud-rep/*study-report-3*
	Comment	
352	Number	5.3.6
	Title	Reports of Postmarketing Experience
	Element	m5-3-6-reports-of-postmarketing-experience

	Directory	m5/53-clin-stud-rep/536-postmark-exp
	Comment	
353	Number	5.3.7
	Title	Case Report Forms and Individual Patient Listings
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	m5/53-clin-stud-rep/537-crf-ipl
	Comment	
354	Number	
	Title	*Study 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	m5/53-clin-stud-rep/537-crf-ipl/*study-1*
	Comment	
355	Number	
	Title	*Document/Dataset 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-1/filename-1.pdf*
	Comment	The filename and extension should include the description of the file and appropriate file extension according to Appendix 2. Reference should be made to regional guidance for the acceptability of submission of datasets
356	Number	
	Title	*Document/Dataset 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-1/filename-2.pdf*
	Comment	
357	Number	
	Title	*Document/Dataset 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings

	File	m5/53-clin-stud-rep/537-crf-ipl/*study-1/filename-3.pdf*
	Comment	
358	Number	
	Title	*Study 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	m5/53-clin-stud-rep/537-crf-ipl/*study-2*
	Comment	define element
359	Number	
	Title	*Document/Dataset 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-2/filename-1.pdf*
	Comment	
360	Number	
	Title	*Document/Dataset 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-2/filename-2.pdf*
	Comment	
361	Number	
	Title	*Document/Dataset 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-2/filename-3.pdf*
	Comment	
362	Number	
	Title	*Study 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	m5/53-clin-stud-rep/537-crf-ipl/*study-3*

	Comment	define element
363	Number	
	Title	*Document/Dataset 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-3/filename-1.pdf*
	Comment	
364	Number	
	Title	*Document/Dataset 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-3/filename-2.pdf*
	Comment	
365	Number	
	Title	*Document/Dataset 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	m5/53-clin-stud-rep/537-crf-ipl/*study-3/filename-3.pdf*
	Comment	
366	Number	5.4
	Title	Literature References
	Element	m5-4-literature-references
	Directory	m5/54-lit-ref
	Comment	Copies of literature references should ordinarily be submitted as individual files (i.e,. one for each reference).
367	Number	
	Title	*Reference 1*
	Element	m5-4-literature-references
	File	m5/54-lit-ref/*reference-1.pdf*
	Comment	

368	Number	
	Title	*Reference 2*
	Element	m5-4-literature-references
	File	m5/54-lit-ref/*reference-2.pdf*
	Comment	
369	Number	
	Title	*Reference 3*
	Element	m5-4-literature-references
	File	m5/54-lit-ref/*reference-3.pdf*
	Comment	
370	Number	
	Title	
	Element	
	Directory	util
	Comment	utilities
371	Number	
	Title	
	Element	
	Directory	util/dtd
	Comment	DTDs/Schemas – it is not necessary to include regional DTDs/Schemas other than the one for the region to which the application is being made. File names in rows 372 - 379 are illustrative only. Please consult regional guidance for the current name and version of the files.
372	Number	
	Title	
	Element	
	File	util/dtd/ich-ectd-n.dtd
	Comment	DTD for the instance – the version used to create the eCTD submission must be included. “n” denotes the specific version (e.g., 3-2).

373	Number	
	Title	
	Element	
	File	util/dtd/eu-regional-n.dtd
	Comment	DTD for the EU specific documentation. “n” denotes the specific version (e.g., 1-1).
374	Number	
	Title	
	Element	
	File	util/dtd/jp-regional-n.xsd
	Comment	Schema for the Japan specific documentation. “n” denotes the specific version (e.g., 1-0).
375	Number	
	Title	
	Element	
	File	util/dtd/us-regional-n.dtd
	Comment	DTD for the US specific documentation. “n” denotes the specific version (e.g., 1-0).
376	Number	
	Title	
	Element	
	File	util/dtd/xx-regional-n.dtd
	Comment	DTD for the xx specific documentation, where xx is a two character country code from ISO-3166-1. “n” denotes the specific version (e.g., 1-0).
377	Number	
	Title	
	Element	
	Directory	util/style
	Comment	Directory for style sheets – ICH and regional stylesheets
378	Number	

	Title	
	Element	
	File	util/style/ectd-n.xsl
	Comment	The specific version of the eCTD stylesheet used by the applicant as a reference during the creation of the submission should be included. “n” denotes the specific version (e.g., 1-0).
379	Number	
	Title	
	Element	
	File	util/style/xx-regional-n.xsl
	Comment	Stylesheet for the xx specific documentation, where xx is a two character country code from ISO-3166-1. “n” denotes the specific version (e.g., 1-0).

附录 5：区域性信息，包括传输和接收

引言

本部分描述了未在通用技术文档中明确阐述的区域特定信息内容以及通过电子通用技术文档传输和接受的提交文件的组织细节。

区域性信息：模块 1

本模块包含的行政性信息为各区域独一无二的信息。并对模块 1 中电子文件和内容的区域性要求进行阐述。建立 eCTD 主干可用以传输注册文件中的区域性信息。

关于如何提供行政性表格以及详细的产品信息，将在区域性指南中予以阐述。制作模块 1 时请参考此信息和附录 6。模块 1 包含所有行政性文件（如表格和证书）和标签，包括区域指导所述的文件。

并非所有的区域性文件都包含在模块 1。特定区域所需的技术报告，应在模块 2 至 5 中。。这些报告应被置于最适合报告内容的模块中。

针对区域性要求的格式和内容，每个区域均为各模块提供了明确指南。表5-1为每个区域的联系信息。

表5-1

区域	网站地址	电子邮箱
欧盟	http://www.emea.europa.eu	esubmission@emea.europa.eu
美国食品药品监督管理局	www.fda.gov/cber www.fda.gov/cder	esubprep@fda.hhs.gov esub@fda.hhs.gov
日本厚生劳动省	http://www.mhlw.go.jp http://www.pmda.go.jp	ectd@pmda.go.jp
加拿大卫生部	http://www.hc-sc.gc.ca	ereview@hc-sc.gc.ca

提交地址

提交文件应直接发送至相应的监管机构。如何向各监管部门发送提交文件的信息可参阅表5-2的参考地址。

表5-2

监管机构	参考地址
EMEA，欧盟或国家当局	http://www.emea.europa.eu http://www.hma.eu/
日本厚生劳动省	http://www.mhlw.go.jp http://www.pmda.go.jp
美国食品药品监督管理局	http://www.fda.gov/
加拿大卫生部、加拿大卫生防护科	http://www.hc-sc.gc.ca

媒介

关于具体的媒介类型请参阅区域指导。

说明函说明函

申请人应以 PDF 格式文件提供说明函（例如，cover.pdf）。在非电子方式提交的文件中还应包含纸质说明函（如带有签字或盖章的表格以及证明）。说明函应包括：

- 提交资料的说明，包括相关法规信息。
- 以纸质方式、电子方式或纸质和电子混合方式提交的文件的章节列表。
- 根据区域性指南，电子提交的阐述包括电子媒介的类型和数量，提交文件的大小以及相关媒介的特性（如适用）（例如 DLT 磁带使用的格式）。
- 所提交的文件不携带病毒的声明，并提供检查文件病毒的软件说明。
- 提交文件的监管及信息技术的联络人。

传输

建议以通过互联网进行安全的数据交换作为传递手段。但是，在监管机构提供安全的电子网关之前，应继续通过快递或挂号邮件提交申报文件。

安全

在 eCTD 中的每个实体文件应包括 MD5 校验和。校验和使得收件人能够验证每个提交文件内容的完整性。XML eCTD 实例的每个叶元素包含每个文件的位置和计算所得校验和。

XML eCTD 实例的校验和应被包括在内。申请人应命名此校验和的文件为 index-md5.txt，并将其作为一个文件包含在 XML eCTD 实例的同一目录下。申请人应打印该 index-md5.txt 文件的内容，同时提供纸质提交文件并随附说明函。不必要提供包含区域索引文件的校验和的独立文件，因为该文件（及其 MD5 校验和）在 index.xml 文件叶元素中引用。

如果监管机构实施了 ICH M2 中推荐的 4.1，申请人可以根据该建议对 eCTD 加密。该解决方案可对 eCTD 并通过互联网传输（如该区域实施互联网接收），或根据经批准的物理媒介标准之一进行加密。加密的目的是要保护保密信息的机密性，并确保其仅被经授权的接收人收到。通过互联网发送 eCTD 则始终应进行加密。

如果信息通过物理媒介发送，可以选择加密但不必要。申请人应对媒介承担所有责任直至其被传递到监管机构。

在 eCTD 的独立文件中，申请人应不进行任何文件级别的安全设置或密码保护。申请人应允许打印和变更文件，选择文本和图形，添加或变更注释和表格域。监管机构的内部安全和访问控制程序应保持所提交文件的完整性。

接收

递达监管机构后，根据当地规定将提交文件存档。然后将提交文件的只读副本提供给监管机构

的审查小组。这通常通过在网络服务器上添加副本的方式实现。

回执

各监管机构应根据其自己的政策和程序确认收到 eCTD 提交文件。申请人应通过表 5-1 所述地址查阅关于确认的指导。

附录 6：eCTD XML 提交

背景

许多因素都会影响 eCTD 的设计。对设计产生重大影响的因素在下面列出：

- 提交的材料包括完整的监管档案、补充、修改和变更。
- 提交的材料应符合区域指导文件、法规和规章的要求。
- 该技术可扩展，以便随着技术的变更，能够采取新的电子解决方案。

eCTD 是围绕着主干概念设计的。主干类似于一个装有指向部分提交文件的指针（称为叶元素）的容器。主干以 XML 文档类型定义（DTD）为基础。CTD 中界定的文件和 eCTD DTD 中界定的元素两者之间存在密切联系。在骨架中，叶元素将提供指向组成该申报的各种文件和信息的超链接。

在 XML eCTD DTD 基础上产生的文件是 eCTD XML 实例或 XML 主干。XML 主干允许一个以上的叶元素指向相同的物理文件。此项工作应非常谨慎，因为对监管机构来说，如果有超过一个指针指向该文件，管理该文件的生命周期可能会更加困难。

文件名和目录结构

eCTD 的接收者应该能够在文件夹和文件级别直接浏览提交的内容（即，不需要定制软件终端的辅助。）eCTD 结构和如何创建文件夹名称的说明有助于这一类型的定位。

为了保持 eCTD 所载文件中出现的导航链接，目录结构将由监管机构保留。导航链接应为模块内的相对链接。

附录 4 阐述了特定的文件夹和文件名。目录结构的顶层将因区域而异。顶级文件夹标识是各区域申请的独特标识。顶级文件夹命名规范的具体要求参阅区域指导。原始提交文件及随后的修正和变更，应使用相同的顶级文件夹名称。提交文件应通过根据由序列号命名的子文件夹区分。对于所有区域，在整个申请过程中序列号应该是唯一的。对于日本的提交，顺序编号是必需的。对于所有其他区域，倾向于使用顺序编号，但不是必需的。表 6-1 和图 6-1 说明了此命名规范。

表 6-1

顶级文件夹的名称示例	序列号	提交类型
ctd-123456	0000	初始提交
ctd-123456	0001	首次修正、补充或变更
ctd-123456	0002	第 2 次修正、补充或变更
…		
ctd-123456	Nnnn	第N次修正、补充或变更

