Submission of the dossier: Update on Electronic Submissions and PIM

Paul Kershaw
European Medicines Agency
London, UK

eSubmission vs eCTD

- Important distinction: eSubmission ≠ eCTD
- The eCTD is a *particular type* of electronic submission
- EMEA has accepted electronic submissions (CD ROM/DVD with electronic files/folders) for many years, alongside the legally-required paper submission
- Moving now towards the implementation of the eCTD as the specific format for electronic submission
- Moving also towards the acceptance of electronic-only submissions, with eCTD the preferred standard. No paper requirement.
- eCTD offers clear practical advantages, navigation and lifecycle management capabilities:
  - Relationships between dossiers
  - Electronic workflow
  - Better quality dossiers
  - Better quality evaluation
  - Pharmaceutical Industry is global
  - Reduce regulatory burden
  - Harmonise regulatory process

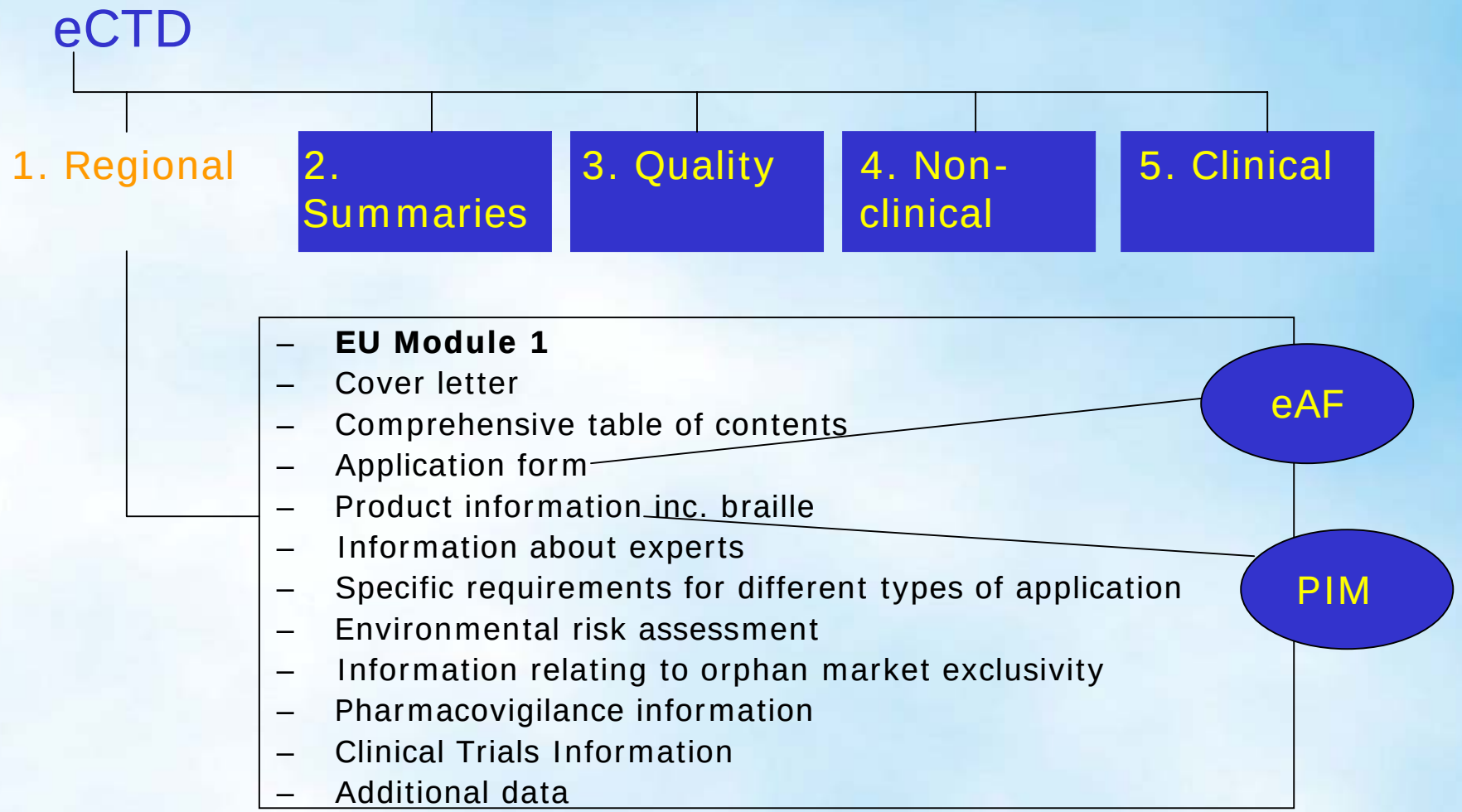
What is the eCTD?

