Building the Drug Safety Body of Knowledge to Enhance Confidence in Safety

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At this crucial time, when the need for effective and safe innovative medicines has never been greater (e.g. due to the emergence of new infectious agents, increasing microbial antibiotic resistance, unmet health needs in the developing world, and large aging populations in developed regions), advances in basic science and technology carry the promise of remarkable therapeutic advances. However, while pharmaceutical companies spend vast sums on R&D, the number of new molecular entities licensed appears to be steadily diminishing. Simultaneously, a recent series of high profile drug withdrawals, due to significant safety issues, has reduced the confidence of health professionals and the public in both the current development process and the regulatory procedures that are intended to ensure the safety of pharmaceutical products. While it is unrealistic to expect all very rare undesired outcomes to be detectable during development, effective application of Knowledge Management (KM) tools for integrating information from a variety of sources could result in earlier and more complete understanding of risks attributable to newly-marketed medicines, and thus possibly prevent the withdrawal of useful products from the market by, for example, targeting more specific patient populations.

We understand data as facts obtained from observations, information as data placed in context and knowledge as information combined with intelligence and certitude. Understanding gained from experience and the "know how" and "know why," in addition to the "know what, enables well informed decision-making related to both known and unknown data and new situations. Knowledge may be explicit or tacit (i.e., can reside in peoples' heads), and individual, local, organisational, multi-organisational, or global. We understand Drug Safety Knowledge Management (DSKM) as an ongoing strategic program of knowledge-based processes and enriched practices for achieving both organisational and healthcare objectives through the creation, acquisition, sharing and utilisation of knowledge and the cultural and technical systems that support such processes. The primary end goal of such a program is providing the patient and physician the understanding to make the best healthcare decisions with regards to benefit/risk for the individual patient.

In our recent InnovationWell community of practice discussions, we have envisioned the creation of a Drug Safety Body of Knowledge (DSBoK) to create, enhance and document strategies, approaches, solutions, methodologies and best practices in drug safety knowledge management. Organisational adoption and use of such KM approaches, as viewed by Douglas Weidner and the International Knowledge Management Institute, must be viewed as a strategic initiative, and be implemented with robust methodologies, described and understood in sufficient detail to be useful rather than mere guidance. Knowledge management approaches, including knowledge repositories and knowledge audits, must be seen as ongoing initiatives, dynamically enriched and changing. Any company which performs a knowledge audit of their drug development processes, summarised in a large report with several steps identified to modify existing processes, has performed a useful exercise. But the exercise will probably prove to have been a futile one down the road unless a much deeper and wider ongoing set of processes and behaviour is truly embraced and vigorously pursued, on an ongoing basis, inside and outside the organisation.

The goal of the InnovationWell DSBoK program is to enhance the organizational appreciation and use of drug safety knowledge throughout product development, clinical use and marketing. More specifically, to look at ways to enhance drug safety knowledge transfer to and from R&D teams; to enhance safety knowledge transfer from clinical research to pharmacovigilance; to identify effective approaches for application of new technologies in drug safety-related decision making and safety signal detection; and to enrich the practice of making drug safety decisions under uncertainty.

We have adopted the theme “Integrating Knowledge across the Product Life Cycle” as a key vision guiding the InnovationWell community of practice and its development of knowledge management enriched practices for drug development and safety. This thinking envisions key business process improvement requiring the introduction of innovative knowledge process management across the product life cycle. As a result, multidirectional knowledge flows are enabled between research, development, clinical and marketing functions, internally and externally between pharma, healthcare and research organisations, physicians and patients. This framework should be flexible and adaptable to quickly incorporate new technology advances or changes in the environment, and should include embedded knowledge-based auditing practices aimed towards continued evaluation and performance improvement.

Life Science Product and Drug Development and Safety both involve complex, difficult and important decision-making by an organisation. In a perfect world, the best decisions should be prepared for and supported by as thorough an understanding, both by individual experts and managers and the organisation as a whole. All available relevant knowledge, both internal and external to the organisation, should be available and actionable at key decision points in the product life cycle. Such a prepared organisation should be able to ask powerful questions, quickly obtain reliable answers, have the ability to react pro-actively and wisely to new and unexpected events and to integrate risk and uncertainty evaluation in the organisation's preparation for the future using all knowledge flows available to it.

However, the world is all too often not perfect and is inherently uncertain. Weak signals may go unnoticed and small changes can result in producing unexpectedly large consequences. Traditional approaches to decision support have relied on screening or filtering data so that the decision maker only sees what is relevant. Unfortunately, such approaches screen out the very data that in retrospect the decision maker will realize they needed. Recent developments, driven in some cases by the information processes of anti-complexity, are offering a new approach to decision support in which all data is made available at all times and the principles of serendipity and necessary ambiguity are used to focus the organization on resilience. Such systems aim to achieve a symbiosis of human and machine intelligence and capabilities.

Although informatics approaches such as data-warehousing in the pharmaceutical industry capture and integrate a vast amount of data, it is questionable if such an approach alone enables the organisation to make the best decisions it could make based on all available knowledge. We raise the question: what methods could enable an organisation to maximise its human capital and knowledge potential in its preparation for decisions it makes in the future involving the currently known and the inherently unknowable?

Sense-making and complex systems analysis, as being developed by David Snowden and co-workers, offers one approach relevant to drug safety decision making. Sense-making draws on a variety of scientific understanding – principally from the cognitive sciences, narrative theory and the science of complex adaptive systems theory – to deal with inherently complex and unknowable realities of the world. The developments in this field have been funded over the last seven years in the complex and uncertain field of anti-terrorism and are now starting to be applied in the agrochemical and pharmaceutical sectors.