图 6-1

XML 骨架文件应以一个名为 index.xml 的单独文件提交，其应放置在该提交的提交序列号文件夹中。在图 6-1 所示的例子中应该有一个 index.xml 文件在文件夹“0000”中，文件夹“0001”和文件夹“0002”中。MD5 校验和文件，index-md5.txt 应放置在与 index.xml 相同的文件夹中。index.xml 的 DTD 应在每个提交的“util”文件夹中。

在每个提交中，区域管理 XML 主干文件应在区域的特定模块 1 文件夹。对于每个序列，涉及本文件的叶元素的操作属性始终为是“新建”。不需要单独对区域索引文件提供校验和文件，因为该文件（及其 MD5 校验和）在 index.xml 文件叶元素中引用。区域 XML 主干文件的 DTD 应在每个提交的“util”文件夹中。

表6-2列出了图6-1示例的文件位置。

表6-2

提交文件夹	文件
ctd-123456/0000	index.xml index-md5.txt
ctd-123456/0000/m1/us	us-regional.xml
ctd-123456/0000/util/dtd	ich-ectd-3-x.dtd
	us-regional-vx-x.dtd
ctd-123456/0001	index.xml index-md5.txt
ctd-123456/0001/m1/us	us-regional.xml
ctd-123456/0001/util/dtd	ich-ectd-3-x.dtd
	us-regional-vx-x.dtd
ctd-123456/0002	index.xml index-md5.txt
ctd-123456/0002/m1/us	us-regional.xml
ctd-123456/0002/util/dtd	ich-ectd-3-x.dtd us-regional-vx-x.dtd

生命周期管理

对于 eCTD 的接收者而言，确立提交申请在产品生命周期中的位置至关重要。

eCTD 能够包含初始提交文件、补充、修正和变更。三个区域在这些方面没有统一的定义，但修正和补充是美国使用的术语。变更适用于欧洲。变更、补充和修正用于为原始监管档案资料提供额外信息。例如，如果一个新的原料药生产商被提名，则其将导致向 FDA 提交修正或补充，向欧

洲提交变更。当监管机构要求其他资料时，该资料也作为原始提交文件的变更、补充或修正提交。因此，监管机构需要一种方法来管理提交的生命周期。此功能将由各监管机构以指南的形式提供，指南包括区域 DTD 和规范。有关的区域 DTD 应由申请人在 eCTD DTD 中引用。

eCTD DTD 在叶元素级提供了一些生命周期的管理功能，但不完全支持在提交级的生命周期。当修改发送到监管机构后，新的叶元素应在主干的同一位置提交增补、替换或删除的叶元素。叶元素的“修改后的文件”的属性应包含被增补、替换或删除叶的叶 ID。这就使得监管机构能够准确地找到原始叶和更新原始叶的状态。修改的文件将在下一节进行详细描述。

操作属性

操作属性是管理提交中每个独立叶元素的关键。申请人使用操作属性向监管机构说明申请人打算在提交文件中准备如何使用叶元素。操作属性描述在药品的生命周期期间随后提交文件的叶元素之间的关系。在首次提交的文件中所有叶元素通常都是新的。在第二次、第三次和随后提交的文件中，所有新提交的叶元素可以因其与原先提交的叶元素之间有关或无关而具有不同的操作属性。表 6-3 描述操作属性各容许值的含义。

表 6-3：理解操作属性

操作属性值	含义	使用代理审查软件时审查员会看到的内容	
		当前叶	先前的叶
新建	叶元素与先前提交的叶元素没有关系。无论是在同一申请序列中还是整个申请的生命周期中，一个 eCTD 元素中有多个新建的操作是可以被接受的	当前	
增补、	这意味着有一个现有的元素，此新叶元素应与之相关的。(例如，为该叶元素提供丢失的或新的信息)。不建议在同一申报中使用增补来关联两个元素(例如，由于文件大小限制而将文件分割)。但是，如果通常与增补的关系一起提交的叶元素在同一序列中被提供（例如，一个文件及其修正）使用增补则是适当的。在使用增补将在同一提序列的两个叶元素关联起来之前，请咨询监管机构。	当前	当前-增补
替换	这意味现有的叶元素被新叶元素替换。	当前	替换
删除	在这种情况下没有新的文件提交。相反，叶元素具有“delete”和“modified-file”操作属性标识不再视为与审查有关的先前的提交的叶元素。由于没有文件将被提交，校验和属性值将是空的，即，双引号之间没有输入内容 (“”).		不再与审查有关

modified-file 属性的目的是为了提供在之后序列中被修改叶元素的位置（即替换，增补或者删除)。当操作属性有增补、替换或删除值时，修改后的文件属性应该有一个值。modified-file 属性指向“index.xml”文件和将被改变的叶元素的叶 ID。modified-file 属性可以只针对一个单个的叶元素。此外，一旦叶元素已被另一个叶元素替换或删除，则其不能成为之后序列中叶元素的修改目标。

修改后的文件属性值的例子如下：

修改后的文件="../0001/index.xml#a1234567"

其将提供定位文件所需的信息，带有叶元素 ID“a1234567”并且在编号为“0001”的文件夹中提供。

如果修改后的文件属性没有值（即，在引号之间没有字符或空格，修改文件=“”），则其将与不包含叶元素的属性一样。

下面的案例说明了各个操作属性值的使用。这些例子并不包括全部可能的情况。关于操作属性使用的具体问题，请征询相关监管机构。在实际填入 XML 实例时，使用叶 ID 来引用文件。

案例 1 – 资料的首次提交。

表 6-4

提交序列号 #	文件名	操作	将被修改的文件	在审查工具中的试样逻辑显示
0000	0000\…\structure.pdf	新建		structure.pdf （当前）

案例 2 - 两个提交。0000 号提交是资料的首次提交。0001 号提交是随后的修正或变更，其中申请人打算完全替换在 0000 号提交中的 structure.pdf 文件。这样做的目的是为了保持原有的 structure.pdf 作为历史参考，但仅考虑 0001\…\structure2.pdf 的内容，因其与审查有关。这两个提交可描述如下：

– 0000 号提交是文件 structure.pdf 的首次提交，此文件为当前版本文件。

– 0001 号提交，在稍后时间提交，是文件 structure2.pdf 的提交，其为当前的并替换在 0000 号提交中的文件 structure.pdf。

在生命周期变更期间无需保存文件名称，事实上，如果两个文件同时打开进行比较或用于其他目的时，文件名的逻辑差异可以在审查时有所助益。

表 6-5

提交序列号 #	文件名	操作	将被修改的文件	在审查工具中的试样逻辑显示
0000	0000\…\structure.pdf	新建		structure.pdf （当前）
0001	0001\…\structure2.pdf	替换	0000\…\structure.pdf	*structure.pdf （替换）* structure2.pdf （当前）

案例 3 - 两个提交。0000 号提交是资料的首次提交。0001 号提交是申请人打算在原来的 structure.pdf 文件（0000 号提交中）中加入新的资料时所作修正或变更。其目的是使审查者认为这两个文件的内容与提交有关。这两个提交可描述如下：

- 0000 号提交是文件 structure.pdf 的首次提交，此文件为当前版本文件
- 0001 号提交，在稍后时间提交，是文件 structure2.pdf 的提交，其为当前的并补充在 0000 号提交中的文件 structure.pdf。这两个文件应视为与审查资料有关。

在生命周期变更期间无需保存文件名称，事实上，如果两个文件同时打开进行比较或用于其他目的时，文件名的逻辑差异可以在审查时有所助益。

表 6-6

提交序列号 #	文件名	操作	将被修改的文件	在审查工具中的试样逻辑显示
0000	0000\…\structure.pdf	新建		structure.pdf（当前）
0001	0001\… \structure2.pdf	增补	0000\...\structure.pdf	structure.pdf （现行-增补） structure2.pdf （现行）

案例 4 - 两次提交。0000 号提交是资料的首次提交。0001 号提交是申请人打算删除原来提交文件中的一个文件所作的修正或变更。其目的是使审查者不予考虑原始文件的内容，可能是因为其不应该与原始资料一同提交。这两个提交可描述如下：

- 0000 号提交是文件 structure.pdf 的首次提交，此文件为当前版本文件
- 0001 号提交，在稍后时间提交，要求删除在 0000 号提交中的文件 structure.pdf，视为不再与文件审查有关。

表 6-7

提交序列号 #	文件名	操作	将被修改的文件	在审查工具中的试样逻辑显示
0000	0000\...\structure.pdf	新建		structure.pdf（当前）
0001		删除	0000\...\structure.pdf	**structure.pdf（与审查无关）**

文件重复使用

清楚了解文件和叶元素的差异对成功应用 eCTD 非常重要。通过样式表或 eCTD 浏览器查看 eCTD 序列时，内容文件组织的表现方式是以 index.xml 文件中的叶元素的组织为基础的。下层文件和文件夹结构对查看 XML 主干中所引用文件的组织并不重要。eCTD 的此方面使用户能够一次提交一个文件，并通过提供引用该文件的多个叶元素显示其在 eCTD 的多个位置。建议 eCTD 规范的使用者在一个序列中一个文件仅提供一次，如果需要，可以提供多个引用该文件的叶元素。该文件的位置并不重要，其应仅位于文件夹结构中的一处适当位置。建议 eCTD 查看工具供应商开发直观的显示方式以便审查员可以轻易地识别出被引用多次的文件。

此项功能也可以扩展到不同序列之间，乃至于不同申请之间，只要该文件的位置在引述该文件的叶元素的 xlink：href 属性中被准确地引述。建议 eCTD 查看工具供应商开发直观的方式显示在当前序列引述文件的叶元素和在先前序列引述文件的叶元素之间的差异。在此情况下，对存在引用文件的 xml 的骨架进行验证时，应允许 xlink:href 可以引用其他序列的文件，同时不妨碍其他申请人/监管机构审查 eCTD。eCTD 规范使用者在引述跨序列和/或申请内容之前应咨询监管机构。

DTD 的内容模块

eCTD 的内容模块源于通用技术文档组织。内容模块的一部分的图形表示如下。内容模块自“ectd” 开始分层一直到提交文件中包含的具体项目。

图 6-2

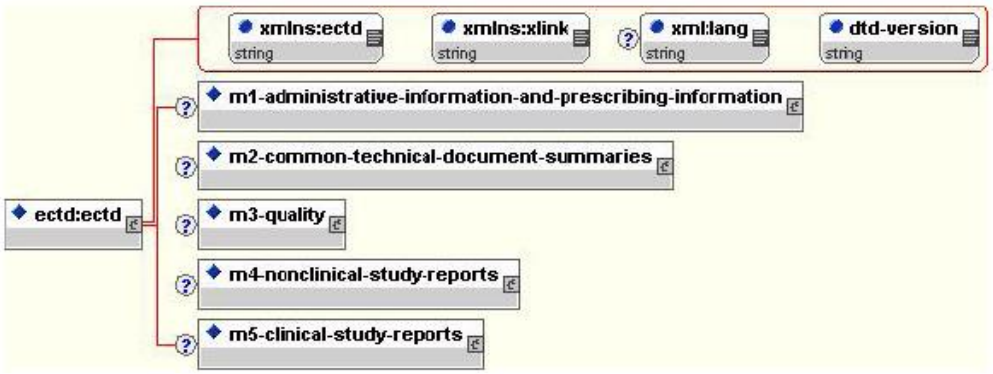
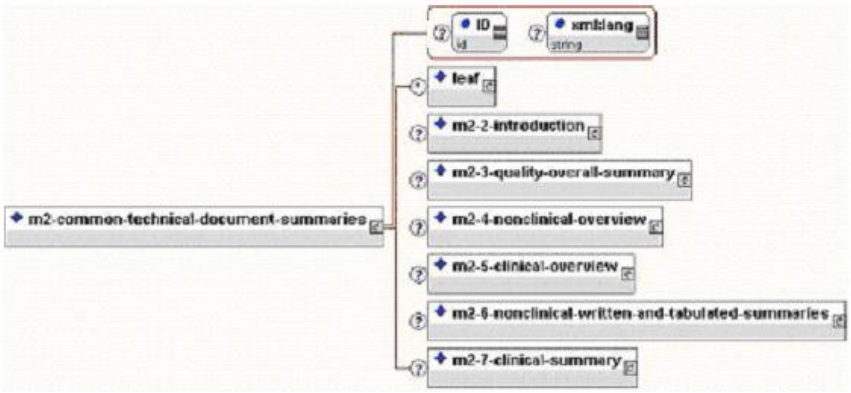


