

Drug informatics – where are the opportunities for STM publishers?

An  Focus Report

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It is now humanly impossible for the unaided healthcare professional to possess all of the knowledge needed to deliver medical care with the efficacy and safety made possible by current scientific knowledge

OpenClinical

[David Bousfield](#)
Independent consultant

[Rebeca Cliffe](#)
Associate, EPS



Executive summary

What is drug informatics?

- According to [OpenClinical](#), an international organisation created to promote awareness and use of decision support, clinical workflow and other computational and database technologies, it is now humanly impossible for the unaided healthcare professional to possess all of the knowledge needed to deliver medical care with the efficacy and safety made possible by current scientific knowledge.
- This situation will deteriorate further as a result of the vast increases in the volume and complexity of knowledge about disease mechanisms created by the genomic revolution.
- A solution is the adoption of rigorous methods and technologies for knowledge management.
- Drug informatics covers the area of overlap where these methods and technologies impact upon the use of drug information in a research, clinical or commercial setting.

What is the relevance to STM publishers?

- Information about drugs comes from many sources
 - Primary level: research lab of a pharmaceutical company or in a university or at a hospital during the course of a series of clinical observations
 - Secondary level: generated as a consequence of the use of data initially collected for non-clinical purposes such as pharmacy benefit management and reimbursement
 - Tertiary level: summarised as a journal article, a reference book, a database or increasingly as a precisely defined evidence-based clinical decision pathway.
- Traditional STM publishers would only recognise part of the third tier as being relevant to their business.
- The purpose of this report is to begin to define the larger market space - the increasing availability and quality of these new types of data create opportunities and may also threaten to undermine the value of traditional content offerings because they can be used to form much more effective tools.

What forces are driving the drug informatics marketplace?

- Problems with the R&D process: despite spending more than any other industrial sector on R&D, the pharma industry is grossly inefficient and its pipeline output stands at a record low even though the automation of the research process has resulted in a huge increase in research data output.
- High level of error: According to the 1999 Institute of Medicine Report *To Err is Human*, many medication errors result in preventable adverse drug events (ADEs), of which approximately 20% are life threatening.
- Products are unsafe: in June 2005, the New York Times reported that a top federal drug official had told a medical advisory board that the nation's drug safety system had 'pretty much broken down' and that there was room for 'a lot of improvement' in the government's

approach to uncovering dangers in drugs already on the market.

- There are a number of high profile initiatives in the US and the UK to accelerate the development of better decision support systems for clinicians.

Future trends

- e-Prescribing will reduce the number of drug information vendors. Much of the information contained in standard drug information reference resources is in the public domain and with over a dozen vendors it is difficult to see how they will be able to differentiate their products in future.
- Patient-centric longitudinal data will drive the growth of the drug informatics market. The ability to link drug usage and cost data with patient-centric information such as outcome, adverse reactions, dosage, age, sex and so forth will enable healthcare providers and payers to evolve schemes of best practise for clinical care, prescription choices and cost management.
- Personalised medicine will enable publishers to add more value to their drug reference databases. It is becoming clear that an individual's genetic profile can dramatically affect drug efficacy and toxicity so several pharmaceutical and biotech companies are working on diagnostic tools to identify responders from non-responders, or people who are likely to suffer a severe adverse reaction to the drug.

Introduction

What is drug information?

Drugs go through three phases in their life cycle. First, research is carried out in an academic, government or industrial lab to understand the basic biological mechanisms underlying a disease process. Eventually, this work will lead to the identification of one or more targets (usually proteins) whose over/under activity is believed to be central to the pathology of the disease. Through an iterative process chemists then synthesise and develop a small chemical molecule that will bind selectively to the target and influence its function in a way that could reduce the severity of the symptoms or cure the disease.

The next phase involves testing the substance in assays, then on animals and eventually using human clinical trials to validate that the drug works and does not have any harmful side effects. The probability of success is tiny. As well as the 'lock-and-key' binding to the target, the candidate compound must be capable of being absorbed by the body, end up in the right organ, not be metabolised or excreted too quickly and not be toxic. Added to this, the new drug must demonstrate clear superiority over alternative existing treatments.

Once the drug has been proven to be effective and safe, its use is endorsed and strictly controlled by national regulatory bodies such as the Food and Drug Administration (FDA) in the US and the European Medicines Evaluation Agency (EMA) in the EU.

Finally the drug reaches the clinic. Many factors will determine its success, such as the effectiveness of its pharmaceutical owner to market it effectively, its cost, its side effects and the other uses or indications found for it. Further clinical trials will be required by the regulatory bodies after launch to assess the incidence of potential rare but serious side effects. This information must be gathered, assessed and fed back into the labelling and other literature about the drug. Occasionally an approved drug will be withdrawn at this late stage with huge consequences for the share price of the pharmaceutical company involved.

