PILLS

Patient **I**nformation **L**anguage **L**ocalisation **S**ystem

Publishing Requirements in the Pharmaceutical Industry

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Pharma publishing and the PILLS approach

A new approach to localisation.

Publishing of information — package inserts, documents required for authorisation purposes, web content or any of the other myriad means of written communication — presents a major challenge to pharmaceutical companies today, in particular those who market their products worldwide. Similar information must be provided to consumer, physician, pharmacist, and regulatory body, adding up to literally thousands of documents per product. Strict regulations, which differ from country to country and are constantly undergoing revision, complicate the issue. Multinational companies struggle to create and publish information appropriate to local conditions and requirements, while maintaining control of centralised product and registration data.

Localisation — translating and adapting information for the needs of specific local markets — is essential for companies operating in a global market. While harmonisation of regulations aims to promote consistency in legal requirements in multiple regions, it also drives requirements for local-language publication of pharma information. This increases the need for coherent strategies for multilingual publishing in the industry. At present, localisation of pharma content requires significant investment in translation as well as solutions for the complex task of maintaining multiple language versions of product information and other relevant content.

PILLS (Patient Information Language Localisation System) is a one-year project in the European Commission's *eContent* program. The objective is to produce a prototype tool which will support the creation of various kinds of medical documentation simultaneously in multiple languages. In the **PILLS** application, pharmaceutical and medical domain knowledge is stored in a knowledge base, and a graphical interface allows the author to "write" a document by selecting the appropriate concepts from the knowledge base. Using innovative "WYSIWYM©" technology (What You See Is What You Meant), each concept is linked to its linguistic representation so that the text is generated automatically from the author's selections. Because of this separation of concept from textual representation, the text can be generated in any language for which the linguistic elements have been stored. Furthermore, by applying stylesheets and linguistic register templates, the same content can be used to produce documents in different publishing formats or even for different end-users (e.g. technical vocabulary for the physician, and layman's vocabulary for the consumer).

The project is coordinated by Berlitz GlobalNET, who are performing market investigation and analysis. The other partners are the Information Technology

Research Institute (ITRI) at the University of Brighton, who have developed the prototype editor and document generator, and the Medical Informatics group at Freiburg University, who have created a domain model (a kind of advanced knowledge base) of pharmaceutical vocabulary and linguistic resources, which the system will use for the creation of medical documents.

Initial reaction to PILLS from the pharma industry

Some comments from those involved in the creation and localisation of pharma documents:

> "The company is working on the PIM initiative from the EMEA. Any tool generated would need to be compatible to this system and to publishing systems."

> "Anything that reduces our translation burden is interesting to see, so we would be interested in seeing what is being developed."

> "I know that for those affiliates who have to translate technical documents at often short notice the workload can be considerable and not very popular."

Localisation is clearly a bottleneck, incurring high costs, delays to product launch and a heavy workload. In addition, translation is often decentralised, being handled by local offices/affiliates, which means that localisation costs are difficult to track and processes are difficult to manage.

Industry Regulators

Worldwide, publishing in the pharmaceutical industry is strictly regulated by various bodies. We take a look at the European legal situation and the implications for U.S. companies entering the European market.

For any pharma company wishing to market their products in Europe, the significant driving force for localisation is EC regulation, which insists that all pharmaceutical products marketed in the EU are localised for all 15 countries of the European Economic Area (EEA). The constraints placed on companies by regulatory authorities and the sheer amount of paperwork and procedures can be a significant challenge.

All medicinal drugs (over-the-counter, prescription, biologicals and so-called "orphan" drugs) are regulated by the same organisational bodies. The creation, marketing, and distribution of these drugs are regulated by government agencies. International agreements are being made to create uniform measures of compliance with all the relevant national laws. The purpose of these international agreements is two-fold: firstly, to facilitate greater consistency between national laws, each borrowing from the other towards the most effective means and measures and secondly, to minimise the time-to-market requirements that have in the past delayed the introduction of new drugs to consumers.

There are drug regulatory agencies in every country, most of which are the central source for approvals of clinical studies/trials, and for marketing authorisations required for the promotion and distribution of the drugs in that country. The most notable are: The United States Food and Drug Administration ("FDA"), the European Medicines Evaluation Agency ("EMEA"), and the Japanese Ministry of Health, Labour, and Welfare ("MHLW"). Other country-specific agencies, especially in the case of EU (European Union) countries and candidates, plus countries of South America and many in Asia and the Far East, rely heavily on the work of these three primary regulators. Increasingly, the major regulators convene scientific and administrative councils to formulate and implement uniformity among nations on drug controls.

