

## Taking On the World: One Size Does Not Fit All

Maximising international opportunities can create a substantial administrative headache, which is why standardisation offers such a positive way forward. But, says *Adam Sherlock*, this could – and should – mean different things to different companies.

Simultaneous multimarket entry is a growing reality for the pharmaceutical industry as regulatory agencies worldwide move to further standardise the format and structure for submissions. Growing acceptance of the electronic common technical document (eCTD) standard for submissions is paving the way for standardisation and greater efficiencies, certainly, but there is still some way to go.

Beyond the US market, where efficient, modern electronic submission standards have been accepted and bedded down, the regulatory environment remains complex and inconsistent.

Outside the US, submission requirements still vary considerably from one country to the next, especially across Europe. This renders the situation challenging, particularly in markets where internal resources begin to thin out – for example, where the responsibility for managing submissions falls to small affiliates that may be overstretched already.

A growing presence across the globe, increased merger activity and more extensive collaboration with partners around the world expand the roles of affiliates in regulatory filings and necessitate improved information sharing.

Since limiting the market opportunity is not a desirable option commercially, pharmaceutical organisations have little choice but to bring down the boundaries and bring new efficiencies to their international regulatory submissions activities – measures that take into account country-specific differences in requirements, and the potential administrative burden on local affiliates.

### The call for collaboration

The growing importance and the changing nature of affiliate relationships are widely accepted. In a survey by US-based healthcare consultancy Gens and Associates, entitled “2008 eCTD Organizational Implications”, 86% of respondents remarked that the changing relationship would require closer collaboration.

Changes affecting the relationship, according to respondents, included life-cycle management (79%), the shift from paper to electronic documents (79%) and the evolving roles and responsibilities associated with the eCTD (79%).

All of this has a strong bearing on how companies manage their relationships with affiliates and on the model they adopt with regard to regulatory submissions – whether centrally managed, decentralised or a blend of both.

When it came to managing a core application for global submissions, Gens and Associates found a more centralised approach in Europe and a more decentralised approach in the US.

To delve more deeply into the issue, ISI, the US parent company of Image Solutions Europe, in January 2009 convened a panel of industry experts from large and mid-size biopharmaceutical companies to discuss such issues as the changing relationships between headquarters operations and affiliate or local operating companies; the goal of simultaneous (or almost simultaneous) global submissions; transparency and consistency of regulatory submissions; and the move to eCTD and lifecycle management.

Asked to outline their current situations, the panellists painted a picture of a gradual shift, or a desire to shift, to a more centrally managed, HQ-hosted IT model. This was based on an assumption that a centralised infrastructure would facilitate greater consistency and control into the global process, while also enabling greater systems, process and skills efficiencies.

### Allowing for affiliates

Yet this is not without its challenges, as the panel noted. These included, significantly, how to address the particular needs of local affiliate companies. As one member put it, “It’s a Mulligan’s stew of things. A lot of the components are generated centrally and then pushed out to the affiliates; after that, it’s up to the affiliates to complete the dossiers. I’m a big advocate for centralisation, not only from the perspective of the assembly, oversight and provision of tools, but also with regard to regulatory tracking and archiving all the information. We are looking more toward a centralised model, but there are challenges to that.”

Another panellist suggested that, within the European Union, a mixed model may be appropriate “where the centralised procedure, the decentralised procedure, and the mutual

*Growing acceptance of the eCTD is paving the way for standardisation*

*The changing nature of affiliate relationships is widely accepted*

*A challenge is how to address the needs of local affiliate companies*

*One panellist advocated a centralised approach for maintaining software*

recognition procedure are all managed centrally, because of the way the eCTD works within those processes". When it comes to the national marketing authorisation application procedure, however, it makes more sense to decentralise the process, he suggested.

Others argued that, certainly from a software hosting perspective, adopting a centralised approach was the most practical approach. "Trying to manage this aspect from our country affiliates would be a nightmare, so having the software and tools maintained from a central point makes the most sense," was one comment. "On one hand, much of the submission preparation and filing may also be conducted from publishing centres. On the other hand, however, the affiliates have the local knowledge, so they need to prepare their part of the submission."

The difficulty with this, the panellist elaborated, is ensuring that those affiliates – which may comprise just two or three people – know how to use the tools and technology.

The panel agreed that, the more that is being handled at the centre, the greater the need to control how that is managed, and for this to be user-friendly. "It has to be simple so someone off-site can get access and find their way around," as one member put it.

"We develop in parallel in the US and the EU, which applies to our regulatory filing procedures, too," said another. "We have market regulatory people on the ground to manage registrations in a variety of places: in five European centres and then regional centres including Canada, Australia and Singapore. This means flexibility is key: having the platform independence to enable us to conduct centralised publishing but also having a hosted platform to accommodate the regional centres."

