Regulatory Information Management & Health Authority Trends

Industry White Paper

Prepared By:

Steve Gens: Gens and Associates Inc.
Greg Brolund: Chicopee Consulting Inc.

Research Support By:

Helen Teichman: Chestnut Solutions Inc.
Steve Scribner: ILSS Inc.
Comply Services of Belgium

Summer, 2011

Introduction

This white paper was written to give a perspective on Regulatory Information Management (RIM) based upon many Bio-pharmaceutical benchmark studies conducted over the past three years and our professional experiences. RIM has quickly become an important topic and strategy for many Regulatory and R&D organizations. Opinions and perspectives are based upon the industry benchmarks and trends. The studies focused on the Top 50 Bio-Pharmaceuticals as defined by Pharmaceutical Executive with high survey participation from European, Japanese, and United States headquartered companies

The Bio-Pharmaceutical Industry is undergoing fundamental change driven by globalization, emerging market criticality, cost cutting, and technology and organizational changes. Regulatory divisions are faced with key challenges and opportunities as the health care market and global regulatory environment evolves and transforms.

Collaboration is also at the center of many organizational, technological and process initiatives. We believe a fundamental shift in how companies operate has taken hold with a business model shift to a "collaborative centric" model. This is driven by the significant co-development and co-marketing relationships, outsourcing of core activities (Clinical Trials, Manufacturing etc.) and increased usage of external services for day to day operations. This requires change to operating policies, information and content structures, technologies, team / organizational competencies, and business processes. The "new normal" is working in a global virtual workplace which requires global systems, 24x7 mobile access to key information and content, seamless and secure content exchange, and the implementation of global information standards.

Analysis Conclusions

Our analysis consisted of our qualitative research and quantitative benchmark information coupled with our professional experience yielded seven key themes:

1. Globalization, virtualization, and increased mobility are fundamentally changing patterns of work, giving a high priority to "rethink" the RIM, collaboration, and content management environment
   - *Requires innovation, not just "step-wise" investments or incremental solutions*
2. Regulatory Information Management is the clear trend as most view R&D content management, submission management, registration management, and labeling at a program level and are looking at individual vendors more strategically
   - *The business criticality of emerging markets requires rapid extension of existing RIM capabilities and several Asia Pacific countries (India and China) are becoming strategic hubs for regulatory operations locally and supporting global operations*

3. Regulatory operational complexities are increasing based on the diversity of regional requirements and the "decentralization" of some standards (submission format divergence in the US and ASEAN block)
   - *Different regions are subject to different priorities from Health Authorities or other Health Government agencies (e-submissions, audits, collaboration etc.)*
4. Business-to-business collaboration and efficient content sharing remains a significant issue for many while Sponsor-to-Health Authority information exchange is effective and continues to improve
5. We believe as companies have secure and flexible access into internal systems, more contractor and vendor support will be virtual (reduce internal physical cost)
6. The majority of vendors are focused on improving solutions for true global and mobile access while also creating new innovative solutions and services to support the shift to a collaborative-centric working environment
7. Many are investigating Software as a Service (SaaS) and Cloud capabilities, but consider mature solutions and implementation for critical systems to be years away

Regulatory Information Management (RIM) Summary

We have been tracking the regulatory information space for over nine years and have found that two fundamental models exist for the management of vital regulatory information: "niche" vs. an "integrated" approach. Industry has been equally split on these two models over the past decade. Current movement toward an "integrated" approach is very clear. As shown in Figure 1, companies are taking a strategic approach to the management of this vital information. Several vendors support this view by providing tools to allow seamless interconnectivity between traditional "silos of information". For example, we estimate that Publishing, Submission Management, and Registration capabilities will move into one capability over the next 2 – 3 years. This will provide a much tighter integration with the submission document management platform to address business needs such as the typical "where used" question for labeling and submission content which is needed to ensure compliance and to track affiliate submission progress. We also see many companies utilizing their registration capability for correspondence, commitment management, and agency Q&A.

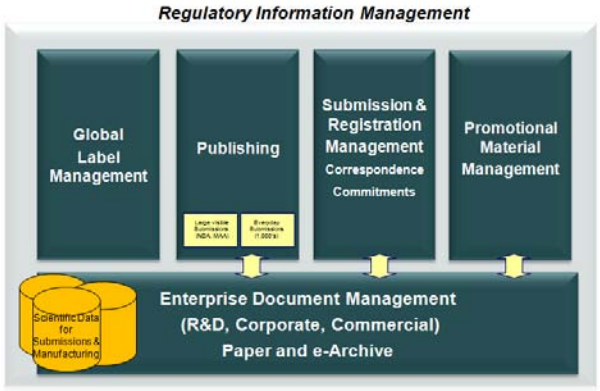


Figure 1 - Regulatory Information Management

We also found significant investments and change in global label and promotional material programs. Our recent benchmark found many of the top 60 companies are making changes to their labeling programs driven by the business need of better core data sheet control and affiliate submission compliance. Changes to promotional material programs are highly focused on

governance and process improvement due to significantly increased government agency attention and punitive fines (reaching billions for several organisations for false claims or off-label marketing). Government agencies such as the United States Office of Inspector General (OIG) is focused on off-label use and will inspect the internal promotional material review process to determine if the right process and controls are in place to eliminate any promotion of off-label use. We also see the significant increase of social media in the promotional material program that leads to greater complex of audits and control.

