DRUG REGULATORY MANAGEMENT SYSTEM

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Overview and Summary: Toward a global vision of Regulatory Affairs environment

Regulatory Affairs (RA) now have to aim at an integrated Drug Regulatory Management System (DRMS), in line with the business realities and the international regulatory requirements. In place of the widespread "home database", or spreadsheets, a global system should enable not only an easy and accurate follow up of the product life cycle, but also a better control of the information loop and workflow activities, which means for the company: a precious gain of time, gain of productivity and a management which comes as close as possible to meeting the global Quality recommended standards. This paper will try to develop a DRMS concept proposal, which should eventually lead to the following benefits for the company:

- Single and rapid access to the most validated and up-to-date master data
- Planning and scheduling RA actions as soon as they are identified
- Follow up and tracking of the Submissions, and Commitments
- Integration to the eCTD world partly through the generation of automated tracking tables
- Attractive, and easy to use tool with harmonized data entry rules and business processes
- Dynamic and integrative approach of the product life cycle between the different departments
- Improvement of the workflow management, timelines follow up, information circulation, and validation review through the enterprise
- Enhancement of internal and external regulatory collaboration
- Improvement of the HQ-affiliates communication and information exchanges
- Decrease in administrative and low added value tasks
- Decrease in implementation-time change, RA procedures deadlines follow up and information retrieval which means finally : a better time-to-market
- Global Regulatory Management system which meets the requirements of both the pharmaceutical companies and regulatory authorities, in terms of a systemic well-conceptualized Quality System

Key words : global tracking; master data referential; improvement of the product life cycle; integration to DMS, eCTD and workflow management; information sharing; flexibility; better time-to-market; compliance to ICH Q9[1] and ICH Q10[2]

Introduction:

The ever-increasing national and international regulatory guidelines as well as the ever-increasing mass-submission documents, require the RA departments to have at their disposal an adapted, flexible and attractive tracking system. A system used not only by the regulatory team but shared with the other departments (Industrial Operations (IO), Pharmacovigilance (PV), Clinical, QA, Pharmaceutical

Affairs, Commercial department…); at a corporate level, as well as at an affiliate and subsidiaries level. A Drug Regulatory Management System (DRMS) represents more than a simple database; it underlies a full comprehension of the regulatory environment and interactions, in order to develop a well designed system for a multidisciplinary and global approach. This paper presents the main awaited functionalities and needs, both from a business and a global Information System management stand point, through the following axes:

- Tracking of the products' main registered data
- Follow up of the Submissions as well as the different Health Authorities (HA) exchanges and Commitments
- Information Sharing through adapted reports and automated information transfer
- Improvement of the activities' workflow and timelines' respect

Anticipating the needs and choosing the best designed IS solution leads to a precious gain of time, an increase in productivity and allows a regulatory evolution in a fully compliant Quality environment.

Tracking Tool for all current registered data (by country/product/ license)

The first objective of a regulatory tracking database is to ensure an easy, rapid and single point of access to up-to-date information, regarding the pharmaceutical product (either drug or medical device). So far, the database ensures the tracking of all registered data, in all countries, for the whole portfolio, whatever the registration process (National, Centralized, MRP, Decentralized…) or the local structure (affiliate, subsidiary or distributor). The database is generally organized by module: Product Module (independent of a specific registration/country) and Registration Module. This registration Module contains all the:

- Administrative information, e.g. license number, local trade name, generic name, marketing Authorisation Holder (MAH), local agent/distributor, local product responsible, procedure type, license type, manufacturing, control and release sites...)
- Technical information, e.g. active ingredient and excipients composition, route of administration, indication, primary and secondary packaging, shelf life and storage conditions, batch size, quality controls tests performed at each step of the process production, specific local release tests performed by local HA....)

All these parameters can be considered as the constitutive parts of the product "master data".

Follow-up Tool for the Life Cycle Management – electronic tracking of the current/anticipated RA activities and HA exchanges

A DRMS allows the follow up of all submissions from a RA standpoint (new registrations, renewals, variations Type I or II, referrals, CBE 30, global documentation update or upgrade…) or a non RA standpoint (Clinical : Clinical Trial Authorisation/Investigational New Drug Application, PV : Periodic Safety Update Reports (PSURs) …) throughout the product lifecycle. All HA exchanges (Questions and Answers, Specific Obligations (SO)…), HA correspondence, meetings and teleconferences are tracked in the DRMS, as well as the Commitments (Post-Approval Commitments, Follow-up Measures (FUMs)…). Finally specific RA events like license expiration, withdrawal, suspension or product production stop

can be part of the tracking scope (*N.B*. all these cases are given as examples. The DRMS is highly flexible and can be configured to meet the customers' and users' needs as closely as possible). The tracking system then becomes an integrated part of the Life Cycle Management process.
Besides, the DRMS should be considered as a "forward-looking" potential tool. This vision goes beyond the "simple" follow-up of pending submissions, encompassing the planning and tracking of anticipated RA actions, as soon as these latter are identified by the company departments (RA, PV, IO…). This should ultimately contribute to a dynamic approach of the business tasks and a critical analysis of RA scheduling (pending/approved tasks *versus* anticipated ones)… At a data management standpoint, having a single access to final approved data, as well as to temporary anticipated ones, through a versioning system or "history" functionality enables the company to develop a master data referential, centralizing the technical and administrative information and ensuring easy retrieval and data consistency.

