# electronic Clinical Trial Applications: Lack of harmonization and challenges for the industry

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Electronic Submission Services

# Topics

- Introduction and Background
- Examples eCTAs EU
- Examples US/CA
- Compiling eCTAs / eINDs
- Impact on Business Processes
- Challenges

# Clinical Trial Applications (CTAs)

## Regulatory Background EU

# CTA Background EU (1)

- Harmonized through Directive 2001/20/EC
- Prerequisite for clinical trials in EU/EEA
- Common documentation requirements
- Common review procedure

→Submission procedures not harmonized

# CTA Background EU (2)

- CTA documents required:
  - Protocol
  - Informed Consent, Patient Information
  - Investigator's Brochure, IMPD (new)
  - EudraCT application
  - Supportive / local documents

# Route to eCTA Submissions

- Amount + complexity of documentation increased (e.g. IMPD)
- Cross-referencing introduced (IMPD – IB)
- Electronic EudraCT XML data required
- More interactions between sponsors and regulators

→ Increased request for electronic CTA documents

# CTA Examples EU

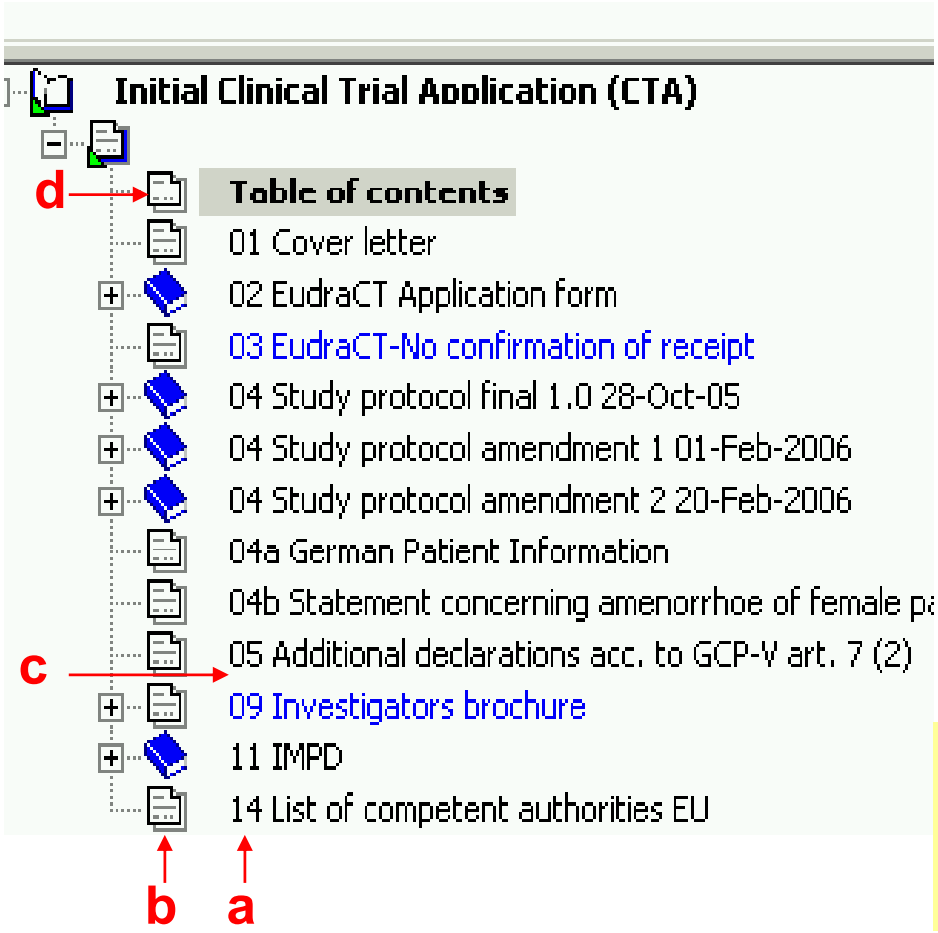
## Examples:

- Germany (DE)
- United Kingdom (UK)
- Portugal (PT)

# Requirements DE

- GCP-V (2004) – legal requirement
- BfArM Guidance (2006):
  - CTA in paper and electronically on CD
  - Single PDF files, no folder structure
  - Specific naming and numbering
  - No further requirements published yet
  - Corresponding decree “in preparation”

# Example (DE)




a) Predefined numbering

b) Individual PDFs

c) Not all mandatory

d) TOC (paper!)