Over the past few years, the company in question has invested heavily in electronic systems to replace paper systems and to ensure everyone has the information they need at their fingertips.

### **The importance of tracking**

*Another approach is for firms to hone the tracking of global submissions*

Another approach is to hone the tracking of global submissions, as another panellist explained. "We have a central database that enables us to share information back and forth. So when it comes to submissions, we submit first either in the US or in the EU, and we share the content across the organisation. We are not focused so much on having a central service but, rather, being able to do global tracking.

"When it comes to national submissions, the local affiliate is responsible for the submission, and going forward, we would want to ensure that the affiliate remains accountable for the relationship with the respective regulatory authorities.

"As to the technology used, we would support platform independence rather than dictating to our affiliates and partners the type of technology they must use. That obviously means that the software we use needs to conform to industry standards so we can share data."

### **Local limitations**

The growing importance of affiliates in the submission process broadens access to new markets but brings with it a host of challenges, including staff expertise and turnover as well as understanding the intricate differences between regions.

In the context of managing submissions, this can throw a spanner in the works at a local level, especially if resources are thin on the ground.

One panellist suggested that staff turnover can be as high as 25 to 30%, noting: "It's difficult to recruit experienced eCTD publishers. The question is: can we really expect a small office in a country such as the Czech Republic or Bulgaria to be able to run an eCTD life-cycle?"

*One panellist discussed how a centralised approach could create serious challenges*

At the same time, the more people that can access a central system, the more structure it needs in terms of when people access data and how they find the information they need. Will that require different databases for different issues, for example?

Here's how another company is tackling the situation: "In companies like ours, where we've got somebody on the ground in most countries around the world, a centrally based group has a major issue to overcome: knowing what the real regulatory requirement is in that country compared with what is the personal flavour that the person on the ground in that country is putting forward with the information they provide.

"That's when you have a situation of dossiers being slightly different country by country. So, for example, if we're making a national submission in Romania, then the local affiliate manager is fully accountable for making that submission. At the same time, we might give the common content that's needed in a neighbouring country or another European country. At present, each of those affiliates is responsible and accountable for making the submission.

"To centralise this could create some serious challenges in terms of trying to streamline submissions while also providing the needed differences for each country. It's extremely difficult to have a centralised function that is able to manage, at every point in time, exactly what's needed

in every submission, submission type, and country. That's a huge task and would require a large number of people, which we're not going to get."

This is where global tracking comes into its own.

"One of the issues with having data available centrally is how to manage tracking," said another panellist. "You need to be able to track all the work you're doing – both data coming in and data going out. Having someone go in after the fact and type up what they did just doesn't work; it's essential to keep track of data transfers as they happen – through metadata or event tracking, for example."

*It is essential to keep track of data transfers as they happen*

## Technology to the rescue

Other suggestions include employing stand-alone virtualisation technology, or VMware, which could prove helpful for some companies – at least at sites where there may be language issues, for example.

The role of sophisticated software is clearly important. As another said: "A potentially helpful solution would be to have something akin to an eCTD box of tricks where the centre can put together 90% of the submission, and the affiliates can add documents only within a designated module, without being able to do too much damage to the overall submission. Alternatively, having a service provider offer a regional submission service would be an option."

This was a popular suggestion. As another member responded, "The question of how to implement a model, whether centralised or decentralised, needs to take into account not only the IT part of this but also the knowledge piece. Having a support service with regard to the knowledge that goes into submissions could be helpful."

And another: "We are pushing towards being able to pull together all the information we have globally about a molecule, from discovery all the way through to the label printing done at the affiliate. To that end, it would be helpful to be able to use business intelligence technologies to pull that information together from disparate sources. Another model that could alleviate a lot of problems for companies is to have a regional support service, especially in some of the regions that have intricate differences around how they expect submissions to be handled."

"For some companies, having an external service provider that has knowledge of what is needed with regard to submissions in each country could be helpful," another panellist concurred. "So, conducting the submissions for Asia and Latin America, for example, as an outsourcing service, while fraught with complexity, could benefit some companies that have many affiliates but no one on the ground to manage the submissions. In that case, a centralised support service makes sense."

*An external service provider with regional submissions expertise may be helpful*

"For other companies, though, having a decentralised model that is supported externally could be more beneficial. In most cases, though, there would be benefit in having a hosted service to support affiliates. In many cases, it's doubtful whether those small affiliate offices have the time or skills to manage an eCTD submission on their own. And a number of complexities arise within those affiliates, such as ensuring local content is in the local language, and ways of accessing that content. Within that model, there are a variety of ways this could be taken up, with some companies asking for widespread support, while others just want help in a certain number of countries. So, really, what I think makes sense is a hybrid model."