Detail on the types, usage, and generation of documents during the regulatory process is an important focus of **PILLS**. These details help to indicate at what points such documents lend themselves to localisation. Those same milestones also indicate where localised content can be leveraged from content which has been translated or locally created in the past.

Figure I. shows a simplification of the actions required to launch a new drug. Shadowed actions generate documents that may be localised. To give an idea of the volumes of documentation involved in drug registration and marketing, the average

number of pages for all the documents represented in this chart is slightly above 120,000 pages per drug and in the year 2000 there were more than 5,000 new substances reviewed worldwide.

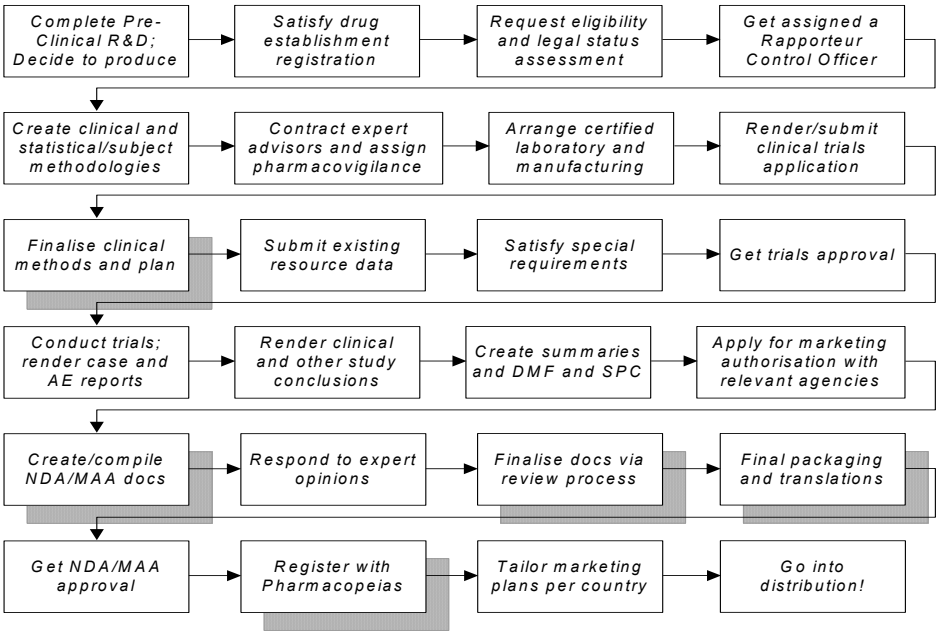

Figure I: ***Profile of Action Phases to Put New Drug on Market*** *(Simplification)*

European Regulatory Agencies

EMEA and EUDRA

The European Agency for the evaluation of medicinal products (EMEA) is the key central body for European regulatory decision-making activities. It was founded in 1995 by authorisation from the Directorate-General ("DG") of the European Commission ("EC"). The EC formulates policy, promotes legislation, monitors adherance, and seeks enforcement through the European Court of Justice. In pharmaceuticals, the DG maintains an advisory unit known as "EUDRA", the European Union Drug Regulatory Agency. These two agencies, EMEA and EUDRA, work together, in that EUDRA formulates legislative initiatives, monitors effectiveness and provides public information resources, and the EMEA uses these resources in its assessment of clinical trials and marketing authorisation applications.

Within EUDRA there are numerous administrative and technical committees, comprising representatives from Member States as well as staff professionals, who advise the EC on relevant issues. Within the EMEA, whose focus is the day-to-day implementation of procedure in its evaluation of applications, the Committee for Proprietary Medicinal Products (CPMP) is responsible for assessing marketing authorisations. This group comprises representatives from each Member State of the EU.

European Country-Specific Agencies

Every country in Europe has its own drug regulatory agency, each of which continues to handle applications that are specific to that country when the pan-European mechanisms are relevant. In the United Kingdom, for instance, the Medicines Control Agency, an Executive Agency of the Department of Health, determines the approval of trials and the granting of marketing authorisations. It works closely with the EMEA on U.K.-related issues.