图 6-3 显示了包含概要的 CTD 章节是如何构建的。

图 6-3



一旦选定了合适的元素（例如，图 6-4），<leaf>元素和属性可用于指定提交中的某个文件。详细阐述见本附录的“eCTD 元素/属性说明”。

图 6-4

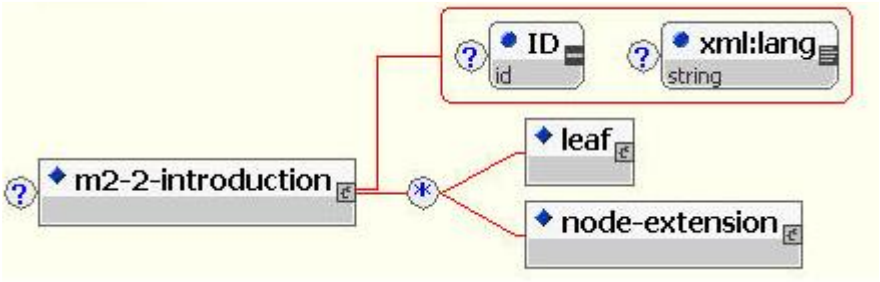
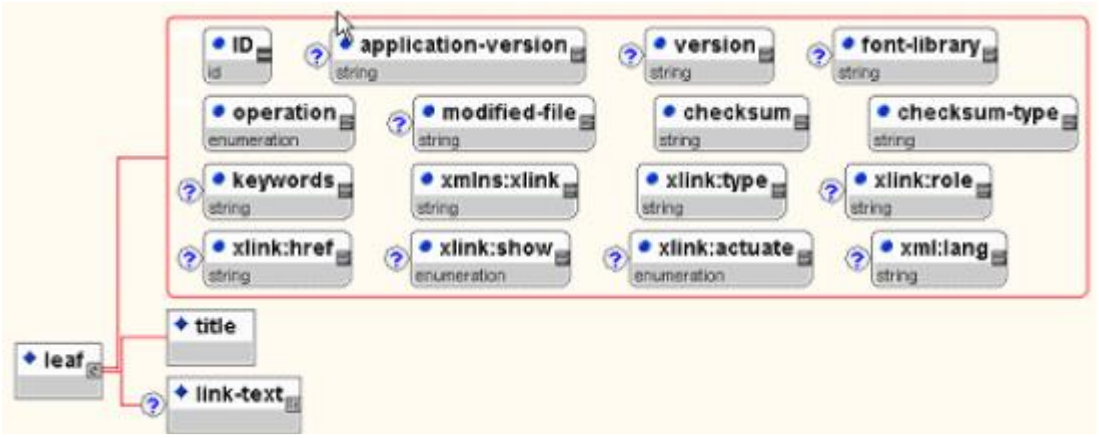


图 6-5



eCTD 元素/属性说明

eCTD 包括 5 个主要模块：

- m1-administrative-information-and-prescribing-information
- m2-common-technical-document-summaries
- m3-quality
- m4-nonclinical-study-reports
- m5-clinical-study-reports

5 个模块的每一个均可以分为一个或多个元素，每一个均具有独特的代表每一个 CTD 目录位置元素标识符。应完成下列步骤，将所有文件置于 M1-M5 中进行提交在下面的例子中展示，所有的文件都是为模块 1 至模块 5 提交的：

1. 为将要提交的文件选择一个最适合 CTD 目录的元素。例如，选择元素<m2-7-3-summary-of-clinical-efficacy>以提交临床疗效总结文件。
2. 适当的情况下说明追加元素属性，在这个例子中，具体说明“适应症”属性以确定在 2.7.3 中的有效性总结的主题。
3. 在<m2-7-3-summary-of-clinical-efficacy>元素内创建一个子<叶>元素。
4. 规定在叶元素的“xlink：href”属性中的实际文件的相对位置和文件名。
5. 提供在叶元素的<title>元素中的文件的描述和简洁的标题。
6. 为表 6-8 所述叶元素的相关属性提供信息。

表 6-8 更详细地描述了这些元素和属性中的每一个。

表6-8

元素	属性	描述/说明	例子
任何目录元素，例如<m2-4-nonclinical-overview>		目录元素代表了与通用技术文件特定章节相关的一个或多个文件的组合。诸多 TOC 元素可通过使用属性作进一步定义。eCTD DTD 定义了在 eCTD 的不同位置的以下属性：原料药、生产商、产品名称、适应症、辅料、剂型（如 2.3.S 和 3.2.S 有两个“free-text”的属性：原料药和生产商； 5.3.5 有附加的“free-text”属性，适应症）。为了与“CTD 一般问答” 一致，，这些属性的值应该放在在适当的指定位置。目前尚没有针对这些属性的任何标准术语，因此申请人应仔细选择这些属性的文本，因为它们在申请生命周期中不能被轻易改变。 一个或多个子<leaf>元素可以被宣布为一个总目录元素。 通过提供<节点-扩展“node-extension”>元素很可能会扩展目录元素。节点扩展仅应在确定的目录元素的最低级添加。不建议利用节点扩展，应该在不可避免的情况下方可实施。采用节点扩展前，请参阅区域指导。参见本附录（示例 6-5）的“扩展 XML eCTD DTD 元素说明”。	
	ID	在XML实例中的位置的唯一标识符。	id403（注意在此级别，ID是可选的）
	xml:lang	在包含全部申报章节的XML中主要使用的语言。采用ISO - 639标准语言缩写。	en
<leaf>		叶元素是文件的参考。一个或多个叶元素可以构成目录元素。	
	应用版本	由用来创建文件的软件应用程序产生的文件格式版本。	PDF 1.4
	字体库	保留供以后使用	
	ID	ID 属性旨在成为可用于提交中的特殊参考，它可以从 XML 文档中的一个项目引用到另一个项目的。XML ID 值以文字字符或下划线开头。如果申请人使用仅生成数字的内部 ID 生成软件，则在生成的数字前加入字母或者下划线，从而创建一个有效的 ID	id050520 注意：关于构成此属性值的组成部分请参阅 W3C 网站上的 XML-ID 建议。(http://www.w3.org/TR/xml-id/#processing)
	校验和	被提交文件的校验值。	e854d3002c02a61fe5cbe926fd97b001
	校验和类	使用校验和算法。	MD5

元素	属性	描述/说明	例子
	型		
	修改后的文件	修改后的文件属性的目的是给出将要被叶元素修改（即替换、增补或删除）的叶元素的位置。当操作属性有一个增补、替换或删除的值时，修改后的文件属性应该有一个值。修改后的文件属性指向“index.xml”文件和将被改变的叶元素的叶 ID。	../0001/index.xml#a1234567
	操作	指示要执行的操作。您应该选择以下有效值之一： • 新建 • 替换 • 增补 • 删除 这些值的具体意义见本附录的操作属性部分。	新建
	版本	由用来创建文件的软件应用程序产生的文件格式版本。	V23.5
	xlink:激活	保留供以后使用	
	xlink:href	提供了实际内容文件的参考。您应该使用到文件和文件名的相对路径。内容文件不需要与引用它的叶元素处于同一序列。	0000/m2/27-clin-sum/literature-references.pdf
	XLink：角色	保留供以后使用	
	Xlink：展示	保留供以后使用	
	XLink：类型	“简单”固定值	simple
	关键词	保留供以后使用	
<title>		作为叶元素的一部分，该元素包含了叶引用的文件的实际名称。	研究报告: 1234 注意：叶标题应简明扼要；建议1024字节（512个字符）为最大长度
	ID	在 XML 实例中此位置的独特的标识符。叶 ID 以文字字符或下划线开头。	a1234567 注意1：请参阅XML-ID 有关此属性值组成的信息，请访问W3C网站（http://www.w3.org/TR/xml-id/#process） 注意2：在此级别，ID是可选的
<link-text>		保留供以后使用	
<xref>		保留供以后使用	

Example 6-1: Instructions for a Simple New Submission[7]

The following XML fragment demonstrates the submission of a clinical overview of efficacy as a single PDF document.

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-x.dtd">
<?xml-stylesheet type="text/xsl" href="util/style/ectd-2-1-x.xsl"?>
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
        <m2-common-technical-document-summaries>
                <m2-5-clinical-overview xml:lang = "en">
                        <leaf ID="s123456" operation = "new" xlink:type = "simple" checksum-type="md5"
                        checksum = "e854d3002c02a61fe5cbe926fd973401" xlink:href = "m2/25-clin-
                        over/clinical-overview.pdf" application-version = "PDF 1.4">
                        <title>Clinical Overview</title>
                        </leaf>
                </m2-5-clinical-overview>
        </m2-common-technical-document-summaries>
</ectd:ectd>
```

This submission includes the file "clinical-overview.pdf" in the relative directory "m2/25-clin-over/" (i.e. the one starting below the dossier number directory). The file is "new" and has a descriptive name of "Clinical Overview"

The regional review application should treat this as a new submission to be associated with the submission identified in CTD module 1, which is region specific.

---

[7] Note that these XML examples are examples only and do not necessarily contain all of the elements and attributes that you should use when preparing an eCTD submission.

If this is the first submission for Dossier CTD 123456, all the files in this submission would typically be in the ctd-123456\0000 directory and below.

Example 6-2: Instructions for an Amendment, Supplement, or Variation

In the previous example, a clinical overview was submitted. In this example, it is replaced by an updated version.

To replace a file, add the replacement <leaf> element under the same element as the original file.
If this is the second submission for Dossier CTD 123456, all the files in this submission would typically be in the ctd-123456\0001 directory and below.

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-x.dtd">
<?xml-stylesheet type="text/xsl" href="util/style/ectd-2-1-x.xsl"?>
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
<m2-common-technical-document-summaries>
        <m2-5-clinical-overview xml:lang = "en">
                <leaf ID="a123457" operation = "replace"  xlink:type = "simple" checksum-type="md5" checksum =
                "502e9ab5827431f077340cea3b5e465a" xlink:href = "m2/25-clin-over/clinical-overview-revised.pdf"
                application-version = "PDF 1.4" modified-file = "../0000/index.xml#s123456">
                   <title>Clinical Overview</title>
                </leaf>
        </m2-5-clinical-overview>
</m2-common-technical-document-summaries>
</ectd:ectd>
```

Example 6-3: Instructions for Multiple Indications

Multiple therapeutic indications use an additional attribute associated with the <m2-7-3-summary-of-clinical-efficacy> and the <m5-3-5-reports-of-efficacy-and-safety-studies> elements to allow multiple indications to be submitted. There is currently no standard terminology list for 'indication'. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change. The following table shows the use of these attributes.