Our benchmark reveals a clear global trend for centralised submission document management (88% have one global solution according to our 2011 study) while publishing locations are becoming more decentralised due to regional requirements, organisational model change, and the significant uptake of outsourcing to third parties or internal work redistribution to publishing centers in India and China. Organizations with five or more publishing locations has grown from 26% (2008 survey) to 41% (July 2011 survey) resulting in a greater distribution of publishing assets; a surprise in our analysis.

Finally, most companies are investigating ways to lower their overall Total Cost of Ownership (TCO). This has resulted in aggressive publishing outsourcing in the pasts two years and analysis of alternative solution hosting concepts such as Software as a Service (SaaS) and cloud computing. We find significant uptake in the SaaS model in small and mid-tier companies, but not yet in large bio-pharmaceuticals. While several vendors are heavily investing in cloud computing for the RIM space, many bio-pharmaceutical companies are interested, however few are making that strategic decision and “leap”.

Collaboration Section Summary

Collaboration methods, practices, and solutions continue to be a top priority for most participants with mixed results. Globalization and organization virtualization are 1) increasing the level and importance of collaboration solutions, 2) opening once closed content management systems and requiring mobile information access, and 3) requiring new leadership competencies to be effective in a global virtual workplace.

Our analysis found the following key points:

- Information exchange effectiveness continues to improve with Health Authorities due to the realization of ICH standards, adoption of HL7 and other standards and the use of electronic information exchange gateways
- Significant challenge for business to business (see Figure 2) information exchange continues since our 2009 benchmark. We believe a strong business case exists for improving this exchange (e.g. productivity, cost reduction,

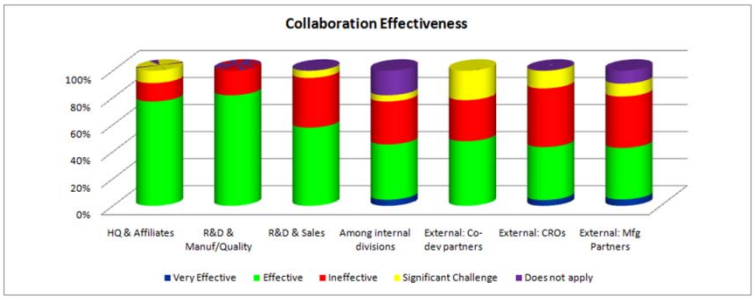


Figure 2 - Collaboration Effectiveness

quality, and time savings)

- Affiliate collaboration levels have dramatically increased since 2009 due to emerging market support and the business goal of information transparency
- Global team effectiveness has strong positive ratings while mobile user access to internal ECM has low effectiveness ratings
- Adoption of social networking tools is slow compared to other industries
- 80% are using SharePoint for temporary collaboration practices

We believe significant investment will continue in this area for the next 2 – 4 years as companies adapt to the "collaborative centric" environment where global virtual teaming and instant "mobile" access to content is the norm.

General Content Management Trends

Overall, Content Management programs saw incremental improvement "across the board" compared to our 2009 survey and satisfaction levels increased for the first time since our initial tracking in 2007. Most participants continue to invest in ECM at a "program" level with several companies currently in a modernization cycle.

Our analysis found the following key points:

- Implementation of Clinical eTMF has grown significantly since 2009 with 80% changing or planning to change within 3 years
- 79% cite their submission content repository as effective and 78% are planning to make changes in this capability over the next 3 years
- Executives view ECM as mainly tactical (e.g. compliance) while several also view it strategically (e.g. processes that impact time to market).
- The industry made a significant move to provide more ECM access for external partners since our 2009 study; this continues to be a key priority (see Figure 3)

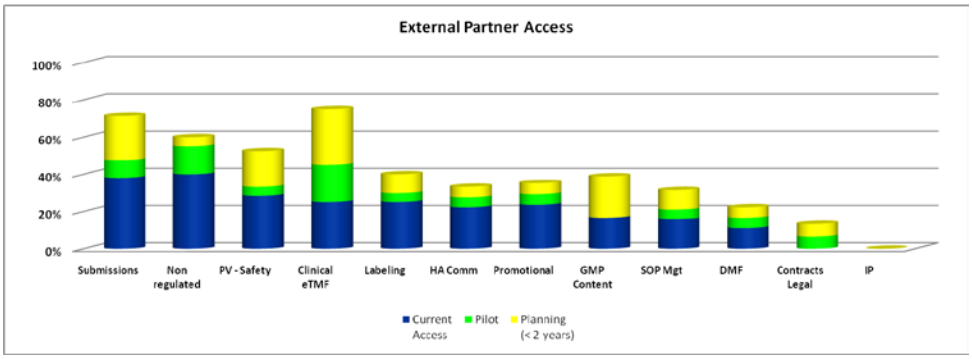


Figure 2: External Access to Content Type

- Electronic signatures are gaining acceptance and demonstrating business results (e.g. improved efficiency)
- Minimal uptake of structured content authoring; industry still in "learn mode" with tool vendor solutions maturing

We believe that companies will make incremental investments to improve their content management capabilities (usability, workflows, e-signatures etc.) and some will make significant investments to improve access by external partners because their business model requires it.

Research and Development (R&D) Initiatives / Content Management Trends

We have tracked many R&D initiatives and specific R&D content management capabilities since 2005 and found the industry as a whole is slow to adopt new standards unless they are mandated by Health Authorities (e.g. eCTD). We are finding this to be true for the DIA Reference Model and likely for the RPS submission format as well. The cancelation of the labeling PIM program earlier this year may result in a more cautious approach to new standard initiatives by industry and solution partners, in our opinion.

We found many participants espouse to have tight information integration with their content management platforms, however when compared to 2007 and 2009 data (see Figure 4), minimal movement from planned to production integrations was realized with the exception of Trial Master File (TMF) and Trial Management systems.

