VICH/IN/07003
Draft 3, 20 July 2007

VICH TOPIC CONCEPT PAPER
ON
ELECTRONIC PRESENTATION OF REGULATORY DOCUMENTS

Introduction

In the veterinary pharmaceutical sector there is a growing interest in electronic submissions from both regulators and companies. This is partly in response to pressure to keep pace with the human medicines sector, and partly to seek efficiencies that technology may offer in the handling, reviewing and storage of large quantities of regulatory documents. Exchange and handling of electronic information is becoming more prevalent in all areas of regulatory activity. Several regions have, or are in the process of, developing guidelines for the human medicines sector and may wish to consider applying similar guidelines to the veterinary sector.

Interest in this area is triggered by the assumption that electronic submissions could facilitate the review process and furthermore could support more efficient and effective archiving and retrieval. Additional benefit could come from more efficient and effective update and alignment (authority-industry) of critical Product Data (bases).

The human pharmaceutical sector has already been working on this topic for a long time expending considerable resources. Although several protocols are available or are being developed, specifying standards, technologies and structure (like e-CTD (electronic common technical document)) for submissions, intended as a replacement for paper submissions, adoption of a single approach is still under discussion.

Problem statement

It is vital that a harmonised and feasible approach to electronic forms of submission for veterinary medicine applications is developed and agreed by all stakeholders before unilateral initiatives lead to an inefficient situation, and before guidelines developed for the human medicines sector are applied to the veterinary sector without sufficient consideration of their impact or appropriateness. Certain lessons must be learnt from the human sector (see discussion).

For the veterinary sector it will be essential that simple and practical solutions are found, using readily available software and technologies, and avoiding expensive systems requiring significant investments. Discussions on the development of electronic standards must ensure that both the direction and the standards adopted can accommodate both the broad range of sizes within the veterinary industry, and also the limited resources of this sector.

The veterinary medicines area is only in the emergent stage; the majority of companies have never made electronic submissions, whilst others have made more extensive use of ‘e-compilation’ or e-submission technologies. Therefore *mandatory* implementation of electronic-only submissions or compilations would create difficulties. The option to make paper submissions must remain.

Security remains a key concern for both applicants and regulatory authorities.

Objectives

The overall aim of this concept paper is to create awareness of E-submission developments within the VICH regions, with a medium or long[1] term view to develop a harmonised approach to the electronic compilation and submission of regulatory documents in an efficient way, taking into account the specific nature and limited resources of the veterinary sector, both from an authority and an industry point of view.

Existing technical requirements in the different regions

Table: Summary of existing technical requirements in the different regions

	ICH	USA FDA /CVM	Europe EFSA	Europe (IFAH-Europe proposal)	Japan	Australia APVMA	Canada
Content format	eCDT	Limited submission types – Adobe Smart Forms	Local	Local (NtA)	Undecided	Local	
Index structure	XML inflexible	PDF	PDF	Any, keep flexible	Undecided	PDF file	
File format	XML, PDF (EU accepts product info in WORD or via PIM system)	PDF	PDF; other formats accepted	PDF, + product info in WORD	Undecided	PDF	
Hyperlinks	Yes	From table of contents, important references and appendices	From table of contents	From table of contents and to important references	Undecided	From table of contents and to important references	
Max file size	Granularity defined in a guideline		20 MB	50MB	Undecided	~10 MBs	
Media	Floppy discs, CD-Rs, DVD		CD-ROMs	Any, keep flexible	Undecided	CD-ROMs or DVD	
Optional or mandatory	Strongly encouraged		Mandatory	Optional	Undecided	Optional	
Paper still needed?	EU: yes USA: ? Japan: ?	No	Yes, 2 paper copies	Yes	Undecided	Yes, 1 paper copy	
Electronic signature	No	Yes	No	No	Undecided	No	

[1] The timeline is to be discussed and determined by the VICH Steering Committee

ICH

The eCTD provides a harmonised technical solution to implementing the CTD electronically, allowing the electronic submission of the CTD from applicant to regulator. It relies on XML technology, PDF file format and the content defined within CTD. The recommended secure information transfer standard is EDIINT AS1. The e-CTD specifies in detail which and how documents have to be stored and which meta-data has to be stored with the particular documents (version etc.).

eCTD is still being implemented across the ICH partner and observer regions. The ICH M2 EWG is monitoring implementation progress and providing solutions and added flexibility found necessary during implementation. Using the change control process, several topics including study report structure, lifecycle management, and consistency with the CTD are being discussed.