Table 6-9

Element	Attribute	Description/Instructions	Example
<m2-7-3-summary-of-clinical-efficacy>	indication	Name of the indication	Pain
<m5-3-5-reports-of-efficacy-and-safety-studies>	indication	Name of the indication.	Pain

Note that the indication attribute is used by the regulatory authority to apply to all the table of contents elements beneath the <m2-7-3-summary-of-clinical-efficacy> and <m5-3-5-reports-of-efficacy-and-safety-studies> elements. The following example expands on the instance showing the submission of information about two indications (pain and nausea).

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-x.dtd">
<?xml-stylesheet type="text/xsl" href="util/style/ectd-2-1-x.xsl"?>
```

```
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
    <m2-common-technical-document-summaries>
        <m2-7-clinical-summary>
        <m2-7-3-summary-of-clinical-efficacy indication = "pain">
            <leaf ID="s123456"operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
            "5aa5c0e630a700af869e4c72535fc922" xlink:href = "m2/27-clin-sum/summary-clin-efficacy-
            pain.pdf">
                <title>pain efficacy summary</title>
            </leaf>
        </m2-7-3-summary-of-clinical-efficacy>
        <m2-7-3-summary-of-clinical-efficacy indication = "nausea">
            <leaf ID="a123457" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
            "bde4d34dc80678a266352daf450c3962" xlink:href = "m2/27-clin-summ/summary-clin-efficacy-
            nausea.pdf">
                <title>nausea efficacy summary</title>
            </leaf>
        </m2-7-3-summary-of-clinical-efficacy>
        </m2-7-clinical-summary>
    </m2-common-technical-document-summaries>
    <m5-clinical-study-reports>
        <m5-3-clinical-study-reports>
        <m5-3-5-reports-of-efficacy-and-safety-studies indication = "pain">
            <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
                <leaf ID="a123458" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                    "a4529c4a257f07f8a0ec591dde854578" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-safety-
                    stud/pain/pain-sr1.pdf">
                    <title>pain study report 1</title>
                </leaf>
            </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
        </m5-3-5-reports-of-efficacy-and-safety-studies>
        <m5-3-5-reports-of-efficacy-and-safety-studies indication = "nausea">
            <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
                <leaf ID="a123459" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                    "c5c39f594b2070a57bea66e58860efcf" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-safety-
                    stud/nausea/nausea-sr15.pdf" >
                    <title>nausea study report 15</title>
                </leaf>
                <leaf ID = "a123460" operation = "new" xlink:type = "simple" checksum-type = "md5" checksum
                    = "15faf198015f3599acabb7755c2d6b0c" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-
                    safety-stud/nausea/5351-stud-rep-contr/xyz0015/nausea-sr15.pdf">
                        <title>nausea study report 15</title>
                </leaf>
            </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
        </m5-3-5-reports-of-efficacy-and-safety-studies>
        </m5-3-clinical-study-reports>
    </m5-clinical-study-reports>
</ectd:ectd>
```

Example 6-4: Instructions for Multiple Drug Substances, Manufacturers, and Products

Multiple drug substances use additional attributes associated with the <m3-2-s-drug-substance> element to allow unique combinations of the drug substance name and manufacturer to be submitted. There are currently no standard terminology lists for these attributes. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value.Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change. The following table shows the use of these attributes in 3.2.S.

Table 6-10

Element	Attribute	Description/Instructions	Example
<m3-2-s-drug-substance>	substance	Name of one of the drug substances	Acetaminophen
	manufacturer	Name of the manufacturer of the drug substance	My Supplier

Example 6-4A:
This is an example of a section of the instance showing the submission of information about two drug substances (acetominophen and codeine), one of which is supplied by two manufacturers:

```
<m3-2-body-of-data>
        <m3-2-s-drug-substance substance = "Acetaminophen" manufacturer = "My Supplier">
                <leaf  ID="a123456" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "b002e4544c02361fe54be926ae777012" xlink:href = "m3/32-body-data/32s-drug-
                sub/acetaminophen-my-supplier/acetaminophen.pdf">
                        <title>Acetaminophen - My Supplier Data</title>
                </leaf>
        </m3-2-s-drug-substance>
        <m3-2-s-drug-substance substance = "Acetaminophen" manufacturer = "Bulk Company 2">
                <leaf ID="a123457" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "0000cdfa05b1e995f88057150414a783" xlink:href = "m3/32-body-data/32s-drug-
                sub/acetaminophen-bulk-company-2/acetaminophen2.pdf">
                        <title>Acetaminophen - bulk company 2 data</title>
                </leaf>
        </m3-2-s-drug-substance>
        <m3-2-s-drug-substance substance = "Codeine" manufacturer = "Drug company 2">
                <leaf ID="a123458" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "f555a3234f65623fe54be926ee435354" xlink:href = "m3/32-body-data/32s-drug-sub/codeine-
                drug-company-2/codeine-quality-data.pdf">
                        <title>codeine - drug company 2 data</title>
                </leaf>
        </m3-2-s-drug-substance>
</m3-2-body-of-data>
```

Multiple drug products use additional attributes associated with the <m3-2-p-drug-product> element to allow unique combinations of the drug product name and dosage form to be submitted. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change. The following table shows the use of these attributes in 3.2.P.

Table 6-11

Element	Attribute	Description/Instructions	Example
<m3-2-p-drug-product>	product-name	Name of one of the drug products	Wonder drug
	dosageform	Dosage form	Capsule
	manufacturer	Manufacturer of the drug product	Company A

Example 6-4B
This is an example of a section of the instance showing the submission of information about two drug products (a capsule and a tablet):

```
<m3-2-body-of-data>
        <m3-2-p-drug-product product-name = "Wonder drug" dosageform="Capsule" manufacturer="Company
        A">
```

```
                <leaf ID="a123456" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "f27cd9e659d8acf7baab10cc753d733c" xlink:href = "m3/32-body-data/32p-drug-prod/capsule-
                5mg/32p1-desc-comp/description-and-composition.pdf">
                        <title>Wonder drug capsule product information</title>
                </leaf>
        </m3-2-p-drug-product>
        <m3-2-p-drug-product product-name = "Wonder drug" dosageform="Tablet" manufacturer="Company A">
                <leaf ID="a123457" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "7490d74c3d5e442ad57daa155253eb16" xlink:href = "m3/32-body-data/32p-drug-prod/tablet-
                5mg/32p1-desc-comp/description-and-composition.pdf">
                        <title>Wonder drug tablet product data</title>
                </leaf>
        </m3-2-p-drug-product>
</m3-2-body-of-data>
```

Example 6-5: Instructions for Extending XML eCTD DTD Elements

An applicant can extend the definition of an element by creating node extensions beneath a defined table of contents element. Using node extensions is discouraged and should be done only when unavoidable. Please refer to regional guidance before using node extensions. The child element <node-extension> should be used for each new table of contents node created. The <title> element value is inherited from the parent element. You should only extend the lowest level of defined elements. For example you can extend the <m2-3-r-regional-information> element but not the <m2-3-quality-overall-summary> element since the latter is not the lowest element defined in the table of contents.

The following is an example of a section of an eCTD instance in which the applicant extends the <m2-3-r-regional-information> to provide specific regional information as requested by a regulatory authority. The title element associated with the <node-extension> describes the extension. Alternatively, the regional information in this example could have been provided as a <leaf> element under the <m2-3-r-regional-information> element without the use of a "node extension".

```
<m2-common-technical-document-summaries>
        <m2-3-quality-overall-summary>
        <m2-3-r-regional-information>
        <node-extension>
                <title>special-summary</title>
                <leaf ID="a123456" operation = "new" xlink:type = "simple" xlink:href = "m2/23-qos/extra-
                quality-sum.pdf" checksum-type="md5" checksum = "7490d74c3d5e442ad57daa155253eb16">
                        <title>Extra Quality Summary </title>
                </leaf>
        </node-extension>
        </m2-3-r-regional-information>
        </m2-3-quality-overall-summary>
</m2-common-technical-document-summaries>
```

To update a file that has been submitted as an extended node, you should submit the replacement file using exactly the same element and "node extension" information, including the <title> element for the <node-extension>. This makes it possible for the regulatory authority to locate the original file and update its status.

Example 6-6: Instructions for Submitting Sections as Paper

During the transition to fully electronic submissions of the CTD, some regions will accept that some sections can be submitted as paper only. Please refer to regional guidance. These sections should be identified in the XML eCTD instance by including a PDF file in the instance that describes the content and location of the paper section. For example, the PDF file might consist of only one page with the name of the CTD document and the physical volume number and tab identifier. The <title> element in the XML eCTD instance could indicate that this is a paper submission.

This is an example of the instance showing the submission of a paper efficacy overview document.