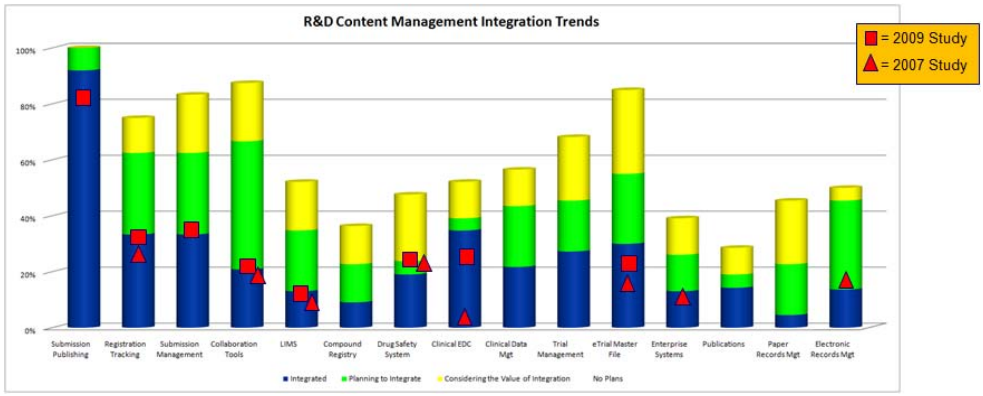


Figure 3: Integration Status

The top priorities for R&D content management programs changed slightly since 2009. Today collaboration tool integration, system performance, external partner access, and reduce total cost of ownership are the top 4 priorities respectively.

Other key points from our analysis include:

- The largest investment in R&D Content Management is SharePoint implementation
- The DIA Reference Model has significantly improved in terms of awareness and perceived value as it progresses towards a more widely used standard
  - Vendors are starting to adopt the model and provide actual implementation options
- The RPS standard is progressing toward adoption; however many participants cite implementation concerns /challenges
- The EMA announcement ending the PIM program has stopped all progress on PIM implementation and it is unknown if the EMA will “restart”, “rethink”, or “retire” PIM

- Regulatory Submission Outsourcing has high satisfaction levels with the most focus on affiliate e-submission support and report level publishing (e.g. clinical study report). A variety of new methods have been piloted in industry with positive results (e.g. remote use of sponsor systems and processes by offshore labor).

Publishing

Publishing programs are going through an interesting transformation. Most organizations view publishing as the final stop in getting the few "big" marketing application compiled and sent to health authority within a tight timeframe that often require a "heroic" effort. What most don't *appreciate* is the high volume of smaller submissions managed "behind the scenes" support a large percentage of the revenue base. The reality is a publishing operation spends a majority of its available time and resources on the thousands of daily "small" submissions to respond to health authority requests or to keep individual country registrations current. We call this "the iceberg effect" as depicted in Figure 5.

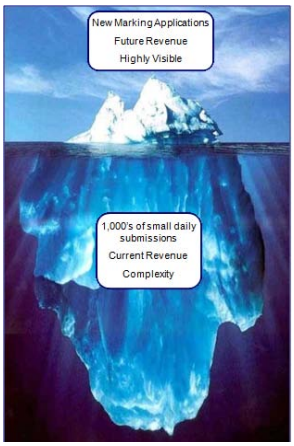


Figure 4 - Iceberg effect

We see two significant factors that are affecting most, if not all publishing operations: growing operational complexity and a focused effort to reduce cost. As more products move to "legacy" status; these factors are amplified. Publishing complexity has grown substantially over the past three years driven by a combination of the following:

- Multiple e-submission formats, validation tools and electronic gateways, but no current standard format retirement in sight (e.g. NeeS)
- National affiliate support for electronic submissions (primarily in Europe)
- Move to a global regulatory business model
- Emerging Market focus (submission and tracking support)
- Resourcing model (outsourcing and / or work redistribution to low cost regions)

The resourcing trend is dramatic as companies are moving aggressively with outsourcing or internal work redistribution to internal sites in India and China. Several top 20 companies have entered into novel outsourcing agreements such as functional outsourcing (e.g. all clinical study reports) or utilizing offshore vendors that access their internal systems (quickly scale up or down with quality low cost publishing resources). The trends in our outsourcing benchmarks are very interesting as 2008 and 2011 were key decision point years as industry determines to outsource more (new or expand) or not. Our 2011 benchmark (see figure 6) finds 71% of top 50 doing some type of project or functional outsourcing with 29% in

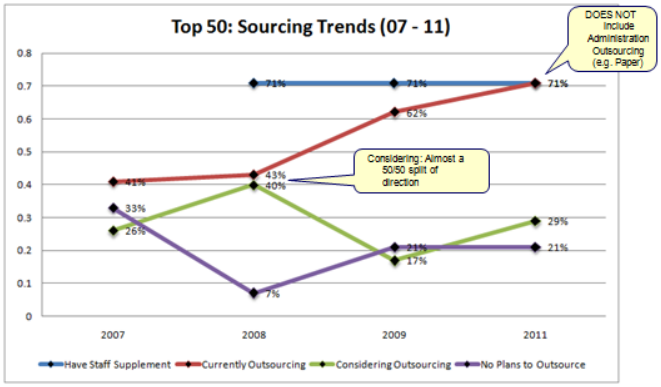


Figure 5 - Dossier Outsource Trends

analysis mode. Several companies are investigating a hybrid approach where outsourcing is utilized in the interim while internal capabilities are built in low cost regions; typically side by side with other R&D and commercial functions in India or China.

