

eCTD Validation in the EU: goal, status and next steps

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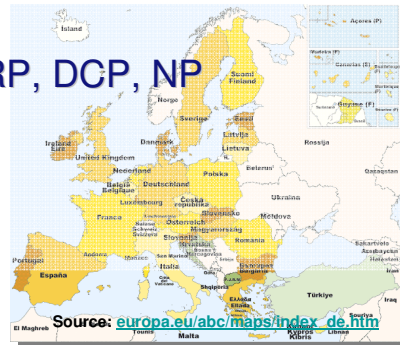


AGENDA

- The eCTD in the EU (complexity & status)
- Criteria of the evaluation
- Status of processing eCTD and NeesS in the EU
- eCTD Validation in the EU
- NeesS Validation in the EU
- The future of the eCTD in Europe

The complexity of Europe

- As of 1 January 2007, 27 EU Member States and 3 EEA Countries (+2 candidate MS)
- More than 36 National Competent Authorities (NCAs)
- Multiple procedures: CP, MRP, DCP, NP
- Various submission types
- Task: **Managing consent !**



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Objectives: Status, Motivation, Challenges

- Status of a fully adopted electronic drug approval process in Europe:
 - No paper required anymore
 - eCTD (& NeeS) valid for all procedures and all submission types
 - Relevance of harmonized and applied eCTD validation criteria and additional challenges.

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Motivation for the topic

- European Regulators experience various movements of how the eCTD is processed. This results into certain risks which have to be resolved:
 - How can applicants be sure that the electronic submission will be accepted by the regulators and can be processed as intended?
 - The risk for an RtF cannot be estimated currently and is potentially hindering the eCTD transition process in the EU.
 - Do EU NCAs still have consens that at some day 1 eCTD format will be accepted at all MS?

RtF: Refuse to File/ Return of File

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The questionnaire - scope

- A 4 page questionnaire had been send to EMEA and 35 European NCAs
- 19 NCAs returned a completed questionnaires (incl. EMEA)
- Only participating NCAs have been taking into account for this analysis
- Profile of contributing NCAs
 - Front runners in the EU (*DE/ BfArM, BE, EMEA, NL, UK*)
 - Adaptors in the EU (*CY, DK, ES, FI, GR, IT, SE*)
 - Adaptors in the enlarged EU since 2004 (*BG, EE, LT, SK*)
 - Adaptors beyond EU candidates (*HR, TR*)
 - Adaptors beyond EEA countries (*NO*)

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The questionnaire - objectives

- Objectives:
 - Motivation and Status of processing eCTD and NeeS
 - Validation and Processing of eCTDs
 - Importance of certain criteria
 - RtF (experiences, plans)
 - Validation and Processing of NeeS
 - eCTD vs NeeS
 - The future of eCTD in Europe
 - Success drivers to be concentrated on in 2009 and beyond

Basis for moving from p- to e-submissions

- 18 out of 19 agencies consider an electronic archival policy of importance when going electronic.
 - Submissions and submission data to be accessible for more than 30 years
 - Quality of submissions and referenced electronic documents needs to be high
 - Archives are supposed to be large (e.g. 36 km of paper submissions and more)

Certain legal basis to support empowerment

- 16 out of 19 agencies do receive management commitment from the HoA
- 9 out of 19 agencies do define their e-submission strategies supported by a certain legal basis.
 - Underlines the clear commitment towards going electronic.

Internal Migration of e- to p-submissions

- 14 out of 19 NCAs will migrate paper submissions to electronic submissions (+NL no paper submissions accepted)
 - Are focussing to establish 1 core process for reviewing and approval.
 - e-Submissions are clearly preferred by NCAs

Preferred Format when migrating p- to e-

- 9 out of 19 agencies prefer to generate eCTDs out of submitted paper submissions
- 4 out of 19 agencies prefer to generate NeoS out of submitted paper submissions
- Other are still evaluating or did not provide a preference

Validation of eCTDs

Integrating Technical eCTD Validation

- 9 out of 19 agencies do already today perform a technical eCTD validation in advance of importing.
- 8 out of 19 agencies do NOT perform an eCTD validation before importing.
- Conclusion:
 - eCTD validation is not standardized yet.
 - eCTD validation will become more important soon
 - Some NCAs have not considered yet the concept of an RtF.

Publishing of clear eCTD Validation Criteria

- Only 3 out of 19 NCAs published clear eCTD validation criteria
 - EMEA, Belgium, Bulgaria
- 11 out of 19 agencies are already clear to apply eCTD validation requirements which are fully in-line with the *EU Validation Criteria v2.0 - July 2008-1.xls*

Being not in-line with the EU validation criteria

- Why are NCAs currently not in-line with the EU validation criteria?
 - eCTD not in a production, but in a pilot phase yet (no routine process)
 - NL: if eCTD requirements are not passed, the submission will be processed as a Nees (*changes to be expected due to mid 2009*)
 - BE: own validation requirements covered by the *BE checker*

Providing a common eCTD validator to applicants

- 18 out of 19 NCAs (TR n/r) **do agree** that a common free eCTD validator helps to improve the eCTD quality and NCA internal procedure
- Only BE currently provides a free validator *for eCTD* to applicants
- The following tools are planned to be provided to applicants free of charge:
 - EURS Validator (8 out of 19)
 - BE checker (4 out of 19)
 - Under evaluation or no answer (10 out of 19)

Refuse to File (eCTD) in the EU

- Currently 6 NCAs are conceptually refusing eCTDs if the applied validation requirements are not passed (EMEA, BG, ES, NL *mid 2009*, BE, DE/ BfArM)
- RTF Status:
 - BG informs about 27 RtF
 - ES informs about 4 RtF
 - BE informs about RtF of less than 15%
 - DE/ BfArM informs about approx. 20 RtF
 - EMEA and NL had no RtF yet.