```
<m2-common-technical-document-summaries>
        <m2-5-clinical-overview xml:lang = "en">
        <leaf ID="a123456" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
        "e854d3002c02a61fe5cbe926fd973401" xlink:href = "m2/25-clin-over/clinical-overview.pdf" application-
        version = "PDF 1.4">
                <title>Paper Submission </title>
        </leaf>
        </m2-5-clinical-overview>
</m2-common-technical-document-summaries>
```

附录 7：提交格式规范

引言

本附录介绍了纳入 eCTD 的文件的构建方法。本部分阐述了在电子格式提交中通常用到的文件格式。其他格式可以根据各地区公布的指导使用其他格式。

PDF

便携文档格式（PDF）是由 Adobe 系统公司（http://www.adobe.com）创建的已发布的格式。没有必要使用由 Adobe 或任何指定公司的产品生成 PDF 文件。PDF 作为在本规范中定义的文件标准被接受。下面建议支持创建能被监管机构有效审查的 PDF 文件。对于日语版本的 Adobe Acrobat 特定规范，或者含有日语字符的文件，请参阅该区域的指导。

为了确保 PDF 文件可以被有效访问，PDF 文件应不大于 100 兆字节。优化 PDF 文件以便进行快速网络视图。

版本

所有 ICH 地区监管机构均能够阅读并同意接受保存为 PDF 1.4 版的 PDF 文件。监管机构不需要任何额外的软件来阅读和浏览 PDF 文件。PDF/A-1（ISO 标准 - ISO 19005-1:2005）是存档格式，不符合 ICH 与使用 eCTD 来审查的需求。如果需要提交其他版本的 PDF，请查阅区域指导原则。

字体

如果用于创建文本的字体在审查者的计算机上无法使用，则 PDF 浏览软件会自动替换字体来显示文本。字体替换可能会影响文档的外观和结构，并且并在某些情况下，会影响文件所传达的信息。监管机构不能保证除 Times New Roman、Arial 字体、Courier 和 Acrobat 产品自身支持的字体以外的其他任何字体的可用性。因此，在 PDF 文件中使用的所有其他字体应该被嵌入，以确保那些字体始终能够被审阅。嵌入字体时，该字体的所有字符应该被嵌入，而不仅仅是在文件被使用的字体的一个子集。

嵌入字体需要额外的计算机存储空间。嵌入字体采用的三种技术帮助限制存储空间的措施包括：

- 限制在每个文档中使用的字体的数量
- 仅使用全真字体或 Adobe 类型 1 字体
- 避免定制的字体

日文字体（2 个字节的字体）比罗马字体（1 个字节）字体大，因此，规范允许为所有日文字体嵌入一个子集。嵌入字体的目的是使该文件的接收人能够使用个人计算机正确显示和打印文件而不必在电脑上安装相同的字体。因此，没有必要向嵌入所有日文字体。嵌入日文字体的一个子集应

该就可达到满意的效果。

子集的定义

子集是指嵌入仅在文档中使用的那些字符。嵌入一个完整的集是指嵌入所有组成字体的字符，乃至在文件中没有使用的字符。所有 2 个字节的字体，例如日文，应该作为一个子集嵌入。

嵌入日文字体的说明：

嵌入字体时应考虑以下内容：

优势：

- 嵌入字体使得 PDF 文件可以在任何接受着电脑环境下正确显示和打印。
- 该计算机不需要安装原来的字体。

缺点：

- 字体嵌入时该文件的大小增加。
- 文档中包含很多页面时，会使文档打印速度较变慢。
- 许多 eCTD 文件包含大量页面。在这种情况下印刷时间就成为需要考虑的问题。
- 使用日文字体时，应在发送者和接收者之间建立操作规则。（见区域指导）
- 流行的字体的使用仅允许发送者和接收者正确地查看和打印文件而没有嵌入字体。

字体大小

因为内容太小无法阅读而调整文件的大小是低效率的。Times New Roman，12 号字体，本文件使用的字体，在大小上对叙述性文字是适当的，应尽可能使用。有时表格和图表可以尝试使用小于 12 号的字体，但应该尽可能避免使用。在为一个表选择字体的大小时，应在在单页上提供充足的信息以方便审查者进行数据比较和同时保持字体大小使文字清晰之间寻求平衡。由此得出的必然结果是，使用较大的字体，可能需要更多的表格，其使得数据比较变得复杂，因为数据现在可能包含在不同的表格中。一般来说，Times New Roman 字体 9-10 大小或者同等大小的其他推荐字体被认为是可以接受的，但应避免更小的字体。

使用彩色字体

建议使用黑色颜色字体。蓝色可用于超文本链接。浅色在灰度打印机上打印效果差，因此应避免。在提交之前使用灰度打印机打印文件的样页以测试色彩再现效果。应避免使用背景阴影。

页面方向

页面方向应该适当以便所有纵向页面可以在纵向和横向显示，所有横向打印格式页面横向显示。为了实现这一目的，在 PDF 文件在最终格式保存之前横向打印格式页面应设置页面方向为横

向。

页面大小和页边距

页面打印区域应放适合 A4 纸（210×297mm）和信纸（8.5”×11”）。每一页页面左侧应保留充分的页边距（至少 2.5 厘米），以避免审查者为临时使用而打印并装订时信息模糊。横向页面（通常为表格和刊物），较小的边距（至少顶部 2.0cm，左、右 0.8cm）可以在该页清晰地显示更多的信息（见字体）。页眉和页脚信息可以出现在这些边缘内，但不应该过于接近页边距面而导致信息在打印时丢失。

页眉和页脚

M4 粒度文件规定一个文件的所有页面应包括独有的页眉或页脚以简要标识其主题。eCTD 有大量的元数据可供审查者查阅，从而易于识别文件，但在每一页（页眉或页脚）都有独有的标识仍然是恰当的（例如，一个文件被打印或者多个文件同时在屏幕上被查阅时）。独特的标识符不一定要包含 CTD 部分标识符或其他元数据。其应足以识别文件的一般主题（例如，研究编号、批号）。

电子文件来源

通过扫描纸质文档制作 PDF 文件通常劣于从电子源文件生产的 PDF 文件。扫描的文档保存为图像文件比较难读，并且不允许审查者搜索或复制和粘贴文本以进行编辑。应尽量避免使用扫描。

创建 PDF 文档和图片的方法

创建 PDF 文件的方法应展示纸质文档复制的最佳效果。为确保纸质和 PDF 文档的版本是相同的，应从 PDF 版本打印文件。仅以纸质版本提供的文件应以在电脑屏幕上和打印版本中均可清晰可读的分辨率进行扫描。同时，应该限制文件的大小。建议以每英寸 300 点（dpi）的分辨率进行扫描，以寻求清晰度和文件大小之间的平衡。因为文件的大小，不建议使用灰度或彩色。扫描后，应该避免以较低的分辨率重新采样。

创建包含图像的 PDF 文件时，不应该降低图像分辨率采样。降低图像分辨率不能保留原始图像的像素。对于 PDF 格式图像，应采用下面的无损压缩技术之一：

- 对于彩色和灰度图像的无损压缩，使用 CCITT Group 4 Fax 压缩技术。其在因特网 RFC 1950 和 RFC 1951（http://www.ietf.org/rfc/rfc1950.txt）中阐述。
- 对于黑白图像的无损压缩，使用 CCITT 组 4 传真（CCITT Group 4 Fax）压缩技术。此技术作为 CCITT 建议 T.6（1988）“第 4 组传真机传真编码方案和编码控制功能”中被阐述。

包含手写注释的纸质文件应以至少 300dpi 的分辨率扫描。为了达到清晰的效果，手写注释应该采用黑色墨水。扫描含有非西方文字（如汉字）的文件时，特别要求使用高分辨率，建议 600dpi。

对于照片，图像应采用 600dpi 的分辨率。如果提交黑白照片，应考虑 8 位灰度图像。如果提交

彩色照片，应考虑 24 位 RGB 图像。拍摄的图像不应该进行非均匀缩放（即，大小）。

凝胶和染色体组型应直接进行扫描，而不是从照片复制。扫描应采取 600dpi 和 8 位灰阶深度。

绘图仪输出的图形应以 300dpi 分辨率扫描或拍摄。

高校液相色谱图或类似的图像应以 300dpi 分辨率扫描。申请人应验证这些扫描版本的质量。

超文本链接和书签

超文本链接和书签提升了 PDF 文件的导航定位能力。超文本链接可以由使用细线的矩形标明或采用适当的蓝色文本。

一般来说，对于带有目录的文件，应为在目录中列出的每个项目都应建立书签，包括所有表格、图片、发表文献、其他参考和附录。书签应遵循目录的层级和顺序。这些书签对于在文件间进行有效的导航是必不可少的。书签层级应与目录层级一致，不应有超出目录层级的额外的书签层级。每个增加的层级增大了阅读书签所需的空间。建议在同一级中所使用的书签不超过 4 个层级。

整个文件中支持不在同一页中的注释、相关章节、参考文献、附录、表格或数字的超文本链接是非常有帮助的，可以提高导航效率。创建超文本链接时应使用相对路径，以便最大限度地减少文件夹在磁盘驱动器之间转移时的超链接功能损失。一旦提交的文件加载到监管机构的网络服务器后，引用特定驱动器和根目录的绝对链接将不再起作用。

创建书签和超链接时，应使用倍率设置*承前缩放*，以便目标页在审查员在文件余下部分使用时其能以相同的倍率显示。

各监管机构在关于书签是否应扩展或合并的规定方面经验不足。打开所有的书签可能被认为是不适当的，因为，在某些情况下，过量书签对审查没有用处并且可能影响在 Web 浏览器刷新的时间。同样，对完全合并书签也有可能是无益的，因为审查员总是会打开它们。因此，建议申请人考虑审查员如何显示书签对审查员的有用性，并在提交的文件中使类似的文件类型保持一定程度的一致性。

页码

文件仅要求具有内部页码（1 - n）。在整个文件中没有附加页/卷数。在文档和 PDF 文件的页码是相同的情况下，电子文件更容易浏览。为达到容易浏览的目的，文档的第一页应编号为第 1 页，所有后续页（包括附录和附件）应以阿拉伯数字连续编号。罗马数字不应该用来标记页数（例如，标题页、目录），任何页均不应无编号（如标题页。）以这种方式进行的编码使 Acrobat 编号与内部文件页码同步。

唯一的例外情况是，一个文件因为其大小（例如，>100MB）而被拆分，第二个或后续的文件应基于第一个或前面的文件连续编号。

文档信息域

建议在区域指导中就特定类型的提交提供文档信息域。

打开对话框

文件被打开后打开的对话框设置文档视图。PDF 文件的初始视图应设置为书签和页面。如果没有书签，应仅设置页面初始视图。放大倍率和页面布局应设置为默认。

安全

应包含无安全设置或密码保护的 PDF 文件。安全域应设置为允许打印、变更文档，选择文本和图形，并添加或更改注释和表单域。

PDF 文档索引

ICH 相关地区目前尚无计划使用全文索引。

Acrobat 插件的使用

使用插件来协助创建提交文件是适当的。然而，除了与 Adobe Acrobat 同时提供的插件外，审查提交文件不应要求使用任何插件，因为监管机构并不一定具有使用额外的插件功能的权利。

XML 文件

万维网协会（W3C）工作组开发了 XML。这是一种开发的非专有语言，用以改善以往的标记语言，包括标准通用标记语言（SGML）和超文本标记语言（HTML）。

在 XML 文件中的信息分为具体的部分。这些部分被称为对象或元素类型。元素类型标识了信息部分。例如，以 eCTD 形式提交申报文件的公司名称可以以元素类型<applicant>进行识别。

所有元素类型名称被括在特殊字符< >之内。在 XML 文档内，元素类型名称正好放置信息片之前和信息之后。这就是标记。因此，在 XML 文件中，申请人可被标记如下：<applicant>全球制药公司</applicant>。在元素类型之前的“/”表示申请人的信息结束。

利用 XML 描述文件内容普遍被认为是一种趋势。然而，目前的规范仅支持结构化信息使用 XML。这点可以说明提交摘要、报告和其他 XML 格式的描述性文件当前不被规范支持。监管当局和申请人可以商定在其区域使用其它格式（包括使用与上述方式不同的通用格式）。因此，如果申请人希望为描述性文件使用 XML，申请人应与申请人自己地区的监管当局联系，并且了解其他监管当局可能不接受这些 XML 文件。

通过使用分层结构，XML 允许与两个或更多的元素联系起来。这是通过将一个元素嵌套到另一个元素中来完成的。

关于元素类型的其他信息可在属性中提供。属性被放置在元素类型内，并用引号（“ ”）包围。例如，如果您想表明申请人的名称以英文表达，那么您可以添加此信息部分作为一个属性。在 XML

文件中其会被表达为<applicantXML:LANG=“EN”>全球制药公司</applicant>。

XML 文件可通过互联网浏览器中找到的解析器读取。样式表为浏览器提供了创建表格、字体、和显示颜色的信息。

元素类型和属性的具体名称，以及定义 XML 元素的有效语法、结构和格式包含在一个名为文档类型定义（DTD）的文件中。如果 XML 文档不符合 DTD，那么将无法正确使用该文件。

XML 文件的前三行应包括 XML 版本，样式表类型和地址，以及 DTD 的名称和地址。

有关 XML 标准的更多信息可在 W3C 网站 www.w3.org 上查阅。

SVG 文件

SVG 是一种在 XML 中用来描述二维图形的语言。SVG 可以构造三种类型的图表主题：矢量图形（例如，直线和曲线组成的路径）、位图图象和文字。图形对象可以被组化、样式化、变形和重新组合到先前提交的对象中。文本可以在适合于申请的任何 XML 命名空间中，其增强了 SVG 图形的可搜索性和可存取性。所设定的特性包括嵌套转换、剪辑路径、alpha 蒙板、过滤效果、模板对象和可扩展性

SVG 的图形可以是动态的、互动的。SVG 的文档对象模型（DOM）包括完整的 XML DOM，可通过脚本编写实现简单有效的矢量图动画。丰富的事件处理程序，如在地图上移动、点击鼠标等，可分配给任何 SVG 图形对象。由于其与其他 Web 标准兼容并对其加以利用，因此脚本编写等特性可在相同的 Web 页面上同时作用于 SVG 元素和来自不同命名空间的其他 XML 元素。[8]

在提交文件中关于 SVG 的具体的使用应当与监管当局进行讨论。

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[8]SVG 的描述见 http:www.w3.org/graphics/svg。

Appendix 8: XML eCTD DTD