- Internationally agreed (ICH) standard for structured electronic submissions
- Standard for exchange from applicants to agencies – based on paper CTD structure
- Supports internationally agreed (CTD) and regionally-defined (M1)content for submission

…or rather, what is it *not*?

- Not a review system
  - Each individual agency can implement its own review system
  - Custom-built or off-the-shelf solutions
- Not a single implementation across regions
  - Agencies progressing at differing rates and with different scopes (although try to harmonise EU implementation, particularly for joint procedures)
- Not a definition of scientific content
  - Regional agencies define content but adhere to a common format (CTD)
- Not a simple electronic submission (set of files and folders)
  - Use of XML backbone, operation attributes etc. which provides more structure and functionality in terms of navigation and Lifecycle Management (LCM).

A View of the eCTD in the EU



EU Implementation Timeline

- By a 2009 deadline the European Regulatory Network will have the infrastructure and processes in place to handle electronic submissions, including eCTD, to successfully support the related decision-making processes for medicinal products within the European Union.

- Full adoption is defined as:
  - No requirement for any accompanying paper submission or paper archive copies
  - eCTD valid for *all* European procedures (Centralised Procedure, Decentralised / Mutual Recognition Procedure, National Procedures); and,
  - eCTD valid for *all* types of submissions (Marketing Authorisation applications and renewals, Type I and Type II Variations, Responses to the LoQ, other MA related Follow-Up Measures)

- Does not imply that the electronic submission of a new dossier will be mandatory by 2009.

- *EMEA also working to implement eSubmission and eCTD within this EU context – aims to accept electronic submissions/eCTD-only by Q4 2007 (**TO BE CONFIRMED**)*

eCTD Implementation at EMEA

- What does successful ‘implementation of eCTD’ entail for EMEA?
  - The eCTD is accepted as a ‘common currency’ for product marketing authorisation applications.
  - Electronic-only submissions are accepted
  - The use of the eCTD at the EMEA is supported by appropriate SOPs for receipt, validation, storage etc
  - The use of the eCTD at the EMEA is supported by appropriate business processes

Current Status

- EMEA:
  - Acceptance of electronic submissions alongside paper for several years
  - Acceptance of eCTD alongside paper (now reduced paper) since June 2003
  - 2006 80% of submissions in e-format
  - 2006 up to 30% of new applications in eCTD format, % growing
  - Aiming to accept electronic submissions, with eCTD the preferred format, with no paper by Q4 2007 – **to be confirmed**, project underway

  - Many important issues/pre-requisites:
    - Appropriate electronic archiving policy/implementation rules
    - Appropriate hardware/software for storage and review
    - Mature and unambiguous standards
    - Business Process and SOPs
    - Understanding of LCM and its benefits
    - Effective change management

Electronic Only Target

- Date for EMEA eCTD/electronic-only implementation is crucial in the context of:
  - The EU target date (2009)
  - The EMEA business case
  - The applicants' business case
  - The international situation
  - The EU situation
    - Several NCAs now require electronic-only submissions, and there are initiatives to harmonise e-submission requirements throughout EU NCAs