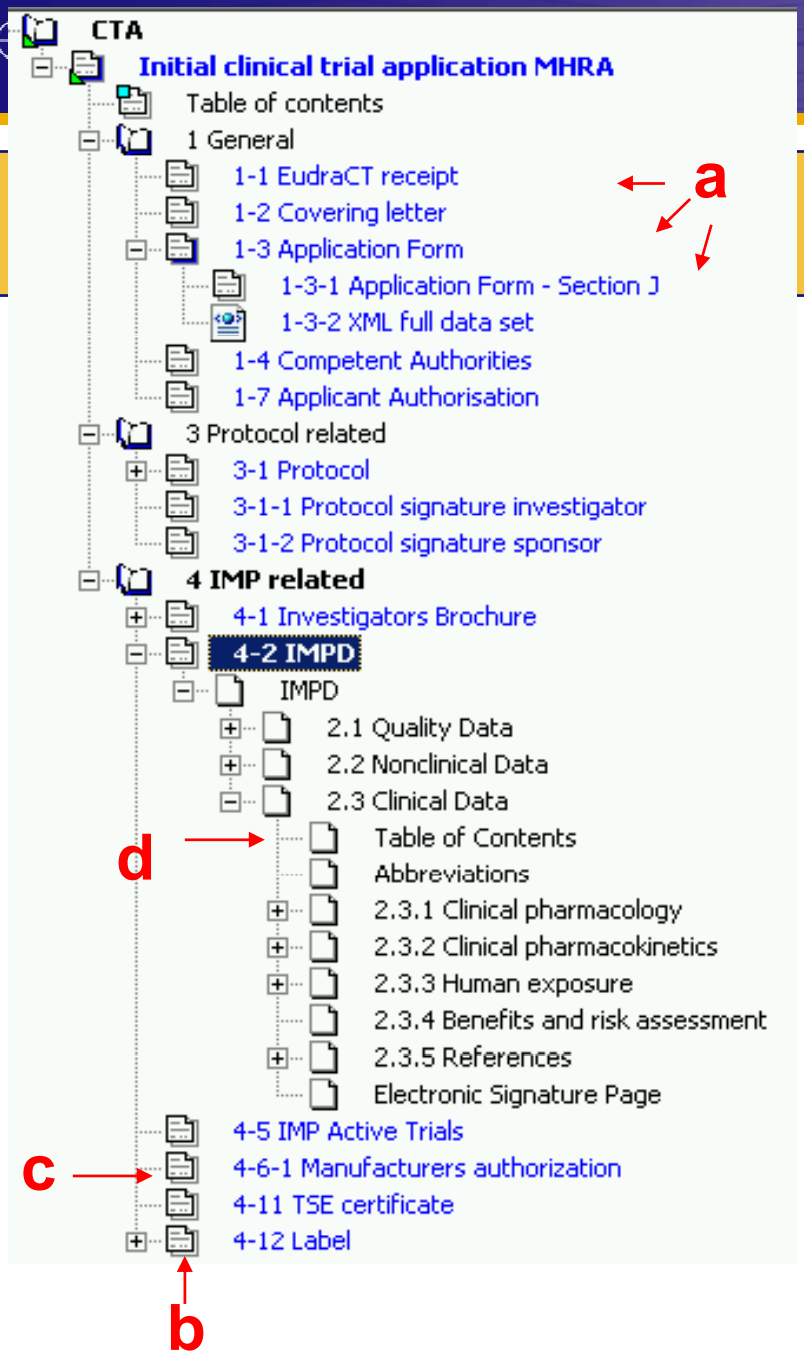
- XML backbone (not mandatory)