```
<?xml version="1.0" encoding="UTF-8"?>
<!-- Changes prior to Version 1.00 captured in file
      "Historical Changes.txt

    ICH eCTD DTD
    Version 1.0 - March 6, 2002
    Version 3.0 - Sept 11, 2002
    Version 3.0 - Oct 1, 2002
    Version 3.0 - Oct 8, 2002
    Version 3.1 - Nov 11, 2003
          Version 3.2 - Nov 21, 2003

Changes in version 3.1
-         ID was changed to REQUIRED in the following four locations:
                  <!ENTITY % att " ID      ID    #REQUIRED
        xml:lang CDATA  #IMPLIED">

      <!ELEMENT leaf (title, link-text?)>
                  <!ATTLIST leaf
                        ID ID #REQUIRED  <attlist continues>

            <!ELEMENT xref EMPTY>
                  <!ATTLIST xref
                        ID ID #REQUIRED  <attlist continues>

            <!ELEMENT node-extension (title, (leaf | node-extension)+)>
                  <!ATTLIST node-extension
                        ID ID #REQUIRED
                        xml:lang CDATA #IMPLIED>


Changes in version 3.2

-         Indication attribute was changed to REQUIRED in the following two locations:
                  <!ATTLIST m2-7-3-summary-of-clinical-efficacy
                  %att;
                  indication CDATA #REQUIRED

                  <!ATTLIST m5-3-5-reports-of-efficacy-and-safety-studies
                  %att;
                  indication CDATA #REQUIRED

-         Since ID is only needed for files referenced in a LEAF, changed ID back to IMPLIED for:
                  <!ENTITY % att " ID      ID    #REQUIRED
                        xml:lang CDATA  #IMPLIED">

                  <!ELEMENT node-extension (title, (leaf | node-extension)+)>
                  <!ATTLIST node-extension
                        ID ID #REQUIRED
                        xml:lang CDATA #IMPLIED>


End of changes
-->
<!ENTITY % att " ID      ID    #IMPLIED
  xml:lang CDATA  #IMPLIED">
<!-- ============================================================= -->
<!-- Top-level element -->
```

```
<!-- ============================================================= -->
<!ELEMENT ectd:ectd (m1-administrative-information-and-prescribing-information?, m2-common-technical-document-summaries?, m3-quality?, m4-nonclinical-study-reports?, m5-clinical-study-reports?)>
<!ATTLIST ectd:ectd
        xmlns:ectd CDATA #FIXED "http://www.ich.org/ectd"
        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
        xml:lang CDATA #IMPLIED
        dtd-version CDATA #FIXED "3.2"
>
<!-- ============================================================= -->
<!-- Leaf content -->
<!-- ============================================================= -->
<!ELEMENT leaf (title, link-text?)>
<!ATTLIST leaf
        ID ID #REQUIRED
        application-version CDATA #IMPLIED
        version CDATA #IMPLIED
        font-library CDATA #IMPLIED
        operation (new | append | replace | delete) #REQUIRED
        modified-file CDATA #IMPLIED
        checksum CDATA #REQUIRED
        checksum-type CDATA #REQUIRED
        keywords CDATA #IMPLIED
        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
        xlink:type CDATA #FIXED "simple"
        xlink:role CDATA #IMPLIED
        xlink:href CDATA #IMPLIED
        xlink:show (new | replace | embed | other | none) #IMPLIED
        xlink:actuate (onLoad | onRequest | other | none) #IMPLIED
        xml:lang CDATA #IMPLIED
>
<!ELEMENT title (#PCDATA)>
<!ATTLIST title
        ID ID #IMPLIED
>
<!ELEMENT link-text (#PCDATA | xref)*>
<!ATTLIST link-text
        ID ID #IMPLIED
>
<!ELEMENT xref EMPTY>
<!ATTLIST xref
        ID ID #REQUIRED
        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
        xlink:type CDATA #FIXED "simple"
        xlink:role CDATA #IMPLIED
        xlink:title CDATA #REQUIRED
        xlink:href CDATA #REQUIRED
        xlink:show (new | replace | embed | other | none) #IMPLIED
        xlink:actuate (onLoad | onRequest | other | none) #IMPLIED
>
<!ELEMENT node-extension (title, (leaf | node-extension)+)>
<!ATTLIST node-extension
        ID ID #IMPLIED
        xml:lang CDATA #IMPLIED
>
<!-- ============================================================= -->
<!-- CTD Backbone structures -->
<!-- ============================================================= -->
<!ELEMENT m1-administrative-information-and-prescribing-information (leaf*)>
<!ATTLIST m1-administrative-information-and-prescribing-information
        %att;
>
```

```
<!ELEMENT m2-common-technical-document-summaries (leaf*, m2-2-introduction?, m2-3-quality-overall-summary?, m2-4-nonclinical-overview?, m2-5-clinical-overview?, m2-6-nonclinical-written-and-tabulated-summaries?, m2-7-clinical-summary?)>
<!ATTLIST m2-common-technical-document-summaries
        %att;
>
<!ELEMENT m2-2-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-2-introduction
        %att;
>
<!ELEMENT m2-3-quality-overall-summary (leaf*, m2-3-introduction?, m2-3-s-drug-substance*, m2-3-p-drug-product*, m2-3-a-appendices?, m2-3-r-regional-information?)>
<!ATTLIST m2-3-quality-overall-summary
        %att;
>
<!ELEMENT m2-3-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-3-introduction
        %att;
>
<!ELEMENT m2-3-s-drug-substance ((leaf | node-extension)*)>
<!ATTLIST m2-3-s-drug-substance
        %att;
        substance CDATA #REQUIRED
        manufacturer CDATA #REQUIRED
>
<!ELEMENT m2-3-p-drug-product ((leaf | node-extension)*)>
<!ATTLIST m2-3-p-drug-product
        %att;
        product-name CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        manufacturer CDATA #IMPLIED
>
<!ELEMENT m2-3-a-appendices ((leaf | node-extension)*)>
<!ATTLIST m2-3-a-appendices
        %att;
>
<!ELEMENT m2-3-r-regional-information ((leaf | node-extension)*)>
<!ATTLIST m2-3-r-regional-information
        %att;
>
<!ELEMENT m2-4-nonclinical-overview ((leaf | node-extension)*)>
<!ATTLIST m2-4-nonclinical-overview
        %att;
>
<!ELEMENT m2-5-clinical-overview ((leaf | node-extension)*)>
<!ATTLIST m2-5-clinical-overview
        %att;
>
<!ELEMENT m2-6-nonclinical-written-and-tabulated-summaries (leaf*, m2-6-1-introduction?, m2-6-2-pharmacology-written-summary?, m2-6-3-pharmacology-tabulated-summary?, m2-6-4-pharmacokinetics-written-summary?, m2-6-5-pharmacokinetics-tabulated-summary?, m2-6-6-toxicology-written-summary?, m2-6-7-toxicology-tabulated-summary?)>
<!ATTLIST m2-6-nonclinical-written-and-tabulated-summaries
        %att;
>
<!ELEMENT m2-6-1-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-6-1-introduction
        %att;
>
<!ELEMENT m2-6-2-pharmacology-written-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-2-pharmacology-written-summary
        %att;
```

```
>
<!ELEMENT m2-6-3-pharmacology-tabulated-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-3-pharmacology-tabulated-summary
        %att;
>
<!ELEMENT m2-6-4-pharmacokinetics-written-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-4-pharmacokinetics-written-summary
        %att;
>
<!ELEMENT m2-6-5-pharmacokinetics-tabulated-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-5-pharmacokinetics-tabulated-summary
        %att;
>
<!ELEMENT m2-6-6-toxicology-written-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-6-toxicology-written-summary
        %att;
>
<!ELEMENT m2-6-7-toxicology-tabulated-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-7-toxicology-tabulated-summary
        %att;
>
<!ELEMENT m2-7-clinical-summary (leaf*, m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-
methods?, m2-7-2-summary-of-clinical-pharmacology-studies?, m2-7-3-summary-of-clinical-efficacy*, m2-7-4-
summary-of-clinical-safety?, m2-7-5-literature-references?, m2-7-6-synopses-of-individual-studies?)>
<!ATTLIST m2-7-clinical-summary
        %att;
>
<!ELEMENT m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods ((leaf | node-
extension)*)>
<!ATTLIST m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods
        %att;
>
<!ELEMENT m2-7-2-summary-of-clinical-pharmacology-studies ((leaf | node-extension)*)>
<!ATTLIST m2-7-2-summary-of-clinical-pharmacology-studies
        %att;
>
<!ELEMENT m2-7-3-summary-of-clinical-efficacy ((leaf | node-extension)*)>
<!ATTLIST m2-7-3-summary-of-clinical-efficacy
        %att;
        indication CDATA #REQUIRED
>
<!ELEMENT m2-7-4-summary-of-clinical-safety ((leaf | node-extension)*)>
<!ATTLIST m2-7-4-summary-of-clinical-safety
        %att;
>
<!ELEMENT m2-7-5-literature-references ((leaf | node-extension)*)>
<!ATTLIST m2-7-5-literature-references
        %att;
>
<!ELEMENT m2-7-6-synopses-of-individual-studies ((leaf | node-extension)*)>
<!ATTLIST m2-7-6-synopses-of-individual-studies
        %att;
>
<!ELEMENT m3-quality (leaf*, m3-2-body-of-data?, m3-3-literature-references?)>
<!ATTLIST m3-quality
        %att;
>
<!ELEMENT m3-2-body-of-data (leaf*, m3-2-s-drug-substance*, m3-2-p-drug-product*, m3-2-a-appendices?, m3-2-r-
regional-information?)>
<!ATTLIST m3-2-body-of-data
        %att;
>
```