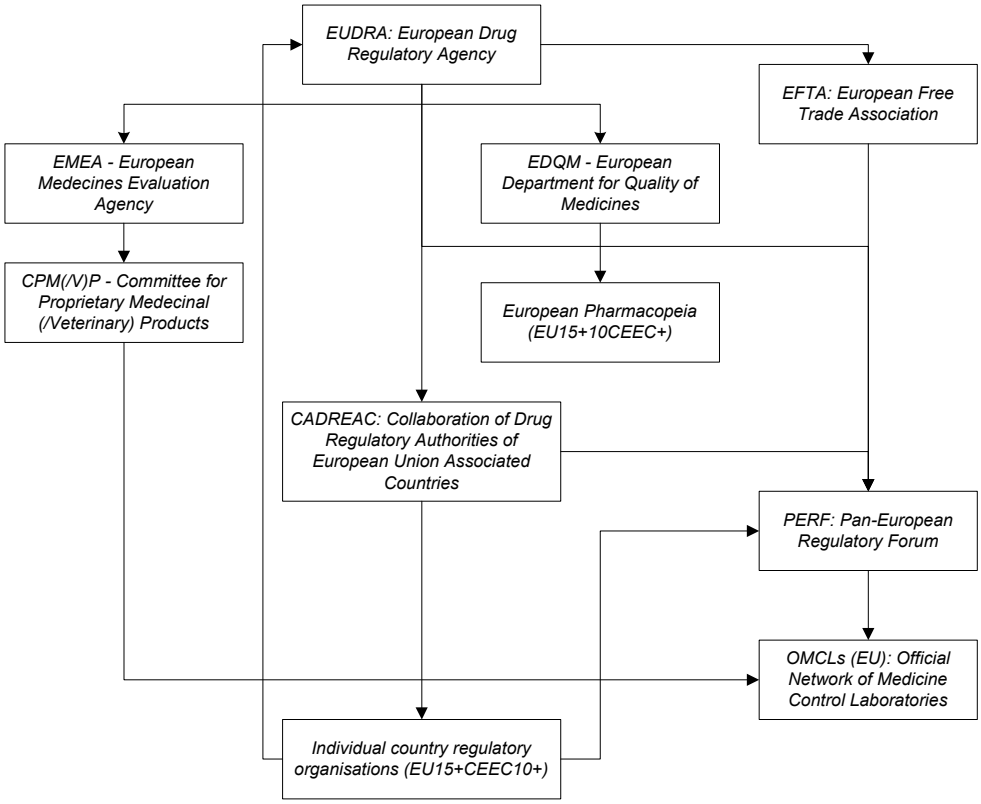

Figure II: European Agencies Summary

Clinical Studies/Trials

Clinical trials are the most time-consuming and labour-intensive part of the approval process for a new drug. Because of this they are often undertaken in multiple countries simultaneously. Clinical trials involve hundreds or thousands of discrete documents and modular data prior to completion for approval of a marketing authorisation. A simplified view of the categories of components, from initial registration through to the conclusions of the clinical trial and presentation for approval, is presented in figure III

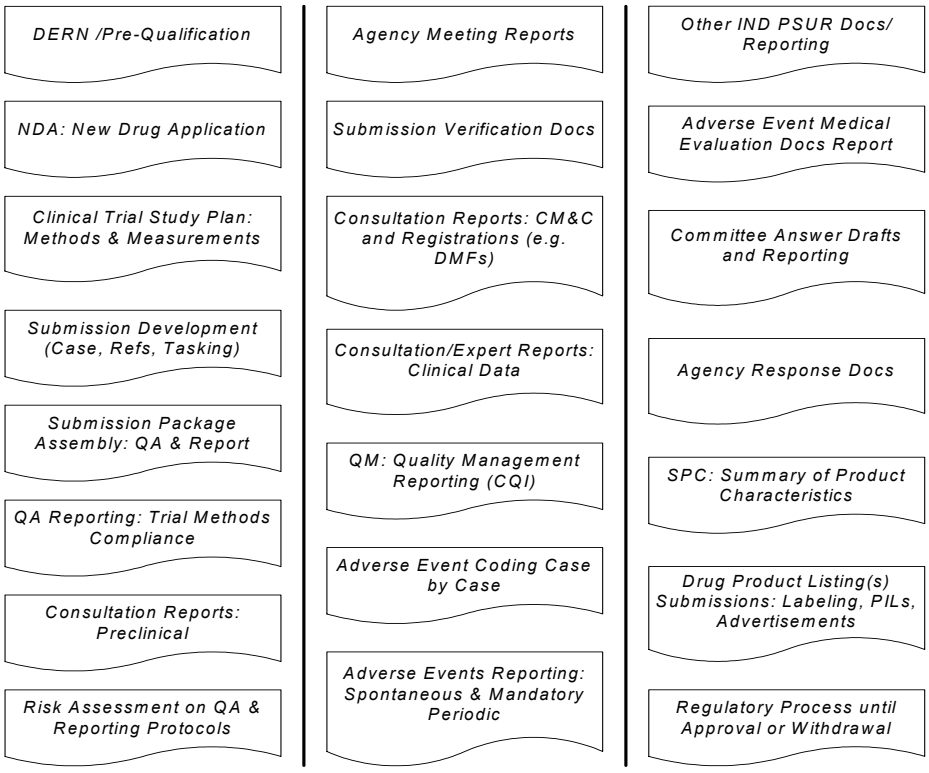

Figure III: ***Typical Documents Required Overview*** *(Averaging 100,000 pages)*

Applying for Drug Marketing Authorisation

Once the clinical trial data is available and the drug has been approved, the entire summary data must be formulated for the marketing applications. Until a drug has been given a marketing authorisation to distribute in the relevant territory /country, it cannot be distributed nor promoted. Various forms of authorisations are needed, depending upon the marketing plan.