Organisational culture can critically impact business success, including how critical decisions are made. Clarity of purpose, speed to market, employee commitment and transparent internal processes are all key success factors. Large organisations often suffer from over-reliance on established decision-making processes and procedures. By conducting organisational assessments, one can identify trends by looking, for example, at how well understood, agreed and supported is the organisational strategy and direction, how coordinated internally are the various organisational activities and how close and responsive externally is the organisation to its customers and the marketplace. We can prepare the organisation for improved decision-making readiness and prowess for the future through leadership assessment, competency requirements and gap analysis, human capital management and change management during industry change, mergers and acquisitions. Strategic and tactical attention to such organisational development factors are important contributors to auditable, continuous improvement in organisational drug safety knowledge management performance.

Across the R&D spectrum, improving internalization of knowledge is at the crux of making better and more informed product development decisions. Using advanced technologies such as the semantic web, life science Ontologies and novel approaches to retrieval of unstructured information, companies will enhance knowledge discovery, transform complexity into awareness and facilitate weak signal detection, all of which are key to filling product pipelines going forward. We recognize "proactive/prospective knowledge internalization" cf.

reactive behaviour as a key competitive advantage of the healthcare organizations of the future. Active internalization of knowledge will drive innovation as the industry searches for opportunities to leverage more "personalized" therapeutic approaches and medicines. We believe those organizations that are best able to internalize new knowledge will be the leaders.

For any medical product or procedure, the key question with regard to optimizing its safe and effective use is how well and accurately we can assess how much of its benefit-risk profile is known and understood.The reductive approach to drug development pre-supposes a scope of what needs to be known and proceeds to answer questions within those boundaries. Alternatively, "Confidence in Safety" assumes that all medically relevant information needs to be known, but that we cannot realistically presume to have such complete knowledge until late in a product's lifecycle, if ever. In order to assess the risk associated with a marketed product, we need to be able to assess how much we know about a drug's safety profile or, more importantly, how much is not known.

Confidence in Safety is the level of assurance that we:

- know and understand the safety information available to your organization
- know what information is missing
- know of the missing information, and what you can get when and from where and
- can measure organizational effectiveness in applying safety knowledge to support the development and clinical use of novel medicinal products.

We define "Confidence in Safety" here as the degree of assurance, based on objective assessment criteria, that the best possible medically relevant benefit and risk information is available to support the prescribing decision, and that all known or reasonably suspected adverse outcomes are understood.

InnovationWell has established an initiative to help improve Confidence in Safety by:

- developing and/or enhancing a standardized terminology for communicating benefits and risks
- enhancing methodologies for assessing what is and is not known about a drug's risks
- identifying technologies that improve internalization and dissemination of safety knowledge, and
- defining objective measures of how effectively an organization utilizes knowledge of benefits and risks.

Pharmaceutical companies, regulatory authorities, physicians and patients will all benefit from an improved basis for understanding and communicating Confidence in Safety, both before a drug enters the market and as it is dynamically enhanced by new medically relevant information.

Several strategies are emerging to improve practice in managing drug safety. Their specific objectives include:

- Reduce the likelihood of unanticipated and medically relevant adverse events
- Enhance the use of drug safety knowledge and increase transparency of safety related decisions made by drug makers and regulators
- Respond rapidly and more effectively to potentially relevant safety signals through enhancement of signal identification and evaluation capabilities, and
- Reduce risk through more effective communication of the benefit/risk relationship by enhancing collaboration between drug makers, providers and patients.

Organisations want to improve their ability to use the available knowledge they have accumulated in-house, in addition to integrating external knowledge, so as to further improve their performance in drug safety, and to continuously adjust to the ever changing regulatory climate. KM approaches should link with initiatives already under way, e.g., electronic labeling (e.g., SPL) and electronic patient records, which promise to improve knowledge flow in the future to reduce medical errors in decision situations. It is also considered of merit to apply new KM approaches and technologies to the existing set of safety data such as accumulated by, e.g., the FDA and in-house by pharma companies, but such data needs to be defragmented and accessible in a unified way for expert queries. At present, data mining of existing FDA safety data appears to be limited by the quality of existing adverse event data within and without the Adverse Events Reporting System (AERS) system. Furthermore, approaches are needed to evaluate both new unstructured and structured data arising to enable the earlier detection of patterns for a potentially problematic new safety issue arising, which may be unpredictable and unexpected.

Public funding could be of benefit in funding exploratory pilot projects, but the private sector players, such as pharmaceutical companies, chain pharmacies, pharma benefits management and health insurance companies, will need to drive new systems and the financial issues of who pays what will need to be solved. Knowledge management approaches and systems will need to link and integrate to these new systems. Ways for quickly integrating new observations, such as, for example, cardiograms from physicians in sentinel event situations, are needed, and approaches for improved pattern identification need to be available. The Prisoner's Dilemma solution of cooperation between different parties to achieve the best result will be required in many of these situations and initiatives.

Footnote:

Applying drug safety knowledge management to confidence in safety will be presented and discussed by the authors at the InnovationWell Community of Practice Autumn meetings on October 11 in Philadelphia, USA, and on November 9 in Basel, Switzerland. (See http://innovationwell.net/ for further details.)

The program for Basel also includes a special kind of workshop, a Life Science Innovation Café, run by Victor Newman of KnowledgeWorks with the support of drug safety experts, will focus on the topic of Confidence in Safety to identify and develop new approaches to increase Confidence in Safety.