The figure hereafter sums up the potential scope of a well-managed DRMS.

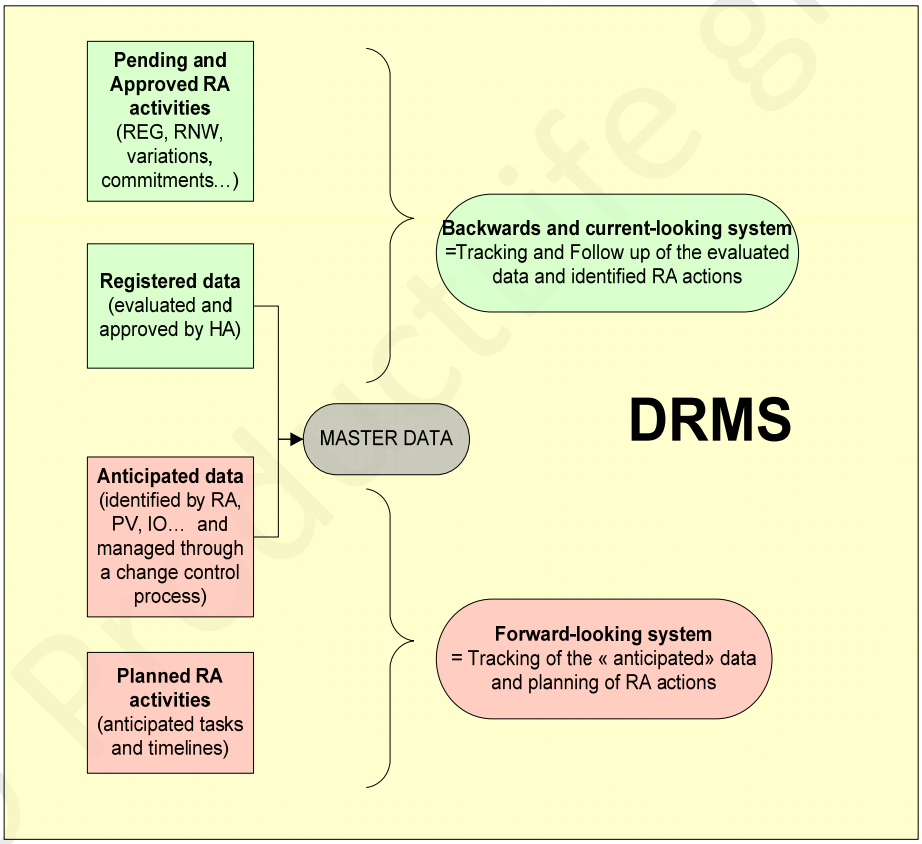

Figure 1 : DRMS scope : Make "to do" approach go together with "pending" or "approved" attributes and build a master data referential

Information Sharing tool – Integrated approach of the Headquarter -affiliates relations, Report functionalities, eCTD Life Cycle and Global interface with the other company's departments

From a Headquarter (HQ) point of view, the DRMS becomes an essential tool for the coordination of regulatory activities with the countries, allowing providing detailed product information to, and gathering submission and approval information from, the affiliates. Different models can be accommodated by the DRMS:

- a centralized approach where HQ distributes reports to the affiliates but remains in charge of the data entry (plus: in terms of process rules harmonisation, data quality; minus: in terms of information and time lost risk),
- a distributed one where each affiliate is responsible for entering local data (plus : in terms of local knowledge of RA specificities and affiliates proximity to HA, gain of time, affiliates integration to corporate issues and objectives; minus : in terms of data entry quality and process harmonisation)
- a combined one (according to affiliates' size and local product portfolio)

In addition to the geographical scope, the DRMS is essential for cross-functional communication. The DRMS will be of benefit to RA department such as Compliance, Labelling, Facilities, and non RA departments like IO, Batch Release, PV, Clinical, QA or Commercial Operations, through "Reporting" functionality. Automated reports and/ or tabulated extracts, designed according to specific business needs, make it possible to retrieve the critical information in an efficient and quick manner. The extracts can be performed by product, group of products, franchise, countries, groups of countries, statuses... or whatever meaningful classification purpose, across a certain period of time. Those reports can be produced for specific business needs (Composition Report, Steps and Tests Reports...), global corporate needs (Annual Product Review Report, number of new licenses/renewals approved or number of variations sent by period of time for example) or to meet the HA's regulatory requirements (e.g. PSUR Report).