```
<!ELEMENT m3-2-s-drug-substance (leaf*, m3-2-s-1-general-information?, m3-2-s-2-manufacture?, m3-2-s-3-characterisation?, m3-2-s-4-control-of-drug-substance?, m3-2-s-5-reference-standards-or-materials?, m3-2-s-6-container-closure-system?, m3-2-s-7-stability?)>
<!ATTLIST m3-2-s-drug-substance
        %att;
        substance CDATA #REQUIRED
        manufacturer CDATA #REQUIRED
>
<!ELEMENT m3-2-s-1-general-information (leaf*, m3-2-s-1-1-nomenclature?, m3-2-s-1-2-structure?, m3-2-s-1-3-general-properties?)>
<!ATTLIST m3-2-s-1-general-information
        %att;
>
<!ELEMENT m3-2-s-1-1-nomenclature ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-1-1-nomenclature
        %att;
>
<!ELEMENT m3-2-s-1-2-structure ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-1-2-structure
        %att;
>
<!ELEMENT m3-2-s-1-3-general-properties ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-1-3-general-properties
        %att;
>
<!ELEMENT m3-2-s-2-manufacture (leaf*, m3-2-s-2-1-manufacturer?, m3-2-s-2-2-description-of-manufacturing-process-and-process-controls?, m3-2-s-2-3-control-of-materials?, m3-2-s-2-4-controls-of-critical-steps-and-intermediates?, m3-2-s-2-5-process-validation-and-or-evaluation?, m3-2-s-2-6-manufacturing-process-development?)>
<!ATTLIST m3-2-s-2-manufacture
        %att;
>
<!ELEMENT m3-2-s-2-1-manufacturer ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-1-manufacturer
        %att;
>
<!ELEMENT m3-2-s-2-2-description-of-manufacturing-process-and-process-controls ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
        %att;
>
<!ELEMENT m3-2-s-2-3-control-of-materials ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-3-control-of-materials
        %att;
>
<!ELEMENT m3-2-s-2-4-controls-of-critical-steps-and-intermediates ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-4-controls-of-critical-steps-and-intermediates
        %att;
>
<!ELEMENT m3-2-s-2-5-process-validation-and-or-evaluation ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-5-process-validation-and-or-evaluation
        %att;
>
<!ELEMENT m3-2-s-2-6-manufacturing-process-development ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-6-manufacturing-process-development
        %att;
>
<!ELEMENT m3-2-s-3-characterisation (leaf*, m3-2-s-3-1-elucidation-of-structure-and-other-characteristics?, m3-2-s-3-2-impurities?)>
<!ATTLIST m3-2-s-3-characterisation
        %att;
>
<!ELEMENT m3-2-s-3-1-elucidation-of-structure-and-other-characteristics ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-3-1-elucidation-of-structure-and-other-characteristics
```

```
        %att;
>
<!ELEMENT m3-2-s-3-2-impurities ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-3-2-impurities
        %att;
>
<!ELEMENT m3-2-s-4-control-of-drug-substance (leaf*, m3-2-s-4-1-specification?, m3-2-s-4-2-analytical-procedures?, m3-2-s-4-3-validation-of-analytical-procedures?, m3-2-s-4-4-batch-analyses?, m3-2-s-4-5-justification-of-specification?)>
<!ATTLIST m3-2-s-4-control-of-drug-substance
        %att;
>
<!ELEMENT m3-2-s-4-1-specification ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-1-specification
        %att;
>
<!ELEMENT m3-2-s-4-2-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-2-analytical-procedures
        %att;
>
<!ELEMENT m3-2-s-4-3-validation-of-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-3-validation-of-analytical-procedures
        %att;
>
<!ELEMENT m3-2-s-4-4-batch-analyses ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-4-batch-analyses
        %att;
>
<!ELEMENT m3-2-s-4-5-justification-of-specification ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-5-justification-of-specification
        %att;
>
<!ELEMENT m3-2-s-5-reference-standards-or-materials ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-5-reference-standards-or-materials
        %att;
>
<!ELEMENT m3-2-s-6-container-closure-system ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-6-container-closure-system
        %att;
>
<!ELEMENT m3-2-s-7-stability (leaf*, m3-2-s-7-1-stability-summary-and-conclusions?, m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment?, m3-2-s-7-3-stability-data?)>
<!ATTLIST m3-2-s-7-stability
        %att;
>
<!ELEMENT m3-2-s-7-1-stability-summary-and-conclusions ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-7-1-stability-summary-and-conclusions
        %att;
>
<!ELEMENT m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment
        %att;
>
<!ELEMENT m3-2-s-7-3-stability-data ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-7-3-stability-data
        %att;
>
<!ELEMENT m3-2-p-drug-product (leaf*, m3-2-p-1-description-and-composition-of-the-drug-product?, m3-2-p-2-pharmaceutical-development?, m3-2-p-3-manufacture?, m3-2-p-4-control-of-excipients*, m3-2-p-5-control-of-drug-product?, m3-2-p-6-reference-standards-or-materials?, m3-2-p-7-container-closure-system?, m3-2-p-8-stability?)>
<!ATTLIST m3-2-p-drug-product
        %att;
```

```
        product-name CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        manufacturer CDATA #IMPLIED
>
<!ELEMENT m3-2-p-1-description-and-composition-of-the-drug-product ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-1-description-and-composition-of-the-drug-product
        %att;
>
<!ELEMENT m3-2-p-2-pharmaceutical-development ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-2-pharmaceutical-development
        %att;
>
<!ELEMENT m3-2-p-3-manufacture (leaf*, m3-2-p-3-1-manufacturers?, m3-2-p-3-2-batch-formula?, m3-2-p-3-3-
description-of-manufacturing-process-and-process-controls?, m3-2-p-3-4-controls-of-critical-steps-and-intermediates?,
m3-2-p-3-5-process-validation-and-or-evaluation?)>
<!ATTLIST m3-2-p-3-manufacture
        %att;
>
<!ELEMENT m3-2-p-3-1-manufacturers ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-1-manufacturers
        %att;
>
<!ELEMENT m3-2-p-3-2-batch-formula ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-2-batch-formula
        %att;
>
<!ELEMENT m3-2-p-3-3-description-of-manufacturing-process-and-process-controls ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-3-description-of-manufacturing-process-and-process-controls
        %att;
>
<!ELEMENT m3-2-p-3-4-controls-of-critical-steps-and-intermediates ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-4-controls-of-critical-steps-and-intermediates
        %att;
>
<!ELEMENT m3-2-p-3-5-process-validation-and-or-evaluation ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-5-process-validation-and-or-evaluation
        %att;
>
<!ELEMENT m3-2-p-4-control-of-excipients (leaf*, m3-2-p-4-1-specifications?, m3-2-p-4-2-analytical-procedures?,
m3-2-p-4-3-validation-of-analytical-procedures?, m3-2-p-4-4-justification-of-specifications?, m3-2-p-4-5-excipients-
of-human-or-animal-origin?, m3-2-p-4-6-novel-excipients?)>
<!ATTLIST m3-2-p-4-control-of-excipients
        %att;
        excipient CDATA #IMPLIED
>
<!ELEMENT m3-2-p-4-1-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-1-specifications
        %att;
>
<!ELEMENT m3-2-p-4-2-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-2-analytical-procedures
        %att;
>
<!ELEMENT m3-2-p-4-3-validation-of-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-3-validation-of-analytical-procedures
        %att;
>
<!ELEMENT m3-2-p-4-4-justification-of-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-4-justification-of-specifications
        %att;
>
<!ELEMENT m3-2-p-4-5-excipients-of-human-or-animal-origin ((leaf | node-extension)*)>
```

```
<!ATTLIST m3-2-p-4-5-excipients-of-human-or-animal-origin
        %att;
>
<!ELEMENT m3-2-p-4-6-novel-excipients ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-6-novel-excipients
        %att;
>
<!ELEMENT m3-2-p-5-control-of-drug-product (leaf*, m3-2-p-5-1-specifications?, m3-2-p-5-2-analytical-
procedures?, m3-2-p-5-3-validation-of-analytical-procedures?, m3-2-p-5-4-batch-analyses?, m3-2-p-5-5-
characterisation-of-impurities?, m3-2-p-5-6-justification-of-specifications?)>
<!ATTLIST m3-2-p-5-control-of-drug-product
        %att;
>
<!ELEMENT m3-2-p-5-1-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-1-specifications
        %att;
>
<!ELEMENT m3-2-p-5-2-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-2-analytical-procedures
        %att;
>
<!ELEMENT m3-2-p-5-3-validation-of-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-3-validation-of-analytical-procedures
        %att;
>
<!ELEMENT m3-2-p-5-4-batch-analyses ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-4-batch-analyses
        %att;
>
<!ELEMENT m3-2-p-5-5-characterisation-of-impurities ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-5-characterisation-of-impurities
        %att;
>
<!ELEMENT m3-2-p-5-6-justification-of-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-6-justification-of-specifications
        %att;
>
<!ELEMENT m3-2-p-6-reference-standards-or-materials ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-6-reference-standards-or-materials
        %att;
>
<!ELEMENT m3-2-p-7-container-closure-system ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-7-container-closure-system
        %att;
>
<!ELEMENT m3-2-p-8-stability (leaf*, m3-2-p-8-1-stability-summary-and-conclusion?, m3-2-p-8-2-post-approval-
stability-protocol-and-stability-commitment?, m3-2-p-8-3-stability-data?)>
<!ATTLIST m3-2-p-8-stability
        %att;
>
<!ELEMENT m3-2-p-8-1-stability-summary-and-conclusion ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-8-1-stability-summary-and-conclusion
        %att;
>
<!ELEMENT m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment
        %att;
>
<!ELEMENT m3-2-p-8-3-stability-data ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-8-3-stability-data
        %att;
>
```