Pre-Application Guidance from Regulators

Pre-application guidance is available from each of the government agencies for their respective regions. It is expected that this pre-application guidance can average 4-5 months of duration or be streamlined to as little as 3-4 weeks. The process itself can require interpreters if the key staff for eligible companies do not speak the language of the regulators involved. Certain process documents, plus clinical and other data, may be translated for presentation to an agency if the applicant company is using materials from other regions. Normally, however, applications are made by professional representatives of the drug company in the country for which the application is made, eliminating language barriers during the pre-application guidance interaction with agency administrators and scientific experts. Agency guidance to drug companies is often time-consuming because of the experts who must be involved in assessments at each stage of the development. Interviews, and review meetings, are interspersed between scheduled submissions of portions of

the methodology (if a clinical study is required) or the components of a request for marketing approval. The interviews are intended to streamline the process as a form of "pre-review" so that problematic issues or other factors are identified prior to the formal submission of the components due during that part of the process.

Importance of "Rapporteur"

Most important is the role of the "Rapporteur", as the regulatory agent is known in Europe. Repetitive liaising, between the expert committees, agency administrators, and the applicant drug company, is done by the Rapporteur to ensure that each phase is carried out properly. Most importantly, when the expert opinions and other assessments are responded to by the applicant, it is the Rapporteur who determines whether the response is relevant, complete, and merits the further attention of the officials involved.

Actions & Documents in MAA (EMEA) Process

A step-by-step illustration of the process for obtaining a Marketing Authorisation (MA) under the "Centralised Procedure" (CP) in Europe gives an overview of the numerous documents generated. Approval of an MA under the CP authorises the drug company to then distribute their product in any of the 15 countries of the European Economic Area. Additionally, with a submission to CADREAC for "parallel authorisations", the company can apply for approval to distribute in the official EU candidate nations of Eastern Europe.

EMEA requires submission of process documents 4-6 months prior to application, with indication of the intended month of application. Once the basic administrative obligations are fulfilled, additional documents are required upon formal application. When the Rapporteur has approved the content and form of the documents listed on the right of the chart, submitted by the applicant, the initial administrative review analyses take place. With the assistance of the Rapporteur, these documents are revised until they are acceptable for the application process. The application then becomes official and the submissions can be routed to the appropriate consultative committees and other administrative divisions of the EMEA.

Drug Registration

In Europe, official registration takes place when the EMEA submits the approved MA documents to the European Commission via EUDRA. The process for each is essentially the same, involving the provision of the approval verification and copies of all the relevant physician and patient leaflets plus all labeling and other packaging. It is important to note that these registrations are not the same as inclusion within official and/or commercial "trusted third-party" pharmacopeias, although the content is most often the same.

Moves towards standardisation and harmonisation

International agreements exist between European, American, Asian, and Far Eastern countries to varying degrees and with different national groupings.

ICH

One significant group is the International Conference on Harmonisation (ICH). The ICH comprises official regulatory involvement from Europe (EMEA), Japan (Ministry of Health and Welfare) and the USA (Food and Drug Administration), with representatives from the industrial associations in the three regions: European Federation of Pharmaceutical Industries Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA). Observers attend from the WHO (World Health Organisation), EFTA (European Free Trade Association), and from Canada, with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) participating as an 'umbrella' organisation for the pharmaceutical industry and providing the ICH Secretariat. The ICH agreements supersede the traditional Mutual Recognition Agreements (MRAs) which were traditionally negotiated on a country-to-country basis. The initial remit for ICH covers 45 harmonisation topics, in four broad categories:

- "Quality" topics, which relate to chemical and pharmaceutical quality assurance (e.g. stability testing and impurity testing);
- "Safety" topics, which relate to in-vitro and in-vivo pre-clinical studies (e.g. carcinogenicity testing and genotoxicity testing);
- "Efficacy" topics, which relate to clinical studies in human subjects (e.g. dose response studies and good clinical practice);
- "Multidisciplinary" topics, i.e. those that do not fit uniquely into any of the above categories (e.g. medical terminology and electronic standards for the transmission of regulatory information). As more and more testing requirements are harmonised by ICH guidelines, discussion has turned to the feasibility of developing a common format, or Common Technical Document (CTD), for submitting this data to the regulatory authorities in all three ICH regions. As this becomes more acceptable to national agencies as well as to the ICH such submissions will become increasingly electronic and automated.