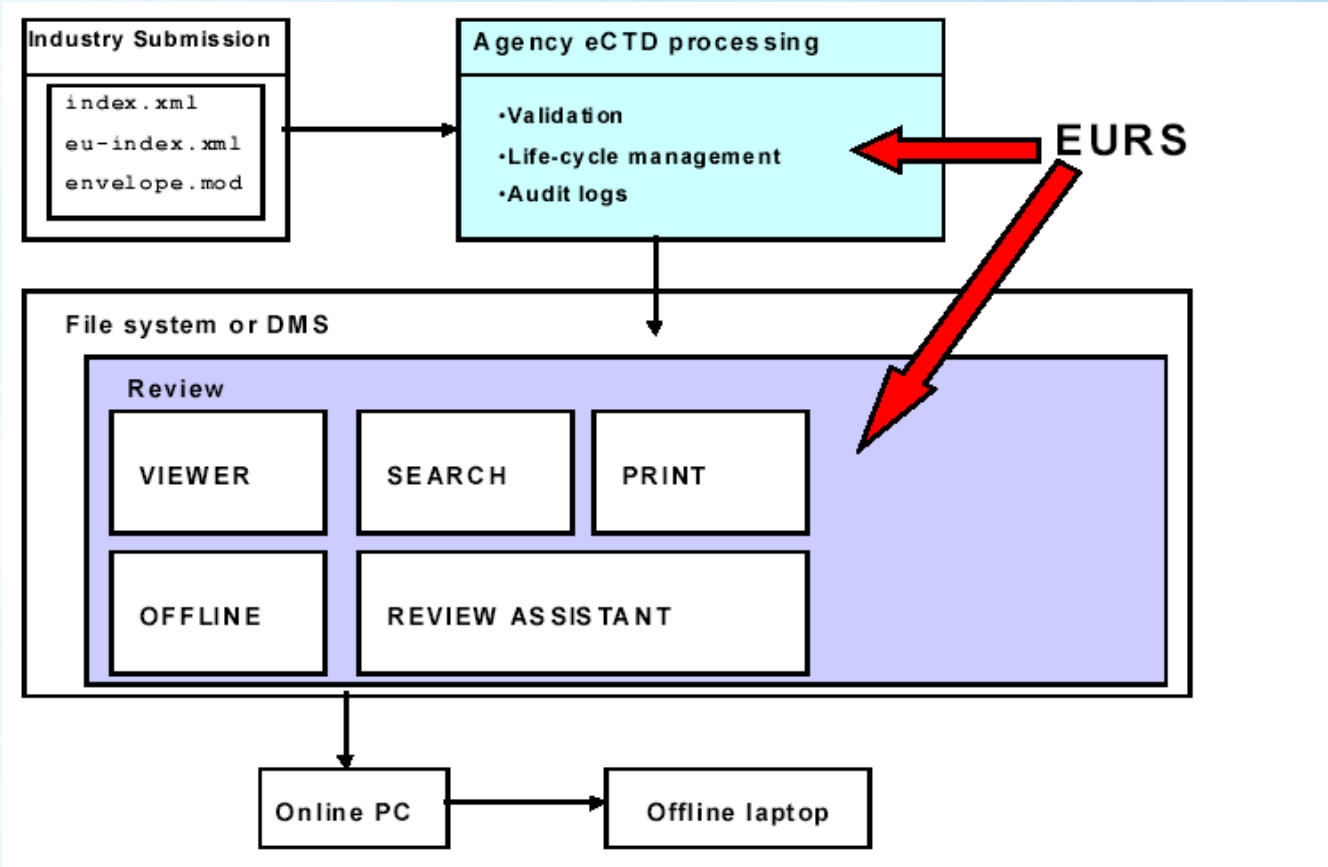
eCTD Review Tool

- No requirement for a dedicated review tool in order to the access the eCTD submission
- eCTD is a self-contained standard – stylesheet means that a browser is the only requirement to navigate through the dossier and view information
- However, without a dedicated review tool, no use can be made of the powerful LCM capabilities inherent in the eCTD

EURS

- A *common* European solution for the validation, management and review of eCTDs
- A solution to be made available for all agencies that choose to implement it.
- Goal is to enable all agencies to have a shared view of submissions, and shared view of lifecycle, for harmonised management during joint procedures (Centralised, MRP):
  - To provide confidence during interactions
  - Shared awareness of how lifecycle may be viewed
- Requirement for compatibility of output/input from builder tools (or hand-built eCTDs) to EURS
- **January 2007, contracts signed to implement a single EURS at EMEA and all MS that choose to implement it, with provision for a central repository, at least for the Centralised Procedure – installation beginning February 2007**
- Many agencies will use this EURS for all eCTD review; some will use bespoke systems or other tools
- Central Repository and connection to this will be a key issue for all agencies, is crucial element of eCTD implementation throughout EU by 2009
- Aim to reduce unilateral development and facilitate joint procedures