With the exception of the USA, only a limited number of human e-submissions have been accomplished in Europe. Furthermore, most authorities (except USA) are not equipped to process e-CTD applications, although European authorities are expected to all be ready by December 2009. The e-CTD requires a dossier structure that differs from the current structure for veterinary dossiers (such as EU's Notice to Applicants). Although this might be acceptable for new submissions, its application to legacy documents is proving a significant hurdle to industry.

USA

Center for Veterinary Medicine (CVM) Guidance (http://www.fda.gov/cvm/esubstoc.html):

CVM has developed and implemented methods to accept electronic files as legal, original submissions for review. This e-submission process was made possible by the publication of FDA's Final Rule on Electronic Records and Electronic Signatures (21 CFR 11) in March 1997, which set the standards for Electronic Records for FDA and its regulated industries. CVM began accepting email submission of specific PDF forms as an alternative to paper in the late 1990s. A guideline was issued in January 1999. The preferred file format is PDF originating from electronic source documents.

CVM has developed Smart Forms for five specific submission types (Notice of Claimed Investigational Exemption, Protocol Submission, Slaughter Notice, Animal Disposition Notice, and Meeting Request). In addition, CVM will consider e-submission of other data and submission types on a case by case basis. Currently the CVM is upgrading their Electronic Submissions System and allowed submission forms to discontinue submission via email and to allow for submission through the FDA Gateway. Use of the FDA Gateway for e-submission of required forms will now require the use of digital signature.

In addition, a regulation has been finalized which states that drug sponsors will provide the content of labeling (Structured Product Labeling – SPL) in XML format to the FDA. Associated with this regulation is the draft regulation to require drug sponsors to provide drug listing in XML format. The XML submission of SPL is not yet a requirement for Animal Health drug sponsors. At this time there is no standard in place for submission of an entire NADA or INAD Technical Section to the CVM.

USDA has been working on electronic submissions since the mid 1990's. Their efforts have been stalled over the last few years due to legal technicalities. They still have concerns over the electronic signatures and security of the submissions. Currently, the USDA's Center for Veterinary Biologics does not accept electronic submissions. Original signed hardcopy submissions are still made.

Europe

The European Federation of Pharmaceutical Industries and Associations (EFPIA) format, issued in February 2000, is a European version of the FDA Guidance to Industry (last issued in October 2003). It relies on Adobe PDF files, stored in a specified folder/document structure. The standards are designed with human medicinal submissions in mind, and some modification needs to take place before the standard could be used for veterinary medicine submissions.

The European Food Safety Authority (EFSA) guidance describes (guideline Sept 2004) the standards for submission of dossiers related to new feed additives. It shares many characteristics with the FDA and EFPIA formats, including use of Adobe PDF files.

For the veterinary sector IFAH-Europe based its own recommendations on the EFSA guideline, in a discussion document issued in March 2006. European regulatory authorities for veterinary medicines already require certain documents to be submitted electronically (the 'SPC', product literature and labelling, and responses to questions, usually in WORD format).

The regulatory authorities and animal health industry are now jointly discussing, in the forum of an EMEA Telematics Implementation Group for e-submissions – veterinary (TIGes-v) a simple guideline for the one-off submission of a veterinary marketing authorisation application (i.e. the electronic version will not be required to be updated). Once this action is completed the TIGes-v will consider whether it is appropriate to develop guidelines that also cover the updating of a vet e-submission.