Recent legislation in Europe has addressed the administrative and legal requirements to enable countries to implement the new ICH guidelines on clinical trials. A directive was published in the Official Journal of the European Community on 1st May 2001, in which specifics of Good Clinical Practice are presented to guide formulation of clinical trial plans. By 1st May 2003, member states must submit their provisions for adherance, and implement those by 1st May

2004, so that all EU countries are consistent with ICH guidelines on or before that time.

Pharmacopoeias

The European Pharmacopoeia is an official body that also serves as a fraternal organisation for the professional involvement of interested outsiders. The EDQM (European Department for the Quality of Medicines) replaced what was formerly known as the "Pharmacopoeia Secretariat". The EU convention that created the EDQM has 28 official members including the European Commission and 27 countries across Western and Central Europe. Numerous other countries have become frequent observers in the work of the European Pharmacopoeia, and are often invited to sessions. These include several Eastern European and North African countries, Australia, Canada, China, Malaysia and the WHO (World Health Organization).

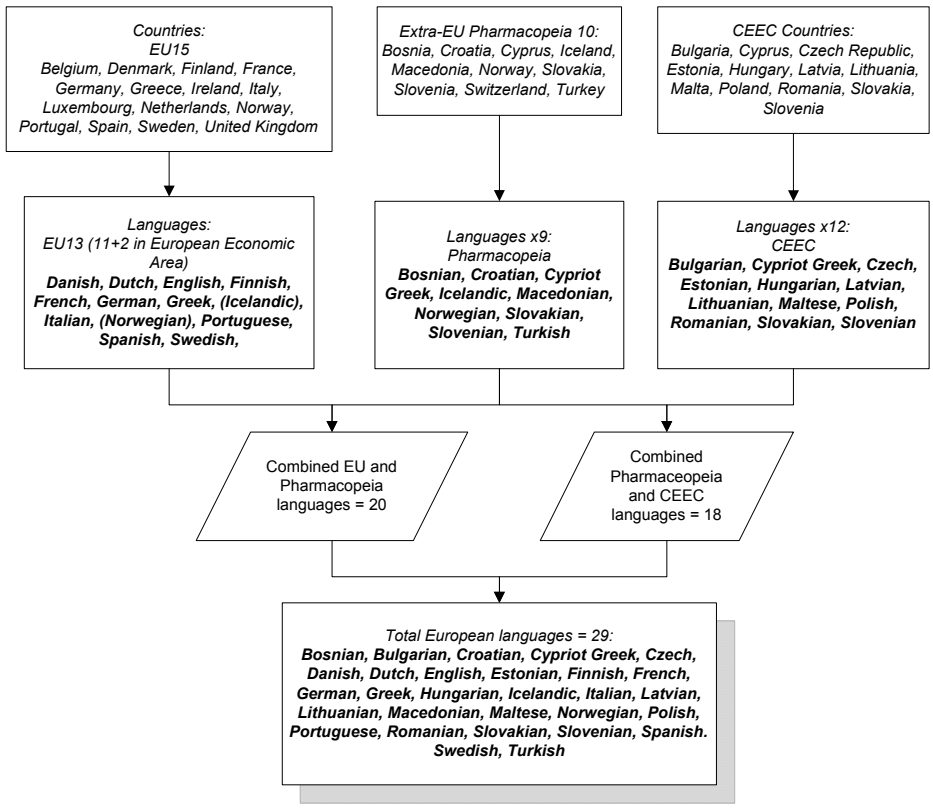

Figure IV: ***European languages***

The Document Creation Process

From authoring through localisation, including quality assurance and printing issues, we look at the processes involved in creating pharmaceutical documentation.

Several related documents detail the purpose and other characteristics of each drug that is manufactured. The first and most comprehensive of these to be produced by the pharmaceutical company is the Summary of Product Characteristics (SPC) which is produced to satisfy the requirements of the regulatory agencies. These are generally created by the Regulatory Affairs department of the company, with input, in terms of data about the drug, from the development scientists and the product marketing managers. In some companies there is a "Medical Information" department through which all such authoring is done, though this department may only be the final step in the production of approved documentation. Because of the detailed nature of the SPC, the type of information and the language used, which may be quite technical, the SPC is suitable for doctors to use as reference, but less so for patients. However, the distinction is becoming more blurred with SPCs becoming more and more accessible to the general public via the web.