The data shows high vendor satisfaction with publishing outsourcing partners with a moderate focus with report level publishing and affiliate electronic submission outsourcing. While the outsourcing satisfaction with vendors is good news, there is mixed results of the internal goals achieved (metrics of cost, complexity, efficiency, and turn-around time). Figure 7 is a result of a July 2011 study on the internal effectiveness of outsourcing programs: those that had project or functional outsourcing for a minimum of six month. 50% stated outsourcing business goals were met while 50% had several or many goals not realized. The definition of success is interesting in this context: column F (see figure 7), a mid tier company had an increase of cost, however their efficiency and turnaround time improved; would this be viewed as a success or not?

Meeting Outsourcing Expectations

Company (size)	Complexity	Cost	Efficiency	Turn Around
A (m)				
B (m)				
C (m)				
D (t)	☺		⊗	⊗
E (m)		✓	☺	✓
F (m)	☺	⊗	✓	✓
G (m)				
H (t)	⊗	✓	☺	⊗
I (m)	⊗	⊗	☺	✓
J (m)				
K (t)	⊗	✓	✓	✓
L (t)				
M (m)		✓	☺	⊗
N (t)				
O (t)				
P (t)				
Q (m)	⊗	⊗	☺	⊗

Figure 6 – Internal Goals Results

Authoring

There is tremendous buzz at conferences and by the vendors offering new authoring tools and techniques such as structure content authoring that is based on XML authoring tools. Our benchmark results suggest that the buzz does not match the actual pilot and implementation activity. In our opinion, industry is still in "learn" mode and will begin several significant pilots in 2011. While XML authoring tools are prevalent in the labeling area; their adoption was driven by very specific health authority regulatory requirements and not by business benefit. Most survey participants cite significant process / change management programs required to support the transition to structure content authoring and don't see any near-term business benefits; they would rather have their peers in industry "test the waters".

What is changing is authoring methods with sponsors and third parties for authoring of late research and development study reports. The traditional model was "write and e-mail", but now significant attention is directed toward utilization of the sponsor's submission-ready templates (incorporated in contracts) and leveraging temporary collaboration spaces to review and "informally approve" content (meaning acceptance of the deliverable). These temporary collaboration spaces can also directly attach to the internal authoritative submission document management source so that internal processing of approved deliverables is significantly reduced; resulting in time and cost savings.

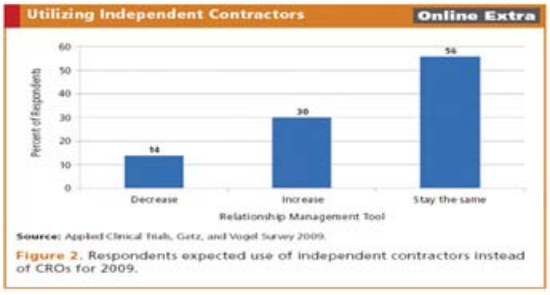


Figure 7 - Independent Contractor Trend

Finally medical writing outsourcing levels (by CRO's) is dropping from 68% (2005) to 61% (2009), however the same study cited a 30% increase with independent

contractors[1](figure 8). The data does not state what percentage is completely outsourced versus supplementing the internal medical writing capability with external help.

Registration and Submission Management

We see significant activity in this area as many companies are investing in establishing a global authoritative source for the first time, modernizing their existing capability, or combining publishing, submission management, and registration tracking capabilities. Our 2009 and 2011 survey's found greater than 60% of the top 50 companies will initiate or continue registration / submission tracking projects over the next 24 months. We also note that most active projects are taking significantly longer than planned due to the gross underestimation of the time to locate and validate the registration and product information from affiliates around the globe and finalize data governance rules to ensure the central database is considered authoritative.

What we find extremely interesting is that most companies share common project goals or expected outcomes of a registration data authoritative source, notifications for registration renewals, product information, and executive portfolio reporting while the implementations are vastly different. We have found no clear trend on project scope and implementation practices. Some companies utilized a central model for data entry while others leave it to the affiliate or regional hub. Some utilize "links" into the authoritative submission document management system to "complete the story" by viewing the content (e.g. health authority correspondence) while others do not. Some have introduced commitment tracking and correspondence management while others utilize other systems.

A very recent trend noted by several of the vendors is that companies that have successfully completed their registration management projects are finding other business functions want to integrate additional functional systems. This is an attractive option as the registration information is now considered an authoritative source. We expect this early trend to pick up momentum as other companies complete their projects and look to increase the value of their system throughout the company.

Regulatory Information Management Vendor Summary

The vendor space has been rather static until last year when three significant mergers were completed (CSC of FCG, Liquent of Datafarm, and then CSC or ISI). Further vendor consolidation is forthcoming driven by company strategy and economic decisions within the next 12 to 24 months. We also believe new players will emerge to support the document management space along side traditional solution vendors; the most promising is cloud computing partners. Finally, all vendors cited priority strategies to provide or expand local support to the Asia Pacific region.

[1] Applied Clinical Trials, Getz and Vogel survey of 245 biopharmaceutical (2009)

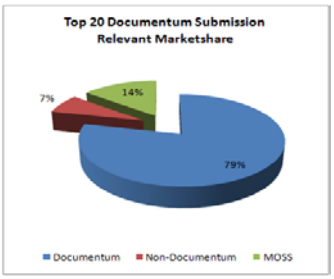
Document Management

We have been tracking the top 50 bio-pharmaceutical movement of internally developed document management solutions to off-the-shelf (OTS) capabilities over the past seven years. The industry has recently flipped from a 75% / 25% (custom to OTS) to 77% having a true OTS solution. Figure 9 depicts the breakdown by market segment with Takeda peer group having the majority of internally developed solutions today. We believe this is in part due to early adoption in the 1990's where only highly customized solutions built on core products such as Documentum were available.