→ NEES (non eCTD electronic submission)

# Requirements (UK)

- MHRA Special Mail 5 (2006):
  - Requirements for eSubmissions defined
  - For MAA, Variations, PSURs, CTAs, etc
  - eSubmission strongly recommended
  - Paper → delay in assessment
  - Compliance with Special Mail 5!
  - MHRA portal (recommended) or on CD

# Example (UK)




a) Naming +numbering

b) Single PDFs

c) Not all docs mandatory

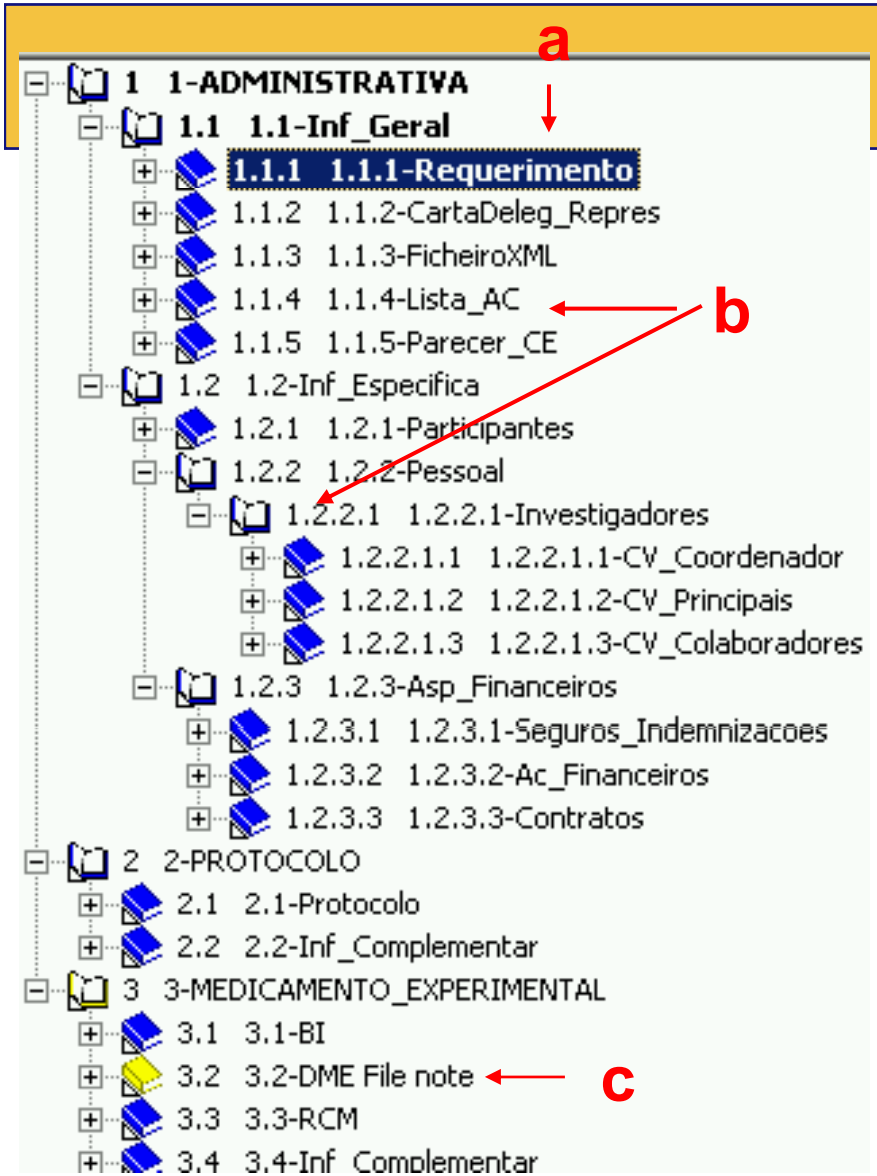
d) Bookmarks + Hyperlinks

- PDF from source files recommended
- Scans → OCR

# Requirements (PT)

- Instructions to CTA applicants (2005)
  - Requirements for eCTA defined
  - Full electronic submission of CTA core documents
  - In paper: EudraCT application / Proof of payment/ Cover letter
  - Detailed specifications for INFARMED and CEIC