The SPC is then used as the basis for the Patient Information Leaflet (PIL), also sometimes called a patient package insert. The PIL is the leaflet inserted into the medicine pack, and includes information about how to use the medicine, contra-indications and side-effects. The PIL has essentially the same information as the SPC but couched in more "patient-friendly" terms.

Other materials that are published, such as the internal (on the bottle/blister pack/tube etc) and external labels (on the box) are reduced versions of the PIL content.

Formats

How the electronic documents are produced varies from company to company, though it is generally the case that initial authoring is done using word processing of some form e.g. Microsoft Word. Later in the process, when either special layout or special characters must be handled then other format files may be used. Often when the actual descriptive content is finalised another format of electronic file will be used to create the printing and packaging layouts. At this stage, when content has been approved but is being formatted for particular usages, PDFs and/or other forms of output may be created to enable use of new technologies for information distribution, such as on CD-ROM or web.

The primary step of filing an application with the regulatory agencies is often done via hardcopies. On the other hand, at the end of the authoring and approvals process, content may be published electronically on the World Wide Web (Internet) as in the case of SPCs and PILs (patient information leaflets) which are submitted by the company to the Electronic Medicines Compendium (EMC) website. SPCs and PILs may also be published on individual companies' websites or in hard copy "compendia" to be used by the physician as reference.

Traditional pharmaceutical publishing utilises a range of file format types from simple text to layered styles-driven desk top publishing (DTP) editors. The reason for so many formats is the multiplicity of sources and approvals steps, both in regulatory and company procedures, that trials data and patient information generally undergo. Even the official regulatory agencies do not have universal submission requirements, so many different systems and software packages are used. In addition, where printed hardcopies for signature approvals is the basis of the quality assurance (QA) system, the most important requirement of a deliverable file format is that it can be reproduced identically on other systems. Currently, PILs and labelling that are being printed commercially are re-created from word processing (WP) to DTP software formats. DTP software such as QuarkXpress, PageMaker, FrameMaker, CorelDraw, Ventura, Publisher, is used as deemed suitable by various printing departments. Most printing houses maintain reprographics or desk top publishing (DTP) departments that re-create client-submitted content into DTP software layout files. These files are then put through the customer's own quality assurance (QA), as well as the QA done by the printer, and through multiple review cycles before printing can start. The most common DTP set adjunct to commercial repro-houses is Mac OS driven Quark Xpress with Adobe Illustrator and PhotoShop support.

Labelling for packages, e.g. bottles, blister packs, aerosol containers, other dispensers, sachets, and boxes, etc., is not consistently manufactured throughout the industry. Nor are the types of materials used for such packaging directly regulated and thus are likely to be of any of a number of types of plastic, paper, and hybrid materials, or varying thicknesses and of different constructions. Though some regulated content will be utilised consistently throughout all of the packaging materials for a particular product, the required information decreases in this order of priority: SPC, PIL, Container Label (outer label), then blister pack or bottle label (inner label). Often the pack and box labelling is produced by completely different means than the PILs if the manufacturing process is not carried out by a single provider.

Maintenance

The large pharmaceutical companies have processed vast quantities of documents for decades and are therefore slow to implement any type of company wide content management. Electronic documents are mostly managed by those who are responsible for them on their chosen fileserver basis. SPCs, PILs, and all other packaging and marketing materials exist in different files in various locations. Documents may be updated 2 or 3 times a year, in response to changes in regulation or in the product information.

Quality Assurance

A strict QA process is necessary to avoid liability costs from errors. The number of people involved in the entire production process is so large that the QA process must be well-defined. Numerous companies have ISO procedures that took decades to evolve to their present form and are therefore difficult to circumvent or adapt. Many of the procedures in place are very restrictive when it comes to making copies of tracking devices (such as control documents having handwritten signature approval pages; and the keeping of cumulative handmarked revision sets as the required archive piece). Many companies still use hardcopy approval procedures, justifying them as the only means of ensuring that a single, physical, revised document serves as the ultimate approved source for submission and further revision.

Localisation

SPCs and related packaging and patient information are generated initially in the native language of the country where the product is being developed. For pharmaceutical companies located within the boundaries of the current European Union, any of the 11 (+2) official EU languages may be used initially. This source language is then usually sent out for translation to regional affiliates. Exceptions are increasing, due to multilingual publishing and cross-borders status, when documents for translation may be sent directly to commercial agencies. Often draft texts are sent to shorten the turnaround time for translation. Most companies are carrying out many tasks multiple times and utilising expensive QA procedures to pull edited subsets of each translated document together into composite documents. Companies who routinely manage multilingual publishing for PILs retain staff with expert language abilities for translations work in-house. Others contract it as needed but then face doing some QA by way of other contractors if they do not have at least review skills for each language on staff.