	By Region			By Company Size		
strategy	EU	Japan	US	Top 20	Mid	Small
OTS	65%	86%	54%	41%	77%	100%
Custom	35%	14%	46%	59%	23%	0%

Figure 8 - OTS vs Custom by Market Segment

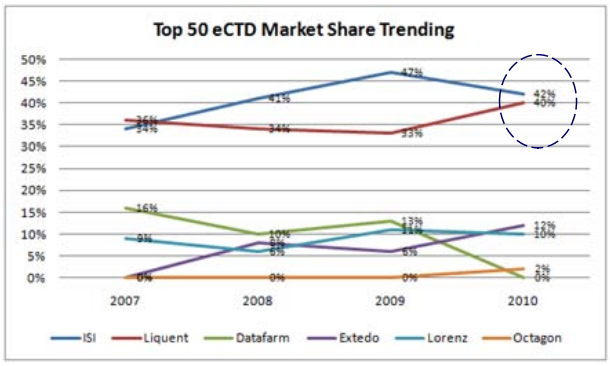
CSC's First Doc retains market leadership with a 46% market share while customized Documentum is second at 41%, but declining. We believe that NextDocs (based on the SharePoint platform) will become a major player over the next three years as they have demonstrated significant project wins in the quality manufacturing and clinical document management space. They have introduced a R&D solution that has gained some traction in small companies. Clearly the NextDocs solution set advantages are ease of use at a reduced cost. We also see a shift in organizations considering leaving traditional Documentum based systems; our 2011 survey found 20 – 30 % of participants citing the potential to change their Documentum based systems within the next 2 years.



We also expect to see new players in this space in 2011 and 2012 with cloud computing capabilities targeted at more silo solutions sets such as promotional materials and quality management (SOP's and Policies). Several vendors also report a pick-up in Trial Master File (TMF) and Clinical DMS activity.

Publishing

Publishing vendors have had relatively little software change since the transition to the eCTD format. 2010 saw the first significant merger of Liquent and Datafarm that resulted in a combined organization that now equals Image Solutions Incorporated (ISI) in market share. ISI was acquired by CSC late 2010 to realize the vision of a "Total Regulatory Solution". Each of the primary publishing vendors (ISI, Liquent/Datafarm, Extedo, and Lorenz) are closely monitoring and preparing for the new FDA format RPS. It is yet to be seen if this will create a new software solution or just an enhancement to their current eCTD capabilities.



We also see vendors creating simple tools to combat the complexity of multiple e-submission formats. For example ISI is preparing to introduce an eCTD to NeeS converter in its popular ISI toolbox. Another conversion tool example is an eCTD to ACTD for ASEAN block submissions. During our interviews with industry, several companies mentioned building their own conversion tools internally until they are provided out-of-the-box by their publishing vendor.

The most significant growth will be in the services side of the business as many vendors are projecting growth of 30 – 50% in this service line as more companies adopt project and functional dossier outsourcing. The momentum is significant and a key question for the service is one of organizational scale. With a significant increase of business, how can their organizations scale effectively AND keep quality and turn-around times equal to customer expectations. We believe Octagon, Liquent, CSC (ISI), and several CRO's to be the main players moving forward. We find that large organizations prefer a global outsourcing partner while the mid-tier and small organizations might partner with a regional niche player.

Registration and Submission Management

As we stated in the RIM peer section, this area is experiencing increased activity with Liquent breaking away from ArisGlobal as the clear market leader. Liquent's strength is the combination of Registration Tracking with their Publishing and Submission Management capability. Liquent began this vision four years ago and has seen an adoption of this RIM strategy. Our 2010 survey shows 67% of those with Liquent's Registration Tracking solution also have their Publishing and Submission Management solutions.

Our vendor interviews coupled with our 2010 Submission Management Survey revealed significant investments by ISI and Extedo in building a credible Registration Tracking capability that will also integrate with their publishing solution. We also found Oracle PLM and Mission 3 trying to make inroads into this market in 2011. We believe some of these organizations will gain some market share by replacing internal home grown systems, however, we project that Liquent will be the market leader for the foreseeable future.

The submission management solution providers are maturing their capabilities in our opinion to completely support planning, tracking, and resourcing from a global framework. The market-share is expected to change significantly over the next three years with Liquent, Planisware, and Octagon sharing market leadership in 2011.

We also believe that looking at Registration Tracking independent of the overall regulatory information management picture is shortsighted. Companies need to determine their overall RIM strategy and be very intentional in their adoption of a "niche" or "information integrated" strategy. We have developed a vendor "Triangle of Truth" (see figure 10) to illustrate the point that RIM strategy and orientation will limit you to a subset of vendors. Some companies make individual