Japan:
Japanese government basically accepts an electronic application in many administrative fields.
In Japan an e-Government promotes the use of online procedures for national application. The system for an electronic submission of the drug dossier is available in Japan and it has been implemented in human medicine by MHLW (Ministry of Health, Labour and Welfare). E-Government provides the special software program for free.

For marketing approval of veterinary medicine, however, JMAFF has not yet issued any guideline on electronic submission of dossiers. Therefore, no submission has been accomplished.

Australia
The Australian Pesticides and Veterinary Medicines Authority issued a guideline in September 2006 for the optional submission of electronic dossiers as Adobe PDF files, in addition to the paper version. The goal is to create a text PDF (smart PDF) rather than an image PDF (dumb PDF). This allows text to be interpreted as words rather than images thus allowing indexing, searching, text comparison, etc. Dumb PDF is only to be used as a last option (and generally only for paper reports, where no electronic version exists). APVMA also requires labeling documentation to be submitted as Adobe PDF files so that different versions can be easily compared. One purpose of using Adobe® Acrobat® is to not restrict original label creation to specific software.

Canada:
Currently, electronic submissions are not accepted in Canada for veterinary biologicals or veterinary pharmaceuticals. The submission on electronic support (CD-ROM) of data is accepted, but the printout is required as well. Both agencies involved are planning to eventually move towards electronic submissions, but that is a few years down the road.

Impact for public health, animal health and animal welfare

A positive impact can be anticipated if appropriate requirements can be agreed that bring increased efficiencies to both applicants and competent authorities.

A negative impact can be anticipated if inappropriate and non-proportionate requirements are enforced leading to the diversion of scarce resources from product development budgets.

Requirement of electronic submissions which do not result in a reduction in the overall time to approval while at the same time adding significant cost for investment into information technology are considered a negative impact, not only resulting in impediments to new product development but can potentially cause smaller firms to pull less profitable products off the market.

Systems with restricted access or liable to fast outdating might create an additional risk by limiting the ready access to the data in the future.

Anticipated benefits of electronic submission:

- **Benefits sought by Industry**
  - Increase efficiencies (e.g. in [multiple] dossier compilation).
  - Reduce the cost (paper, photocopying, shipments, storage) of submitting dossiers to regulatory authorities.
  - Reduce the overall processing time.

N.B. These benefits can easily be outweighed by inappropriate and costly electronic requirements or by lack of security.

- **Anticipated benefits for Regulatory Authorities (and industry)**
  - Efficient dossier navigation (e.g. use of hyper-links from the table of contents to summary documents, and then to individual study reports and data).
  - Search the main body of a submission - across all volumes (*although this is only possible if the source of the documentation has been prepared in a suitable electronic format*).
  - Copy information from the submission and paste it into assessment reports etc. (*although confidentiality requirements may restrict such uses*).
  - Improve portability - instant access to entire submission during review meetings.
  - Reduce storage space requirements where validated electronic storage is available.
  - Increase speed in exchanges (electronic sending vs. paper sending).
  - Improve the review process by making the complete dossier easily available to all assessors.

Discussion

Several regions and sectors have examined the options for the electronic presentation of documents, and have concluded that a simple system based on existing software, such as portable document format (Adobe PDF) and Microsoft WORD, is the most pragmatic solution. One advantage of PDF is that there is an existing ISO norm, so that it can support further development and version improvement.

The human sector did not undertake a cost:benefit analysis before commencing their project, suggesting an assumption that electronic technology automatically brings benefits. The human sector is now experiencing difficulties in the implementation of the eCTD, and has yet to resolve certain key issues, such as life cycle management. The veterinary sector must closely monitor the human sector experience to avoid such difficulties and to safeguard its limited resources. Consequently a clear definition of the objectives will be needed prior to project initiation.