EMEA/CPMP requirements

One of the key requirements for a Marketing Authorisation via the EMEA is production of certain elements into at least 13 languages, plus some particular components must be translated into specific languages for inclusion of the relevant country in the authorisation. At the very least, for a pharmaceutical company to be centrally authorised in Europe, 13 languages must be rendered for the SPC (Summary of Product Characteristics), all Labeling, Patient Information Leaflets, and other packaging; the administrative materials must be submitted in English, Greek, Portuguese and Spanish; the expert reports must be rendered into Portuguese, Spanish and English; and all scientific documentation must be rendered into Spanish.

Within 5 days after the marketing authorisation is given by the CPMP (the EMEA committee responsible for assessing marketing authorisations), initial translations of the SPC, labelling and package leaflet must be provided to the CPMP members. By the 20th day the final revised versions of the translations must be provided to the EMEA in their final publishing format. During the 15 days' evaluation procedure

between the initial and the final translations, the translations are reviewed by the EU Member States, plus Norwegian and Icelandic authorities for those languages.

As other countries achieve member status of the EU in the near future the set of 13 languages will of course expand. At present, most companies believe that Czech, Hungarian, and Polish may soon become required languages in the European Economic Area.

Expanded sets of languages beyond those requirements for the companies that manufacture in the EU are set by each company according to its own distribution plans. Choice of languages to include may be driven by overlapping concerns and not restricted to one particular set of priorities. In multilingual labelling work, for instance, several companies have language combinations that include languages outside the region of the majority, and perhaps even for a minority populace within the target region.

These same languages also serve as the basis for translation work that may be done in the transfer of existing marketing authorisations (e.g. German to Swedish) and also for the "parallel" applications made under the EMEA to transfer authorisation from the EU15 group to any of the CADREAC Eastern European countries (eg. English to Polish). Finally, those languages can be used as the basis for international (ICH-based) transfer of materials.

Different patterns of country groupings for print coverage are common across commercial sectors because of differences in presence, representations, filings, and other operation-specific factors, despite the convenience of conventional groups. For example, several companies routinely do “EC12” plus 4 other individual languages required because of local presence or representation, despite requiring variance in encoding and files delivery to accommodate the extra-regional languages (Polish, Czech, Latvian and Lithuanian) through agents there. The traditional clash between politically-expedient inclusion of languages with different encoding, and the technical difficulties of managing those languages within the same file sets, led to the common problems of multiple different review cycles, repetitive QA, and the re-creation of final materials for printing.

Some corporate planning in these realms of regionalisation, especially for emergent pharma companies using e-commerce where the regional politics have decreasing importance, includes increasing use of pan-global centralisations made possible by web-based software. An example of an emergent e-commerce pharma company is a California-based producer putting 28 languages on labels but only physically distributing to 12 countries.

Meeting the challenge

What does all this mean for publishing in the pharma industry?

It is clear that publishing in the pharmaceutical industry is rooted in traditional processes and procedures, highly regulated and difficult to change because of this. The continued use of hard-copy approval procedures, the multiple conversions of file formats, the lack of any firm content management strategies do not simplify the task of keeping track of thousands of documents per drug. Add to this the number of languages required for marketing pharmaceutical products in the EU marketplace and the problem increases by a factor of 13. As more languages are added with Eastern Europe coming into the fold, the situation is only going to become more challenging.

However, the steps taken by the ICH towards harmonisation of regulations and the creation of a common technical document format, plus EMEA/EFPIA initiatives in the area of electronic submission of documents are evidence of a willingness at the highest levels to bring these processes up to date. Use of the web is precipitating this development, by providing a centralised, easily accessible publishing medium, but also creating a requirement firstly for documents to be available electronically, and above all for a greater volume of information to be at the consumer's fingertips, whether that consumer is a patient, pharmacist or physician.

Even with increased emphasis on common document formats and electronic submission to regulatory bodies, however, localisation remains a stumbling block. With time-to-market critical, and the enforcement of strict timelines by the EMEA, the time taken for translation is a significant cost factor. The 20 days allowed for translated versions of documents by the EMEA is clearly not long enough to produce the translations from scratch, which means that the initial application for marketing authorisation is likely to be delayed until the translations are near completion.