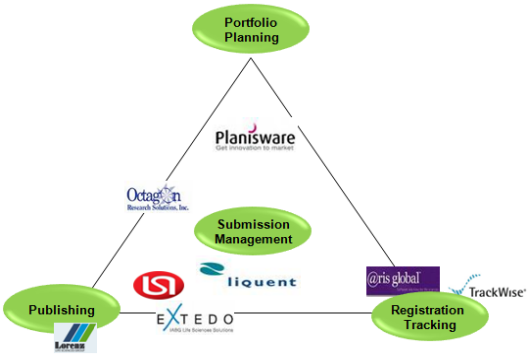
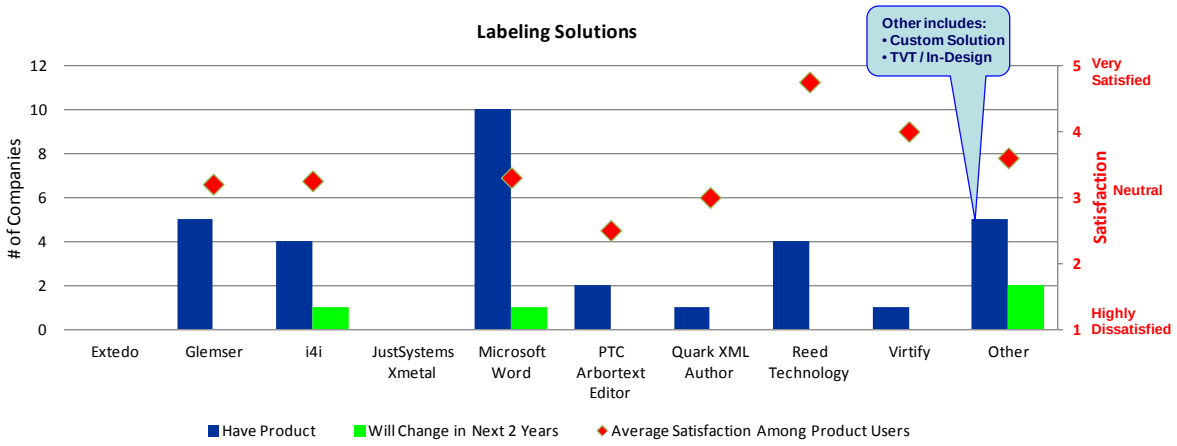


Figure 9 - Triangle of Truth

investments in a "niche" mode even as they espouse of information integrating; leaving them with a limited capability and a costly solution set.

Labeling

There are two discrete aspects to Labeling solutions – Authoring and Document Management processes and tracking of global label usage. The vendor field is mixed with labeling authoring solutions with Glemser and i4i solutions; however with the ending of the PIM program, this might adversely impact these vendors. Outsourcing of SPL is a common practice with many vendors providing effective solutions for industry



Health Authority Submission Formats and Emerging Standards

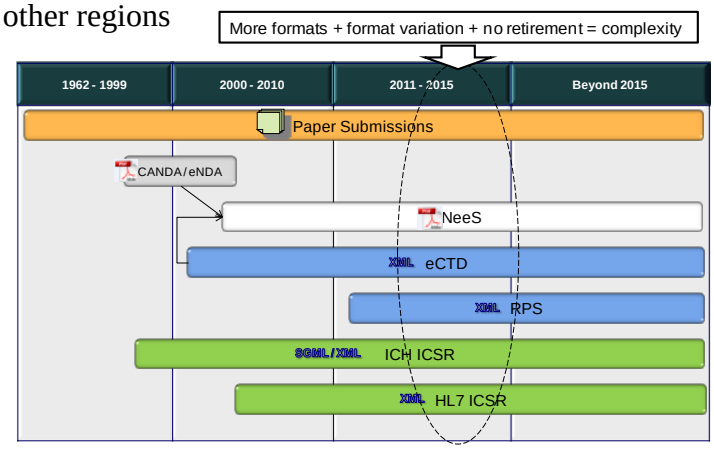
Health Authorities and the pharmaceutical industry are engaged in a significant number of initiatives to develop and expand the use of electronic submission formats and standards for data and content. The unintended result of these global activities is an increasingly complex environment for managing regulatory data and submissions. At the same time, there are opportunities to take advantage of emerging standards and updated internal processes to reduce operational complexities.

Electronic submissions and standards initiatives are being actively pursued by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). A good example of the progress in this area is the eCTD which is the only marketing application electronic format allowed by the FDA and for the EU Centralised Procedure. However, in Europe, extension of the eCTD mandate to the other procedures is likely to be dependent on the implementation of the EMA central submission repository.

To further complicate the European situation, the Non-eCTD Electronic Submission (NeeS) is still the most commonly accepted electronic format for National Procedure submissions. Industry and National Competent Authorities (NCA) support the eCTD but still see a long term future for NeeS for mature nationally approved products. NeeS is expected to continue to be accepted for National Procedure submissions by all but the largest National Competent Authorities.

At the same time, the HL7 Regulated Product Submission (RPS) is being developed to be the next major version of the eCTD. We expect RPS implementation will take at least 3 to 5 years and even longer in some regions. The electronic submission landscape will be even more complicated, if as expected, the FDA will move quickly to adopt the RPS standard for its submissions while the other ICH regions will take a prolonged period of time to adopt.

What we know is regulators adopt new submission formats and standards but rarely fully retire existing ones. On one hand, the acceptance of electronic submissions, and the elimination of paper submissions, continues to grow in the US and in Europe. But there has been relatively little adoption of electronic only submissions in other regions and the adoption of a single electronic submission standard has not been accomplished. For most of the world, it will continue to be paper and business as usual for the foreseeable future.



The development of other standards also continues to move forward at a different pace in each region. In the US, the FDA is heavily invested in the HL7 standards development process and continues to support development and adoption of clinical content and data standards. Standards development by the FDA are designed to support all FDA regulated submissions, even at the expense of internationally applicable standards. Other regions are less interested in some of these standards since they have not actively joined the efforts to include standard data sets as part of their reviewable submission.