EURS Concept of Operations



Initial Conclusions

- EMEA is in a period of transition to full implementation to electronic submission/eCTD for the Centralised Procedure:
  - Applicants currently have the option of submitting an eCTD in parallel with the paper submission –legal basis (for now) is still paper
    - The eCTD will be used for easier review and gaining greater understanding of technical issues, and developing lifecycle management requirements
  - Ability to submit electronic only is a crucial milestone (aiming for Q4 2007)
    - Many interim steps necessary to achieve this milestone, but is an achievable goal
  - For the Centralised Procedure to be truly electronic-only, Member State competent authorities must also be electronic-only
    - This will happen in stages over the coming 4 years
    - The European environment poses a challenge for eCTD implementation, particularly for joint procedures
    - It is hoped that the framework implementation plan will be shared and adapted by NCAs
  - A single EURS (eCTD review tool for EU) has been selected – being implemented from February 2007
  - **Applicants are highly recommended to submit eCTD to EMEA where possible:**
    - Testing before submission is supported to resolve any technical issues: The regulatory procedure is not to be affected by technical issues: *Contact EMEA to discuss.*
  - *NO PLANS (AS YET) TO MAKE eCTD MANDATORY AT EMEA*

What is PIM?

PIM is:

A System

receive

validate

store

review

comment

edit

A Standard

Envelope

Branching

Neutral

Templates

Language Specific

applicant, agency, invented name, INN, ATC code, procedure, submission…

- Product
  - Form
    - Strength 1 – spc
      - Presentation 1 – outer
      - Presentation 2 – outer
    - Strength 2 – spc

Templates (neutral)

Templates (en)

Templates (de)

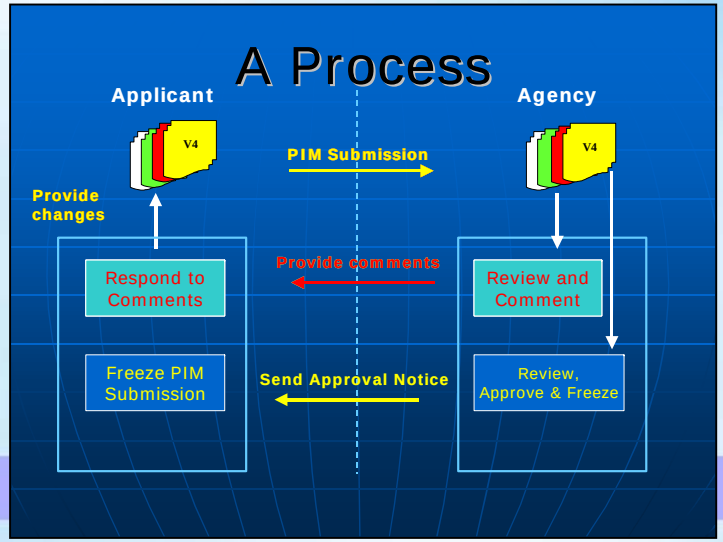
Templates (fr)

…

pim.xml

- defines product structure
- requests PI generation
- refers to templates
- content and layout