```
<!ELEMENT m3-2-a-appendices (leaf*, m3-2-a-1-facilities-and-equipment*, m3-2-a-2-adventitious-agents-safety-evaluation*, m3-2-a-3-excipients?)>
<!ATTLIST m3-2-a-appendices
        %att;
>
<!ELEMENT m3-2-a-1-facilities-and-equipment ((leaf | node-extension)*)>
<!ATTLIST m3-2-a-1-facilities-and-equipment
        %att;
        manufacturer CDATA #IMPLIED
        substance CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        product-name CDATA #IMPLIED
>
<!ELEMENT m3-2-a-2-adventitious-agents-safety-evaluation ((leaf | node-extension)*)>
<!ATTLIST m3-2-a-2-adventitious-agents-safety-evaluation
        %att;
        manufacturer CDATA #IMPLIED
        substance CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        product-name CDATA #IMPLIED
>
<!ELEMENT m3-2-a-3-excipients ((leaf | node-extension)*)>
<!ATTLIST m3-2-a-3-excipients
        %att;
>
<!ELEMENT m3-2-r-regional-information ((leaf | node-extension)*)>
<!ATTLIST m3-2-r-regional-information
        %att;
>
<!ELEMENT m3-3-literature-references ((leaf | node-extension)*)>
<!ATTLIST m3-3-literature-references
        %att;
>
<!ELEMENT m4-nonclinical-study-reports (leaf*, m4-2-study-reports?, m4-3-literature-references?)>
<!ATTLIST m4-nonclinical-study-reports
        %att;
>
<!ELEMENT m4-2-study-reports (leaf*, m4-2-1-pharmacology?, m4-2-2-pharmacokinetics?, m4-2-3-toxicology?)>
<!ATTLIST m4-2-study-reports
        %att;
>
<!ELEMENT m4-2-1-pharmacology (leaf*, m4-2-1-1-primary-pharmacodynamics?, m4-2-1-2-secondary-pharmacodynamics?, m4-2-1-3-safety-pharmacology?, m4-2-1-4-pharmacodynamic-drug-interactions?)>
<!ATTLIST m4-2-1-pharmacology
        %att;
>
<!ELEMENT m4-2-1-1-primary-pharmacodynamics ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-1-primary-pharmacodynamics
        %att;
>
<!ELEMENT m4-2-1-2-secondary-pharmacodynamics ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-2-secondary-pharmacodynamics
        %att;
>
<!ELEMENT m4-2-1-3-safety-pharmacology ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-3-safety-pharmacology
        %att;
>
<!ELEMENT m4-2-1-4-pharmacodynamic-drug-interactions ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-4-pharmacodynamic-drug-interactions
        %att;
>
```

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<!ELEMENT m4-2-2-pharmacokinetics (leaf*, m4-2-2-1-analytical-methods-and-validation-reports?, m4-2-2-2-absorption?, m4-2-2-3-distribution?, m4-2-2-4-metabolism?, m4-2-2-5-excretion?, m4-2-2-6-pharmacokinetic-drug-interactions?, m4-2-2-7-other-pharmacokinetic-studies?)>
<!ATTLIST m4-2-2-pharmacokinetics
        %att;
>
<!ELEMENT m4-2-2-1-analytical-methods-and-validation-reports ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-1-analytical-methods-and-validation-reports
        %att;
>
<!ELEMENT m4-2-2-2-absorption ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-2-absorption
        %att;
>
<!ELEMENT m4-2-2-3-distribution ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-3-distribution
        %att;
>
<!ELEMENT m4-2-2-4-metabolism ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-4-metabolism
        %att;
>
<!ELEMENT m4-2-2-5-excretion ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-5-excretion
        %att;
>
<!ELEMENT m4-2-2-6-pharmacokinetic-drug-interactions ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-6-pharmacokinetic-drug-interactions
        %att;
>
<!ELEMENT m4-2-2-7-other-pharmacokinetic-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-7-other-pharmacokinetic-studies
        %att;
>
<!ELEMENT m4-2-3-toxicology (leaf*, m4-2-3-1-single-dose-toxicity?, m4-2-3-2-repeat-dose-toxicity?, m4-2-3-3-genotoxicity?, m4-2-3-4-carcinogenicity?, m4-2-3-5-reproductive-and-developmental-toxicity?, m4-2-3-6-local-tolerance?, m4-2-3-7-other-toxicity-studies?)>
<!ATTLIST m4-2-3-toxicology
        %att;
>
<!ELEMENT m4-2-3-1-single-dose-toxicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-1-single-dose-toxicity
        %att;
>
<!ELEMENT m4-2-3-2-repeat-dose-toxicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-2-repeat-dose-toxicity
        %att;
>
<!ELEMENT m4-2-3-3-genotoxicity (leaf*, m4-2-3-3-1-in-vitro?, m4-2-3-3-2-in-vivo?)>
<!ATTLIST m4-2-3-3-genotoxicity
        %att;
>
<!ELEMENT m4-2-3-3-1-in-vitro ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-3-1-in-vitro
        %att;
>
<!ELEMENT m4-2-3-3-2-in-vivo ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-3-2-in-vivo
        %att;
>
<!ELEMENT m4-2-3-4-carcinogenicity (leaf*, m4-2-3-4-1-long-term-studies?, m4-2-3-4-2-short-or-medium-term-studies?, m4-2-3-4-3-other-studies?)>
```

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<!ATTLIST m4-2-3-4-carcinogenicity
        %att;
>
<!ELEMENT m4-2-3-4-1-long-term-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-4-1-long-term-studies
        %att;
>
<!ELEMENT m4-2-3-4-2-short-or-medium-term-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-4-2-short-or-medium-term-studies
        %att;
>
<!ELEMENT m4-2-3-4-3-other-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-4-3-other-studies
        %att;
>
<!ELEMENT m4-2-3-5-reproductive-and-developmental-toxicity (leaf*, m4-2-3-5-1-fertility-and-early-embryonic-
development?, m4-2-3-5-2-embryo-fetal-development?, m4-2-3-5-3-prenatal-and-postnatal-development-including-
maternal-function?, m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated?)>
<!ATTLIST m4-2-3-5-reproductive-and-developmental-toxicity
        %att;
>
<!ELEMENT m4-2-3-5-1-fertility-and-early-embryonic-development ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-1-fertility-and-early-embryonic-development
        %att;
>
<!ELEMENT m4-2-3-5-2-embryo-fetal-development ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-2-embryo-fetal-development
        %att;
>
<!ELEMENT m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
        %att;
>
<!ELEMENT m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated ((leaf |
node-extension)*)>
<!ATTLIST m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
        %att;
>
<!ELEMENT m4-2-3-6-local-tolerance ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-6-local-tolerance
        %att;
>
<!ELEMENT m4-2-3-7-other-toxicity-studies (leaf*, m4-2-3-7-1-antigenicity?, m4-2-3-7-2-immunotoxicity?, m4-2-3-
7-3-mechanistic-studies?, m4-2-3-7-4-dependence?, m4-2-3-7-5-metabolites?, m4-2-3-7-6-impurities?, m4-2-3-7-7-
other?)>
<!ATTLIST m4-2-3-7-other-toxicity-studies
        %att;
>
<!ELEMENT m4-2-3-7-1-antigenicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-1-antigenicity
        %att;
>
<!ELEMENT m4-2-3-7-2-immunotoxicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-2-immunotoxicity
        %att;
>
<!ELEMENT m4-2-3-7-3-mechanistic-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-3-mechanistic-studies
        %att;
>
<!ELEMENT m4-2-3-7-4-dependence ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-4-dependence
```

```
        %att;
>
<!ELEMENT m4-2-3-7-5-metabolites ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-5-metabolites
        %att;
>
<!ELEMENT m4-2-3-7-6-impurities ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-6-impurities
        %att;
>
<!ELEMENT m4-2-3-7-7-other ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-7-other
        %att;
>
<!ELEMENT m4-3-literature-references ((leaf | node-extension)*)>
<!ATTLIST m4-3-literature-references
        %att;
>
<!ELEMENT m5-clinical-study-reports (leaf*, m5-2-tabular-listing-of-all-clinical-studies?, m5-3-clinical-study-
reports?, m5-4-literature-references?)>
<!ATTLIST m5-clinical-study-reports
        %att;
>
<!ELEMENT m5-2-tabular-listing-of-all-clinical-studies ((leaf | node-extension)*)>
<!ATTLIST m5-2-tabular-listing-of-all-clinical-studies
        %att;
>
<!ELEMENT m5-3-clinical-study-reports (leaf*, m5-3-1-reports-of-biopharmaceutic-studies?, m5-3-2-reports-of-
studies-pertinent-to-pharmacokinetics-using-human-biomaterials?, m5-3-3-reports-of-human-pharmacokinetics-pk-
studies?, m5-3-4-reports-of-human-pharmacodynamics-pd-studies?, m5-3-5-reports-of-efficacy-and-safety-studies*,
m5-3-6-reports-of-postmarketing-experience?, m5-3-7-case-report-forms-and-individual-patient-listings?)>
<!ATTLIST m5-3-clinical-study-reports
        %att;
>
<!ELEMENT m5-3-1-reports-of-biopharmaceutic-studies (leaf*, m5-3-1-1-bioavailability-study-reports?, m5-3-1-2-
comparative-ba-and-bioequivalence-study-reports?, m5-3-1-3-in-vitro-in-vivo-correlation-study-reports?, m5-3-1-4-
reports-of-bioanalytical-and-analytical-methods-for-human-studies?)>
<!ATTLIST m5-3-1-reports-of-biopharmaceutic-studies
        %att;
>
<!ELEMENT m5-3-1-1-bioavailability-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-1-bioavailability-study-reports
        %att;
>
<!ELEMENT m5-3-1-2-comparative-ba-and-bioequivalence-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
        %att;
>
<!ELEMENT m5-3-1-3-in-vitro-in-vivo-correlation-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
        %att;
>
<!ELEMENT m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
        %att;
>
<!ELEMENT m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials (leaf*, m5-3-2-1-
plasma-protein-binding-study-reports?, m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies?, m5-3-
2-3-reports-of-studies-using-other-human-biomaterials?)>
<!ATTLIST m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials
        %att;
>
```

```
<!ELEMENT m5-3-2-1-plasma-protein-binding-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-1-plasma-protein-binding-study-reports
        %att;
>
<!ELEMENT m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
        %att;
>
<!ELEMENT m5-3-2-3-reports-of-studies-using-other-human-biomaterials ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-3-reports-of-studies-using-other-human-biomaterials
        %att;
>
<!ELEMENT m5-3-3-reports-of-human-pharmacokinetics-pk-studies (leaf*, m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports?, m5-3-3-2-patient-pk-and-initial-tolerability-study-reports?, m5-3-3-3-intrinsic-factor-pk-study-reports?, m5-3-3-4-extrinsic-factor-pk-study-reports?, m5-3-3-5-population-pk-study-reports?)>
<!ATTLIST m5-3-3-reports-of-human-pharmacokinetics-pk-studies
        %att;
>
<!ELEMENT m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
        %att;
>
<!ELEMENT m5-3-3-2-patient-pk-and-initial-tolerability-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
        %att;
>
<!ELEMENT m5-3-3-3-intrinsic-factor-pk-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-3-intrinsic-factor-pk-study-reports
        %att;
>
<!ELEMENT m5-3-3-4-extrinsic-factor-pk-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-4-extrinsic-factor-pk-study-reports
        %att;
>
<!ELEMENT m5-3-3-5-population-pk-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-5-population-pk-study-reports
        %att;
>
<!ELEMENT m5-3-4-reports-of-human-pharmacodynamics-pd-studies (leaf*, m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports?, m5-3-4-2-patient-pd-and-pk-pd-study-reports?)>
<!ATTLIST m5-3-4-reports-of-human-pharmacodynamics-pd-studies
        %att;
>
<!ELEMENT m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
        %att;
>
<!ELEMENT m5-3-4-2-patient-pd-and-pk-pd-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-4-2-patient-pd-and-pk-pd-study-reports
        %att;
>
<!ELEMENT m5-3-5-reports-of-efficacy-and-safety-studies (leaf*, m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication?, m5-3-5-2-study-reports-of-uncontrolled-clinical-studies?, m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study?, m5-3-5-4-other-study-reports?)>
<!ATTLIST m5-3-5-reports-of-efficacy-and-safety-studies
        %att;
        indication CDATA #REQUIRED
>
<!ELEMENT m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
        %att;
```

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>
<!ELEMENT m5-3-5-2-study-reports-of-uncontrolled-clinical-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
        %att;
>
<!ELEMENT m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
        %att;
>
<!ELEMENT m5-3-5-4-other-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-4-other-study-reports
        %att;
>
<!ELEMENT m5-3-6-reports-of-postmarketing-experience ((leaf | node-extension)*)>
<!ATTLIST m5-3-6-reports-of-postmarketing-experience
        %att;
>
<!ELEMENT m5-3-7-case-report-forms-and-individual-patient-listings ((leaf | node-extension)*)>
<!ATTLIST m5-3-7-case-report-forms-and-individual-patient-listings
        %att;
>
<!ELEMENT m5-4-literature-references ((leaf | node-extension)*)>
<!ATTLIST m5-4-literature-references
        %att;
>
```