In the eCTD world, DRMS can optimize the eCTD life cycle management process at two levels:

- When using an MRP/DCP procedure, a key coordination issue is to ensure that sequence numbers are coherent over national submissions. It is re-enforced by the next EU cover letter where a table summing up all sequence in each country has to be submitted [3, 4]). Two potential improvements can be supported by DRMS:
    - Coordination of sequence numbering over affiliates
    - Automatic creation of the cover letter table
- Part of the eCTD meta data are the "could be" registered data. If DRMS is used not only to record actions done but as well to anticipate them (as presented in previous section) then these administrative data could be stored and managed only once in the DRMS and then reused for the eCTD meta data filing

The DRMS must be designed as a global interface system, not only in terms of data access, but also in terms of Information System sharing. Often, information is relevant for different departments. Most commonly, people have to capture the same data several times, in different systems, with the inevitable waste of time, loss of information and risk of error it involves. Building an integrated architecture and data processing allows an easy, automatic information transfer from one system to another and the development of a highly efficient bi-directional communication (from the RA database to the Clinical, PV… databases or to Business Object). This electronically common space will then result in a precious and significant gain of time and productivity for all departments; each user focusing in

activities with higher added value. For example, the automatic download of the expected or real submission date from the regulatory database into the planning tool could be useful. Conversely, the PSUR submission date can be imported in the RA database as soon as captured by PV department.
As far as PV is concerned, a well-designed DRMS will optimize and secure data exchanges between MAHs and HA, both during the development phase, and after the Marketing Authorisation approval. DRMS, as a master data referential, could be used to automatically fill the EudraVigilance Medicinal Product Dictionary (EVMPD). That means a significant improvement in terms of risk management, as the EVMPD will be used by EMEA to analyze the Eudravigilance database.

Finally, with the purpose of improving harmonization and compliance, the DRMS must include a reference dictionary (like MedDRA). Due to the multidisciplinary users' functions, the use of a common vocabulary avoids capturing the same information in different ways, and allows a better understanding and more efficient communication, both inside the company and externally with the HA.

The technical and functional integrations have to be analysed on a case by case basis, depending on the system landscape of the company and the functionality of the DRMS. Typical candidate systems for integration/ interface are: DMS (DRMS, through an electronically interface will allow the access to the submitted documentation files), Master Data Management (MDM), Product Lifecycle Management (PLM), PV, ERP (e.g. SAP), Labelling, Project and resource management…

Improving organization at a time and human resources level, and shortening of time to market

Tracking all the products events, and the HA exchanges optimizes the respect of the deadlines and facilitates the complex follow-up of the procedural calendar, and of the different milestones of a variation, renewal or registration process. Furthermore a DRMS improves the workflow management: on the one hand "Alert" or "warning" functionalities inform actors and authorized profiles about specific tasks to perform or to follow up; and on the other hand, the system enables people to indicate when a specific task has been achieved. This streamlined organization enables a company to shorten the time to market deadline.

Drawing conclusion: The DRMS: an integrated system in the center of Quality and Risk Management (Figure 2):

References

1) *International conference on Harmonization - ICH Q9- Quality Risk Management – Step 5 – November 2005 CCM*
2) *International conference on Harmonization - ICH Q10- Pharmaceutical Quality System- Step 2 – May 2007 CCM*
3) *Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic Submissions (Draft for Testing, version 1.0) May 2009*
4) *Requirements on Electronic submissions for New Applications/ Renewals and Variations within MRP, DCP or National procedures (Doc.Ref.:CMDh/085/200 and CMDh/006/2008) revised on 1st April 2009*

SOME FURTHER THOUGHTS …

Change Control Management: DRMS as a pivotal part of the cross-functional assessment

Change Control management is a key process for the company, in accordance with the ICH Q9 and ICH Q10 recommendations. Each change impacting the manufacturing process, labelling, quality controls

specifications, documents (SOP, monograph updates), packagings… must be assessed from a regulatory standpoint. Most companies have developed separate applications and do not have a global system to ensure change control management.
An integrated DRMS must be able to track the regulatory events both downstream and upstream; it participates then to an efficient Change Control management as well as a Regulatory Impact Assessment tool. Globally, it facilitates the management, validation review and follow-up - in terms of time, communication flow and compliance- of the process which begins with the change identification and finishes with its implementation. Knowing in advance the kind of changes that need to be submitted to the local HA and the associated regulatory requirements, speeds up the assessment review, improves the planning of change and shortens the implementation delays with an anticipated batch release.

Nevertheless, one should keep in mind that although using DRMS to check and to track all this information could be a step ahead, the situation today is that a number of different systems are partially managing the Drug System Management.