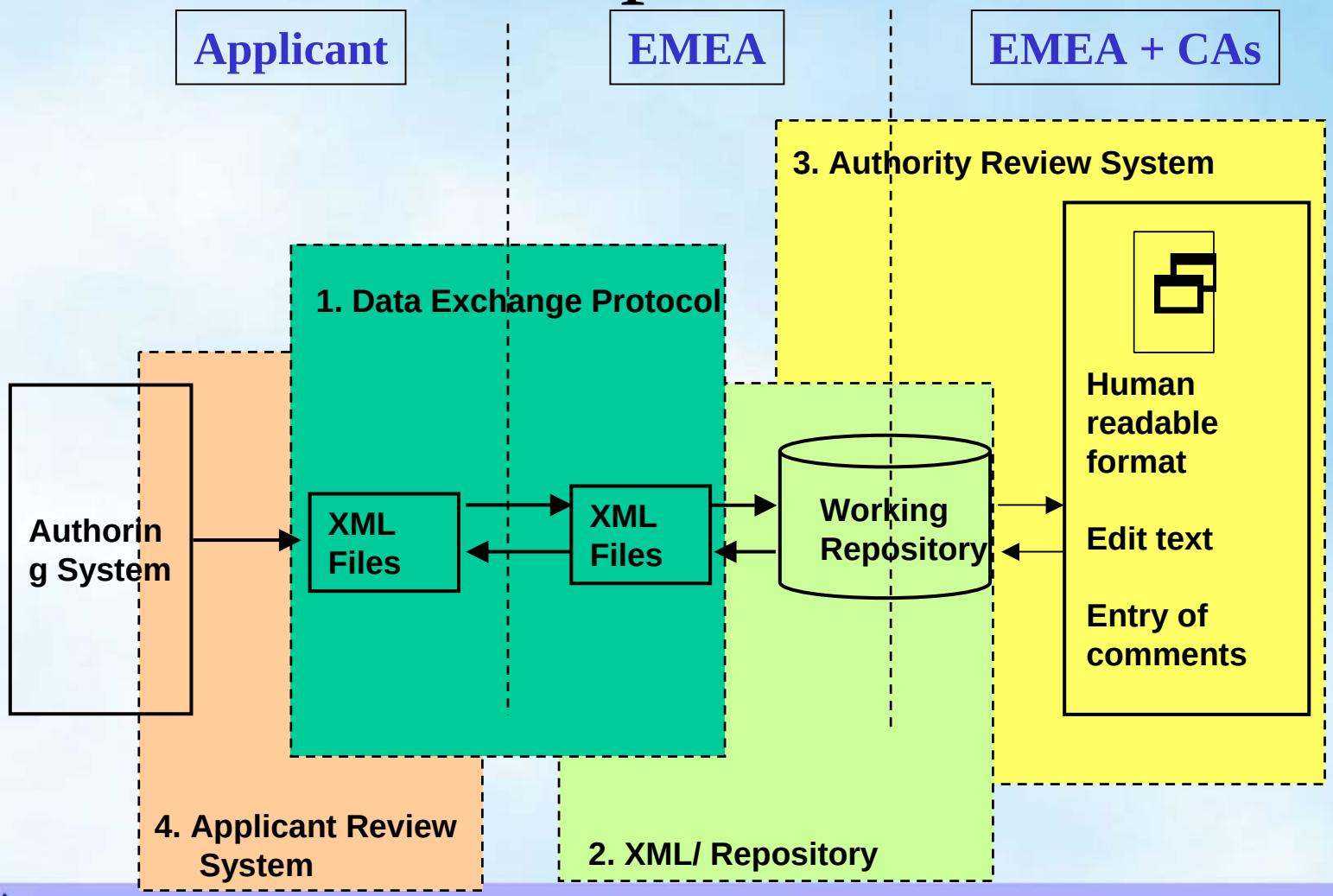
A Process



The PIM Approach

- PIM (Joint regulator/industry initiative):
  - Use XML (structured file format that focuses on content, not format) for managing product information
  - Cease to manage Word documents as the medium of exchange of PI – instead, manage XML information built according to a defined ‘data exchange standard (DES), and presented in a ‘user friendly’ manner using a review system
  - Use centralised repository for increased transparency in the process and improved version management
    - Focus is on transactions in regulatory approval process
    - Goal is ensuring accuracy & reducing work
  - PIM Submissions can be made with, or without eCTD