# Example PT




a) Naming

b) Order / folder structure

c) No empty notes → File notes

- No TOC, no XML backbone, no paper required
- Different specifications for RA and IEC

# Summary: CTAs EU (1)

- Submission requirements not harmonized
- Different approaches on national levels
- Documentation to be submitted:
  1. In paper (e.g. ES, DK, PL)
  2. Paper and electronic version (e.g. DE)
  3. Electronic version only (e.g. UK, PT)

# Summary: CTAs EU (2)

- Electronic documents to be provided:
  - Without special requirements
    “single PDF” files
  - With detailed electronic submission specifications
    (naming, numbering, structure,..)
    in different gradations
  - PDFs rendered from source files preferred
  - Scans should undergo OCR tracing

# INDs and CTAs (CA)

## Regulatory Background US/CA

# eIND requirements /1

- 2002 CBER eIND guidance
- FDA now encourages eSubmissions for INDs - paper still accepted
- eCTD specifications recommended
  (see http://www.fda.gov/cder/regulatory/ersr/default.htm)
- No additional paper documents required

# eIND requirements /2

- IND in eCTD-format:
  - Subsequent submissions related to that IND (serials) to be in eCTD –format, too

→ Usage of eCTD life-cycle functionality

# eIND requirements /3

- Beware of study tagging files:
  - Study protocol to be included in section 5.3 as part of future study report
  - Amendments covered by eCTD serial

→Study report must be compliant to ICH E3

# eCTA requirements (CANADA)

- Health Canada: “Notice to sponsors” in 2003
- Paper and electronic documents
- eCTA dossier should comply “to the extend possible” with eCTD specifications

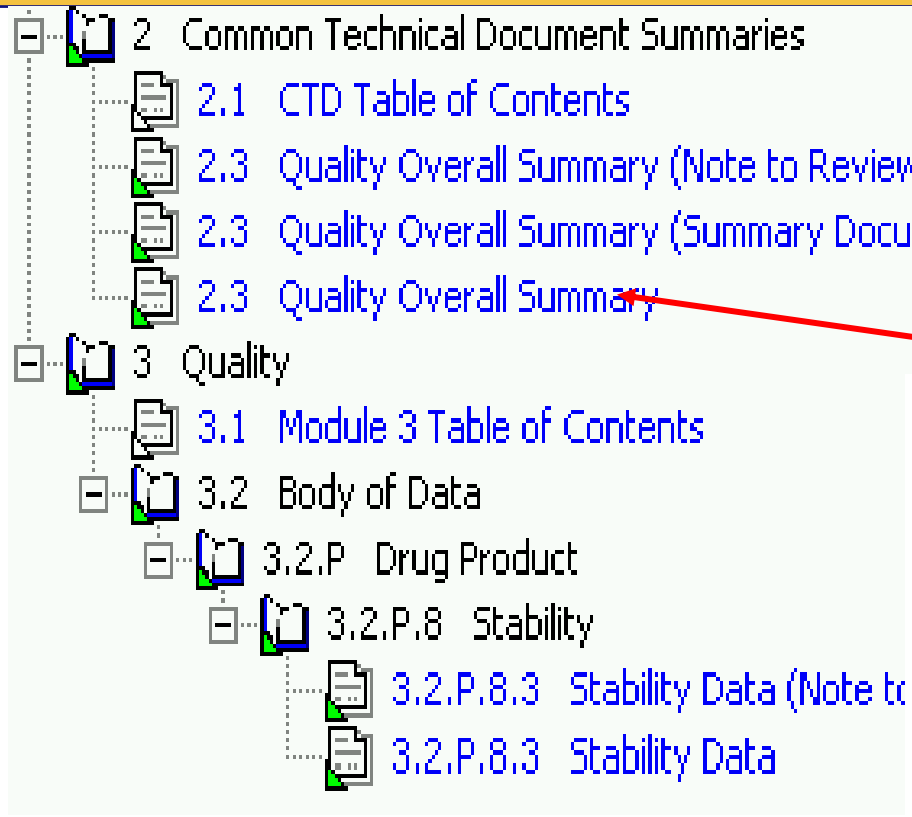
# Example CTA/CTD submission /1


Example eCTA CA

Module 1:

- Application form
- Protocol
- ICF
- Administrative
- ect

# Example CTA/CTD submission /2




Module 2+3

- QoS
- Stability Data

*Potential location for IB / IMPD Summaries for EU CTAs:*

- *2.3 Quality*
- *2.4 / 2.6 Nonclinical*
- *2.5 / 2.7 Clinical*

# Summary: IND / CTA (CA)

- eSubmission of INDs recommended (no paper required)
- eSubmision of CTAs (CA) required (in addition to paper)
- eIND and eCTA (CA) acc. to eCTD
- IND serials managed by using eCTD life cycle submissions

# Advantages using eCTD

1. No additional eSubmission templates required at sponsors and health authorities
2. Starting from IND, eCTD for the NDA can emerge step by step during clinical development
3. Could also be used for EU eCTA dossiers (if accepted by authorities)

# Benefits using compilation tools

- Using templates increases compliance
- Teamwork functionalities, central repository
- Paper and electronic version can be compiled in one task
- Single PDF / individual PDF publishing
- Usable for other submission types

# Using dossier compilation tools

- eINDs, eCTAs (CA) benefit from built-in eCTD functionalities

- Most dossier compilation applications today support non-eCTD dossiers (NEES

# Impact on Medical Writing /1

- Compliance with ICH GCP needed
- Consistency of core documents crucial
- Usage of:
  - automated TOCs (headings, captions)
  - cross-references, hyperlinks
- "Modular" writing of core information that goes into separate documents

# Impact on Medical Writing /2

- Create and maintain document templates
- Provide documents “submission ready”
- Alignment with Regulatory Affairs concerning eSubmission requirements

# Impact on Regulatory Affairs

- Regulatory compliance
- Check (e)CTA requirements frequently
- Maintain CTA dossier templates
- Compile eCTA submission dossiers
- Strategic planning of emerging dossiers ("from eIND to eCTD")

→ Additional resources required

# Challenges

- Different national approaches regarding eCTAs in EU
- Changing requirements in EU
- eCTD as accepted electronic submission standard not used for CTAs in EU
- Adaption of business processes

# Outline

- End of 2009 EU MS RAs to accept eCTD submissions
- NEES Guidance currently in preparation
- It is expected that once the electronic submission of dossiers for MAA/NDA etc has been implemented, focus will be set on other submission types (e.g. CTAs)

# Thank you for your attention!

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# Abbreviations

| | |
|---|---|
| CA | Canada |
| BfArM | Bundesinstitut für Arzneimittel und Medizinprodukte (German federal authority for drugs and medical devices) |
| DE | Germany |
| (e)CTA | (electronic) Clinical Trial Application |
| (e)CTD | (electronic) Common Technical Document |
| (e)IND | (electronic) Investigational New Drug Application |
| EEA | European Economic Area |
| EU | European Union |
| GCP-V | German GCP implementation decree (2004) |
| IB | Investigator's Brochure |
| IEC | Independent Ethics Committee |
| IMPD | Investigational Medicinal Product Dossier |

| | |
|---|---|
| MAA | Marketing Authorization Application |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MS | Member State |
| NDA | New Drug Application |
| NEES | Non-eCTD electronic submission |
| PDF | Portable Document File |
| PSUR | Periodic Safety Update Report |
| PT | Portugal |
| RA | Regulatory Authority |
| TOC | Table of Content |
| UK | United Kingdom |
| US | United States |
| XML | Extended Markup Language |