By contrast to the human field, at present veterinary medicinal product dossiers are normally smaller, contain less information from external sources, and do not use the CTD structure. They are also often long-lived, and contain many 'legacy' documents (only available on paper). Consequently the drivers for the use of electronic technologies are different. Furthermore, the veterinary sector has only a small fraction of the resources of the human medicines sector.

Therefore a veterinary solution would have many similarities to the human sector solution, but with a few key differences, which will be determined. However, it can be assumed that a principle key difference would be the need for flexibility and optionality, built on a base-line minimum standard.

In the long-term, whatever is agreed on lifecycle management for e-submissions must not compromise the critically important lifecycle management and manufacturing compliance processes which are the internal responsibility of companies under GMP and regional medicines law.

Recommendation (action plan, timetable)

Proposed Action	Timing
1. This concept paper should be completed via discussion with the VICH partners and collection of data on existing technical and legislative requirements in the different regions.	September and October 2007
2. This concept paper should be discussed at VICH SC 20th meeting, with a view to agreeing the next steps and the timing.	October 2007
3. One proposed next step would be the drafting of a Project Discussion Document by a Task Force made up of the VICH coordinators. The Task Force should work by written procedure (a face to face meeting should not be required) and make recommendations for a way forward, including timing.	Q4 2007 – Q1 2008

Milestones

Q3 2007: finalise concept paper and submit to VICH SC in July 2007.
October 2007: discuss and agree the concept, and the future plans at Steering Committee.
Subject to agreement at SC:
Q1 2008: Project Discussion Document, laying out the objectives and principles in more detail.
May 2008: discuss and agree the Project Discussion Document at Steering Committee.

Impact assessment for Industry

A simple and pragmatic solution could have a positive outcome for industry, provided that significant investments are avoided and that the need to run two parallel document management systems (paper and electronic) is avoided.

A harmonised system will avoid the cost and logistical headache of a disharmonised approach. A simple and flexible system will allow all companies to participate, improving compliance with the standard, while allowing better resourced companies the choice to go beyond the minimum standard if desired (as some companies have already made significant investments). Using existing technologies should avoid impacts on company IT infrastructure. The implementation of electronic systems should be in exchange for reduced copies of paper submissions and improved processing time.

Expensive or rigidly applied systems will have a negative impact for industry. A key aspect will be security/confidentiality, as industry will be very reticent to utilise insecure systems.

Impact assessment for Regulatory Authorities

A simple and pragmatic solution will not have implications for the IT infrastructure of regulatory agencies, and will be reviewable by all agencies in the VICH regions. The electronic formats however should have sufficient functionality, at least for the key documents, to allow the desired benefits of facilitating the scientific assessment, possibly data storage, and possibly certain documents interfacing with other systems (such as an application form interfacing with a database). Using existing technologies should avoid impacts on competent authority IT infrastructure. Regulatory authorities will need to invest in electronic document management systems.

References to literature, existing relevant international guidelines or standards

1. ICH: Multi-disciplinary Group 2 (M2) EWG - Electronic Standards for the Transfer of Regulatory Information (ESTRI) http://estri.ich.org/
2. EFSA administrative guidance to applicants on the presentation of applications for the request of authorisation of additives for use in animal nutrition (January 2007) available at http://www.efsa.europa.eu/en/science/feedap/authorisations.html
3. Australian Pesticides and Veterinary Medicines Authority requirements for the construction of electronic submissions (dossiers) 8 September 2006. Available on request to tony.delafosse@apvma.gov.au
4. Electronic presentations of Product Documents: IFAH-Europe position & specifications for the European Animal Health Industry (13 March 2006). Available on request to techsec@ifahsec.org
5. FDA/CDER/CVM: Guidance for Industry - Providing Regulatory Submissions in Electronic Format - General Considerations, January 1999 (http://www.fda.gov/cder/guidance/2867fnL.pdf)
6. Pesticides sector: CADDY (Computer Aided Dossier and Data Supply) http://caddy.ecpa.eu/index.html