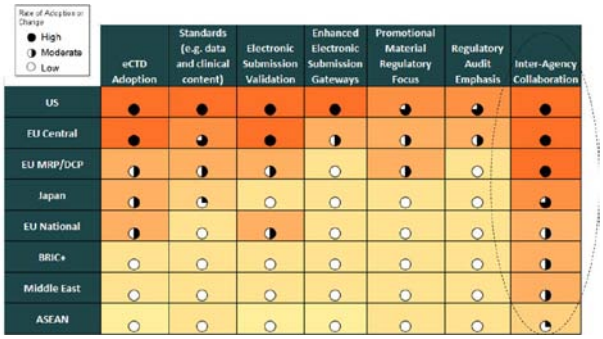
In the current environment, companies find it necessary to adapt to the existence of multiple regulatory "standards" for format and content for each submission. Our industry research shows that most companies explicitly recognize the need for agile systems and processes to meet global needs and have adopted concepts such as the global dossier for multi-market reuse, but they continue to be hindered by legacy information silos and a dependence on manual processes to search for and compile documents and data.

In most companies there is a relatively high cost to implement new standards for submission, content and data, and to adapt existing policies and procedures. Implementation is often driven only by regulatory requirements. We believe there is a real opportunity to simplify operations and integrate information resources with a positive return on investment (ROI) through improved effectiveness and efficiency in internal and external collaboration.

The ROI from global standards will only be realized when data, content and format standards are fully adopted for internal and partner processes. Waiting for regulatory mandates will continue to place the industry in a reactive mode reducing the ability to capitalize on opportunities to improve capabilities for regulatory information management and internal and external collaboration.

Health Authority Audit and Collaboration Trends

Health Authorities continue to increase collaboration programs with other Health Authorities and are trending toward increased scrutiny of electronic records and promotional material. Health Authorities are "raising the bar" for compliance especially in manufacturing and pre and post approval safety programs. At the same time, individual countries like China and South Korea are raising their health authority regulatory profiles in order to exert more influence: others nations may follow this trend.



In the US, FDA statements and industry experience suggest that FDA is shifting compliance / enforcement practices from relatively collaborative to more punitive model. Some believe that risk based enforcement is shifting from "Identify the Risk" to "No Risk Tolerated".

Recent FDA public statements suggest a possible increase in the level of enforcement activities. In August 2009, FDA Commissioner Hamburg identified 6 steps to improve enforcement effectiveness. FDA also identified possible changes that would hold sponsor companies more accountable for the manufacturing processes of outside contractors and for verifying that contractors have followed FDA standards, including the possibility that companies may be required to conduct on-site audits at outsourced manufacturing facilities.

In the US, there is a significant increase in the investigation of the promotion of off-label uses and inspections target internal promotional material oversight processes as well as external advertising. Reviews of traditional and non-traditional media (e.g. Facebook) resulted in a 50% increase in enforcement letters in 2009.

From an industry perspective, the trend is to include the concept development of regulated promotional material earlier in the development process. Many companies are taking a risk management approach to re-think their internal promotional material governance structure and review processes to maximize the effectiveness of available resources and collaboration technologies.

The FDA is also beginning to make 21 CFR Part 11 inspectional assignments to help further assess how to proceed with the possible modification of Part 11 regulation and guidance. The FDA intends to take appropriate action to enforce Part 11 requirements (specifically in violation of predicate rules) for issues raised during the inspection.

Industry Dilemma: There are often two distinct views of Part 11 within the FDA: the e-submission enabler vs. the compliance tool. A company's risk assessment will drive its response to Part 11 focused inspections.

The EMA approach to audits and inspections also continues to evolve. For example, the EU GCP Inspectors Working Group reflection paper (i.e. guidance) effective August 2010, provides a detailed description on the characteristics and processes expected for the use of electronic data capture in clinical trials.

At the same time there is a clear trend of increasing collaboration among health authorities around the world. Major regulatory agencies have entered into regional and cross-regional agreements to share information at each stage of the drug development process.

The EMA has formal agreements with other Health Authorities including FDA, Health Canada, Japanese Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA), Swissmedic and others.

The FDA has over 57 regulatory information sharing agreements with 23 individual countries and the European Union. Formal agreements include information sharing regarding inspections of manufacturing and clinical trial sites as well as reviews of pharmaceutical products and medical devices.

In one example of EMA – FDA collaboration, the two Agencies worked together to each send identical language to a company about a product under active review.

There is especially close cooperation with the EMA through the exchange of confidential information (advance drafts of legislation and regulatory guidance documents) as well as non-public information related to ensuring the quality, safety and efficacy of medicinal products for human and veterinary use.

Safety continues to be a major driver for collaboration in all regions and is being facilitated by the World Health Organization and ICH safety activities as well as individual Health Authority initiatives. For example:

- **Japan:**
  - "There is a growing momentum for international harmonization of safety monitoring of pharmaceutical products in the East Asia region as well as of regulatory review for approval" – Akira Kawhara (Japan, PMDA, 2009)
  - Japan participates in annual pharmacovigilance conferences and staff exchange among Japan, China and South Korea
- **EMA**
  - Promoted the establishment of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
  - This network aims to strengthen the monitoring of authorised medicines in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies focusing on safety and on the balance of benefits and risks.
- **FDA**
  - The Sentinel System enables active queries of diverse automated healthcare data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely

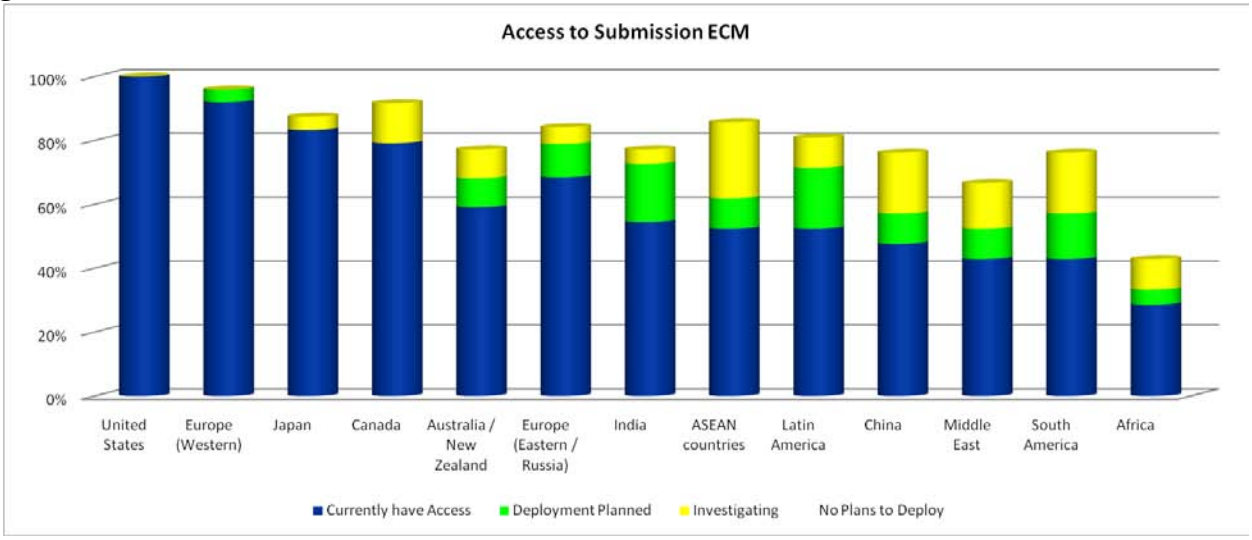
Increasing collaboration among Health Authorities coupled with the continuing trend of "raising the bar" for compliance adds to the need to improve regulatory information management capabilities and practices to be effective, efficient and agile.

Asia Pacific Summary: Systems and Health Authority Status

Emerging markets are expected to grow at a 14-17% pace through 2014, while major developed markets will grow 3-6%. The US will remain the single largest market, with 3-6% growth expected annually in the next 5 years[2]. Given the growth; emerging markets and specifically the Asia Pacific are critical to most pharmaceuticals business strategy. This has lead to significant regulatory information management investments by industry and substantial investments by the solution providers.

During our industry peer interviews, several cited the growing relevance of both the Chinese and South Korean Health Authorities as a critical national driver to attract more local pharmaceutical investments. This has also resulted in modification of regulatory requirements such as conducting local clinical trials as a prerequisite to marketing applications. This brings additional clinical data into a marketing submission and also may require companies to modify their global dossier programs (more in early).

Our research found a clear trend of extending current authoritative submission document management system for major countries in the Asia Pacific region. Several had existing replicating content stores located in Japan for local use and to support local publishing. Those that did not have an existing Japanese presence, but planned to expand, cited an extension of the global model.



The solution vendors overwhelming cited the need to scale their local support organizations; be in solution implementation or business consulting. Several vendors have local partnership and

[2] IMS Press Release
http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=4b8c410b6c718210VgnVCM100000ed152ca2RCRD

are debating whether to scale these relationships or invest in their own local presence. They also cited increased activity in the Japanese market for document management, security, and portals.

As stated in the Health Authority review, we see no trend for the adoption of electronic submissions in the near-term (excluding Japan) and believe that this region will continue to have multiple formats (eCTD for Japan, ACTD for ASEAN block, and paper)

Finally, many peers our investing heavily in commercial and R&D infrastructure in India and China. Several have built significant Regulatory Operations hubs that service this region and also are providing publishing support to North America, Europe, and other regions. This model appears to be gaining traction as an alternative to functional publishing outsourcing.

Gens and Associates Inc. Benchmark References

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9) 2011 *Regulatory Trends*, Gens and Associates Inc.
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11) 2011 *Submission Management Organizational Benchmark*, Gens and Associates Inc.

Primary Authors

Steve Gens has 25 years of business experience with the majority in the biopharmaceutical and healthcare industries. His early career was spent at Johnson and Johnson and then moved into consulting where he managed several healthcare consulting practices for Booz Allen Hamilton and First Consulting Group. Steve has deep experience in strategy formulation and implementation, organization development and performance, global virtual team effectiveness, industry benchmarking, information management strategy, and leading or facilitating strategic change. He consults for many of the largest global biopharmaceutical companies and also with small high growth organizations that are planning for significant or transformational change. Steve has a Master of Science in Organization Development and is certified in Change Management from the NTL Institute of Applied Behavior. President of Gens and Associates Inc. sgens@comcast.net or 267-614-0935

Greg Brolund is a Global Pharma management and technology consultant with extensive experience in business processes and supporting IT for product labeling, submission publishing, Health Authority interactions, pharmaceutical safety and pharmacovigilance programs. He served as the Rapporteur of the ICH M2 Working Group Rapporteur from 1998 through 2002 for the development of the initial production version of the eCTD and the implementation of the E2B ICSR electronic submission. He has 25 years experience with the FDA leading development of FDA's internal IT systems in support of the CDER and CBER submission review process. After leaving the FDA, he served as the US HHS CTO and was a pharmaceutical industry consulting with Booz Allen Hamilton. He holds a Masters of Chemistry degree from the American University in Washington DC