PIM System Global Components



Business Case

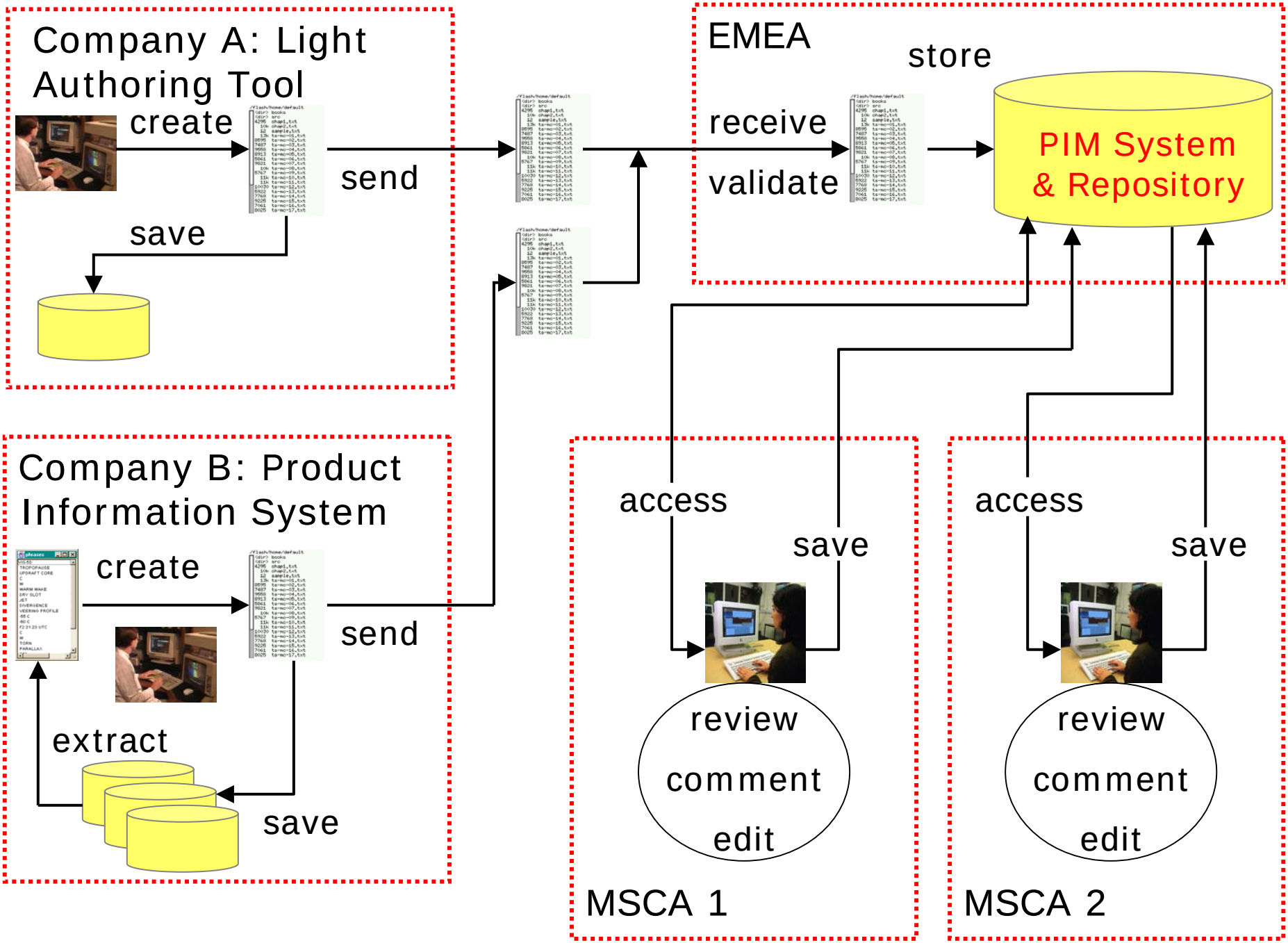
- Improved validation (automated checks)
- Unambiguous display of changes
- Review information only once - avoid redundant information checking
- Shared access to comments
- Better version management
- Increased support for standardisation
- Focus on content – no formatting
- Resource savings and efficiency gains

Current Status

- Data Exchange Standard (DES):
  - Fully-featured DES v2.3 published January 2007
  - Maintained in line with QRD
  - Supports all product types and procedures
  - DES v2.4 to be published May 2007
- PIM Review System:
  - Review System v4.0 in production
  - First ‘live’ PIM submission being processed (currently at Day 121 of the procedure)
- Light Authoring Tool (LAT):
  - LAT v2.0 in production
  - LAT v3.0 to be published February 2007

LAT

- Tool to provide the basic capability to build XML-based product information using an interface that will provide viewing, editing and life-cycle management (LCM) capabilities.
- Will also assist the applicant in packaging the EXM and associated information for submission to the EMEA
- Part of the EMEA's initiative to provide increased administrative assistance for SMEs to allow adaptation to changes arising from EU regulatory and legislative changes.
- PIM LAT will function as a submission tool for use by SMEs or by larger organisations not intending to develop more comprehensive internal solutions.
- It may also function as an interim solution until applicants can deploy their own internally-developed or external purchased alternatives. Not mandatory to use LAT.
- Can be downloaded free of change from EMEA’s PIM website, run on a stand-alone machine, and support/maintenance is provided by EMEA
- Developed in conjunction with SMEs – joint implementation team
- For more information regarding the LAT, please contact pim@emea.europa.eu


Company A: Light Authoring Tool
create
send
save
EMEA
store
receive
validate
PIM System & Repository
Company B: Product Information System
create
send
extract
save
access
save
review
comment
edit
MSCA 1
access
save
review
comment
edit
MSCA 2

Future Strategy

- A second new application to be accepted March 2007
- Consideration/publication of long-term strategy planned for May 2007
- A post-authorisation pilot phase to begin in Q2 2007 – 3 to 4 candidate submissions for this phase to be identified – please contact EMEA for further details
- EMEA committed to a controlled and positive implementation of PIM.

- Further information:
  - http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm (eCTD M1 Specification)
  - http://www.ich.org (eCTD Specification)
  - http://pim.emea.europa.eu (PIM website)

Thank you for Your Attention