## Hybrid models

Given that it will always be a case of "horses for courses" to some degree, the panel went on to explore ideal models of how some of these suggested new approaches might work.

"We're certainly looking more toward a centralised approach but need flexibility," said one company. "When it comes to our international group, roles and responsibilities for submission filing are a somewhat grey area, so it would be helpful to have a hosted environment that affiliates could access and use."

"That would mean those affiliates that have the staff and the know-how could use the centralised tool to publish their submissions, while those that don't have that range can turn to an outsourcing service that could then access the centralised tool to prepare the submission."

"A benefit to such an approach is that it would provide a library or repository of affiliate submissions, which we could draw on and clone and use as a basis for other submissions. At the same time, having a service that can provide us with registration or submission management – one that has regulatory knowledge throughout the world – would be highly valuable, too."

## SaaS & outsourcing

The software as a service model of software delivery emerged as a very viable solution: "A centralised model does have challenges, but one way to handle them might be to have a vendor host different tools and systems through a software-as-a-service (SaaS) model," suggested one panellist.

*The SaaS model emerged as a viable solution*

It would be up to the individual company to decide how far they wanted to go with the outsourcing of the solution, and any related services.

"At the moment, many companies need technology support and solutions to get them up to speed on eCTD and regulatory filings in many countries around the world," noted another member. "But the bigger picture lies with a provider which has the insight and knowledge to oversee the submission and the lifecycle management of the registrations. For a company like ours, being able to turn to a provider that is well versed in the various rules and regulations around the world would enable us to pull back on some of the efforts we have in place in various countries."

### Getting buy-in

*There must be buy-in at all levels*

It was agreed that, for any model to work, there had to be buy-in all the way up the chain of command.

"One option would be to sell it at the corporate level, by saying we don't want affiliates buying individual systems that aren't compatible with the centralised systems, because it's important to have the data centralised and accessible. It has to be presented as a business case, demonstrating the importance of systems compatibility in terms of getting drugs registered worldwide. And because it would cost a lot to put in the kind of hardware, software, and staff required to do this right, it would help to have external support in terms of both the software and the knowledge on a global level."

### eCTD and flexibility

Another suggestion was that relative eCTD maturity could also be used as a determinant for variants in approach: "We'd look for a model that provides support in terms of regulatory knowledge in those countries around the world that are coming up to speed with the eCTD or that are likely to begin implementing eCTD over the next few years. I don't know that we have the expertise within many of our affiliates to manage those first eCTD submissions, and certainly we want to be successful when those do begin."

*A flexible model is paramount due to the rapidly changing submissions environment*

But, above all, flexibility is paramount, because of the rapid pace of change of the submissions environment globally, and the constantly evolving state of individual markets. As one panel member concluded: "We would want a model that can be flexible in terms of having some of the submission publishing handled centrally and some hosted, because requirements differ throughout the world, so flexibility on the technology side is important."

Ultimately, this was felt to be best achieved through some form of central control. "No matter where the submissions are processed, the lifecycle management needs to be managed in one place so we know what's going on all the time."

## Copyright

Under internationally accepted copyright legislation, the subscriber is not allowed to copy copyright materials, such as *The Regulatory Affairs Journal – Pharma*, except in certain circumstances, e.g. you may make a single copy of one article per periodical issue for research or private study. If you photocopy the whole or part of an issue of *The Regulatory Affairs Journal – Pharma* in order to avoid subscription fees, for example, the subscriber is in breach of the law and could be successfully prosecuted. Please contact the publisher for details of fees to cover your copying needs. Alternatively, you may obtain a licence from the Copyright Licensing Agency (90 Tottenham Court Road, London W1P 9HE, UK), or from rights organisations in other countries, which will enable you to make limited numbers of copies for business purposes.

## Reprints

Reprints of articles published in *The Regulatory Affairs Journal – Pharma* are available for use as training and promotional materials, inserts for direct mail, public relations literature and sales support materials. Discounts are available for bulk orders.

For details, contact **Advertising Sales, Regulatory Affairs Journals**, Informa Healthcare (Tel: +44 (0)20 7017 6785, E-mail: [advertise@informa.com](mailto:advertise@informa.com)).

## Circulation

The subscriber is reminded that it is a condition of sale of *The Regulatory Affairs Journal – Pharma* that you circulate it only to members of staff working at the site to which it is sent. Please contact the publisher for details of special arrangements for purchasing multiple copies for domestic and international circulation.

*The Publisher*