Major reasons for eCTD based RtF in the EU

- No valid index.xml (cumulative view incorrect)
- BfArM: Non-compliance with specs of eCTD and/ or EU M1 according to eCTDvalidator v. 2.2 (*Lorenz*)

Validation of NeeS

eCTD vs NeeS

	eCTD		NeeS	
	Yes	No / (n/a)	Yes	No / (n/a)
Are submissions validated?	9	8 / 2	7	9 / 3
Published guidances available?	3	14 / 2	7	10 / 3
Validation criteria in-line with EMEA guidance?	11	5 / 3	11	3 / 4
Refuse of invalid submissions?	6	8 / 5	6	9 / 4
Is a free validator provided?	1	16 / 2	2	17
Do you think a common free validator helps to improve?	18	0 / 1	17	0 / 2

Refuse to File (NeeS) in the EU

- Currently 6 NCAs are conceptually refusing NeeS' if the applied validation requirements are not passed (BG, ES, UK, NL *mid 2009*, BE, DE/ BfArM)
- RTF Status:
 - BG informs about 7 NeeS based RtF
 - UK informs about an unknown number of NeeS based RtF
 - ES informs about 30 NeeS based RtF
 - BE informs about RtF of less than 15% of NeeS based RtF
 - DE/ BfArM informs about approx. 0 NeeS based RtF
 - NL had no NeeS based RtF yet, but starting mid 2009 !

Major reasons for NeeS based RtF in the EU

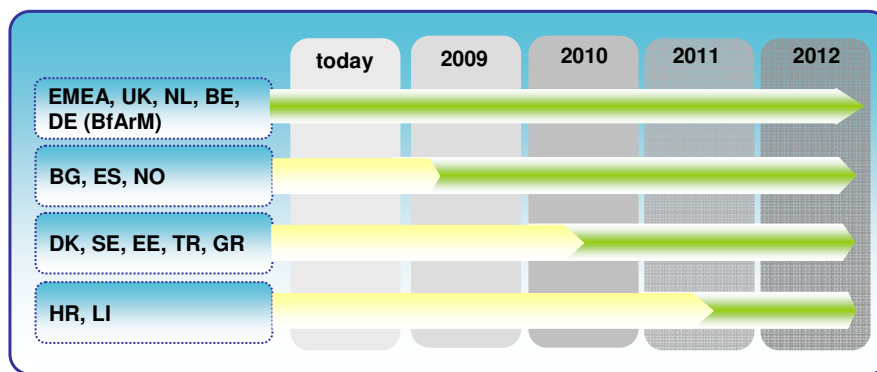
- MHRA rejected NeeS if they do not comply with Mail 5 **and** if they do not comply with NeeS (< 5%)
- File names contain illegal character (only alphanumeric and „-“ are allowed)
- Non-compliance with eCTD structure
- File- and directory naming conventions of the eCTD guidance are not applied

The future of the eCTD in the EU

Which procedures and submission types are supported via eCTD ?

	CP	DCP	MRP	NP
Initial Marketing Authorisation				
Variation Type Ia, Ib, II				
Extension				
Renewal				
Annual Reassessment				
PSUR				
Transfer of Marketing Authorization				
Active Substance Master File				

When do agencies commit to *electronic only* (no paper) ?



Answering a free text question

What do you think are the major items to make eCTD successful in Europe?

7 out of 19 NCAs independently answered:

***Harmonized and clear guidance in all MS
(incl. validation criteria)***

Success drivers for eCTD in the future (1/2)

- **Harmonized and clear guidance in all MS (incl. validation criteria)**
- Reduction of additional national requirements
- Product Lifecycle Management capabilities (easy to use and univocal)
- Budgets at authority and industry side to invest in solutions and infrastructure
- Better and cheaper solutions for industry and authority
- Make eCTD mandatory as for agencies (e.g. Jan.2010)
- Elimination of paper and other electronic formats for all procedures

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Success drivers for eCTD in the future (2/2)

- Incentives as lower fees or faster processing of technical/ logistical items
- Implementation of electronic signature
- Advantages given by digital technology (e.g. searchable dossier data)
- Harmonized software for all stakeholders all over EU
- Practicable Guidance on eCTD in MRP & DCP
- Enhancing quality of submissions and therefore improved assessment
- Motivate SMEs and big pharma to submit eCTDs

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Conclusion – my personal perspective

- Harmonized and mature guidances on eCTD are key.
- A common validator for all engaged European electronic drug approval processes is key.
- eCTD is preferred compared to NeeS.
- The chicken and egg problem has almost been resolved !

**Thanks to the participating NCAs !
&
Thank you for your attention !**

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