One way of addressing this issue is to enforce a coherent content management strategy. Many of the documents produced in the launch of a new product contain repeated information. By creating information once and re-using it in all implicated documents, and keeping track of that re-used information, the quantity of words to be translated can be kept to a minimum, not to mention the vast savings in time and costs which would be made at the authoring stage. As much as 90% of the packaging, labelling, and PIL materials are repetition of information already available in the SPCs. Many of the PILs differ solely from each other in terms of the delivery mechanism for the drug or the size of the dosage. Different size tubes, dosage (e.g. 100 or 200 mg tablets), delivery as a cream or an ointment, effervescent tablets or capsules, and so on, all require separate PILs. But the majority of the

information contained in those PILs will be the same. The active ingredient in the drug may be used in many different products, and the information pertaining to that active ingredient (e.g. codeine) is repeated for every SPC which details a drug containing that ingredient. The SPC, labeling, packaging, and PILs (patient information leaflets) also have wider distribution into other arenas of publishing, such as pharmacopoeias, internet information services, health provider literatures, etc. Again, the concept of a common document format and of linguistic re-use can be applied to produce these other publications.

In order to re-use information across documents, content management must be at a low level of granularity. This implies some sort of generic "database"-style format with components such as contra-indications, ingredients etc being stored separately. There is already a suitable format widely in use in many industries, such as the automotive industry and web publishing, and that format is XML (Extended Markup Language).

The PIM (Product Information Management) project, an EMEA/EFPIA initiative, is investigating and trialling the use of XML as a standard format for electronic submission. A DTD (Document Type Definition) has been developed for the project which defines the XML tags which should be used to "label" the text. Software can then use those tags along with stylesheets to pull together the text elements into documents, and publish those documents in any format for any medium – web, CD, SPC, PIL etc. If all companies were to use the same DTD for creation of SPCs and PILs, this would ensure a standard format, and would enable the creation of a central database of text elements to be re-used, searched, and filtered.

Standard XML-based document creation and submission bypasses many of the DTP/formatting steps outlined earlier in this paper. It also enables easier management of updates to product information which result from changes in legislation, changes to the product or changes to information available about the product (for instance the discovery of new side-effects from long-term usage). These updates generally happen two or three times a year, which is significant considering the number of documents implicated. With an XML content-management strategy, only the changed text components need to be submitted rather than the whole document. At the time of writing, the focus of PIM is submission of documents to the EMEA which conform to the specified DTD (the name of the DTD is XDossier), and component-level submission will be the next stage of the project.

XML however only goes part of the way towards re-use of content across documents. Often the same information is re-used but has to be phrased differently. PILs are usually couched in patient-friendly terms, using the drug name rather than the active ingredient, phrasing warnings and contra-indications in such a way as to inform but not alarm unnecessarily, and addressing the patient directly with instructions. The choice of information provided is more selective, and medical terminology is avoided. The SPC on the other hand includes a lot more information about the drug, and presents that information as raw facts, using

medical terminology, and discussing the active ingredients rather than the brand name of the drug. To illustrate these points, an SPC might explain that:

> In animals, <INGREDIENT NAME> has shown no teratogenic effects but is foetotoxic at high oral doses and administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. The relevance of these findings to humans has not been established. However, combinations of topical steroids with imidazoles should be used in pregnant women only if the practitioner considers it to be necessary.

. The PIL would present this as an instruction to the patient. e.g.:

> If you are pregnant, planning to become pregnant or breast feeding, you should talk to your doctor who will decide if you can use <PRODUCT NAME>.

This is one of the problems which **PILLS** could address. The **PILLS** authoring tool would allow the author to specify the facts and the concepts, and the various documents which need to be produced from those facts. The actual text would then be generated automatically and simultaneously from the facts given by the author, in as many different registers and formats as required – the full set of facts, using technical terminology for the SPC and a condensed version, in layman's terminology for the PIL, both formatted in XML conforming to the XDossier DTD, a version formatted in HTML for publication on the web, and so on.

This is a possible route for the **PILLS** system to follow. But the original intent was to solve the localisation issue which is a particular challenge to those companies marketing their products in Europe. As the text is automatically generated from the concepts/facts chosen by the author, that text can be produced in as many languages as the system has rules and vocabulary for. The system should also take into account the review stage, which would allow easy editing of documents after the initial authoring process. Review processes for each language would then be simultaneous, because edits made to the original document would be automatically propagated throughout all languages. When the Marketing Authorisation Application is submitted, it can be submitted in all languages at the same time, thus resolving the issues of the localisation bottleneck and the lengthy review procedures which are currently in place.

It is imperative that further development of the **PILLS** system ties in with the EMEA/EFPIA initiatives and produces documents which conform to industry regulations, as well as meeting the requirements of usability and integration. The business processes to use such a system are not yet in place, but there is pressure from all sides and all levels to change the existing processes and bring production of pharma documentation up to date, while simplifying the authoring and localisation tasks in the face of additional languages and ever-changing regulations.