One major recent example of this concerns non-steroidal anti-inflammatory drugs Vioxx (Merck), Bextra (Pfizer) and Celebrex (Pfizer), all of which act as inhibitors of the same enzyme, COX-2. Vioxx was voluntarily withdrawn from the market in 2004 by its maker, Merck, after concerns that users of the drug became more susceptible to heart disease. This led to a review of other drugs in the same class and currently only Celebrex is available on the US market, but must will display a 'black box' label warning for the potential risk of cardiovascular events and gastrointestinal bleeding. It is estimated that about 20% of all drugs released into the US market will eventually carry a black box warning at some point in their life.

The measured efficiency of this drug development process is currently at an all time low with fewer and fewer drugs being approved by the FDA each year – despite increasing investment in R&D made by the pharmaceutical industry. Why this is so is not clear. Perhaps it is because in discovery terms most of the low hanging fruit have been picked and the next

generation of drugs are going to be much more difficult to create. Perhaps it is because the massive increase in knowledge created by genomics and proteomics following the successful sequencing of the human genome in 2001 has temporarily overwhelmed scientists with new, but poorly understood opportunities. Or perhaps it is because human beings are genetically variable and these differences mean that people respond differently to the same drug – something that is not easy to pick up in clinical trials involving only 1000s or 10,000s of patients. Almost certainly all of this is true.

Drug information is the sum of all of the data and knowledge generated by throughout this life cycle. The diversity and number of customers for this information is huge, ranging from the researcher, physician, pharmaceutical benefit manager, insurer to the consumer. The relevance of the different types of information will vary with circumstance but little will be totally irrelevant. For example, a particular pattern of gene expression seen in early clinical trials may indicate that a particular patient is susceptible an adverse side effect, such as liver toxicity. Data from earlier animal studies may help identify the mechanism, which in turn may suggest ways in which this unwanted effect can be avoided. Lance Armstrong's book, 'It's not about the bike' provides a particularly cogent message about the importance of clinical information for patients.

So what is drug informatics?

According to [OpenClinical](#), an international organisation created to promote awareness and use of decision support, clinical workflow and other computational and database technologies, it is now humanly impossible for the unaided healthcare professional to possess all of the knowledge needed to deliver medical care with the efficacy and safety made possible by current scientific knowledge. This situation will deteriorate further as a result of the vast increases in the volume and complexity of knowledge about disease mechanisms created by the genomic revolution. A solution is the adoption of rigorous methods and technologies for knowledge management. Drug informatics covers the area of overlap where these methods and technologies impact upon the use of drug information in a research, clinical or commercial setting.

Why is it important for STM publishers?

As we have seen, information about drugs comes from many sources. At a primary level, information is generated in the research lab of a pharmaceutical company or in a university or at a hospital during the course of a series of clinical observations. At a secondary level, drug information is generated as a consequence of the use of data initially collected for non-clinical purposes such as pharmacy benefit management and reimbursement. And at a tertiary level this information is summarised as a journal article, a reference book, a database or increasingly as a precisely defined evidence-based clinical decision pathway. Traditional STM publishers would only recognise part of the third tier as being relevant to their business.

In a report prepared by Frost & Sullivan in 2001 it was estimated that only about 15% of the \$2.4bn global healthcare

publishing market could be attributable to the sale of 'drug information'.

This survey did not include like IMS Health, a 'gold standard' supplier of drug information services and solutions (derived from secondary sources) to the pharmaceutical industry with reported sales in 2001 of almost \$1bn. Nor did it include the many smaller companies then coming into existence such as Celera, Incyte, Deltagen, GeneLogic and Iconix who were beginning to build new business models effectively around the resale of what is primarily experimental data.

The purpose of this report is to begin to define this larger market space, not just because its sales value is significantly larger than the traditional STM market, but because the increasing availability and quality of these new types of data create opportunities, or, alternatively threaten to undermine the value of traditional content offerings because they can be used to form much more effective tools.

Driving forces and the new marketplace

There are big problems with the R&D process

Despite spending more than any other industrial sector on R&D, the pharma industry is grossly inefficient and its pipeline output stands at a record low even though the automation of the research process has resulted in a huge increase in research data output. Most drug candidates fail to reach the regulatory submission stage, and those that do frequently fail because of unexpected toxicity, lack of efficacy, or because they are just too uneconomic to manufacture. But almost all of this data remain hidden in the companies' data silos. Indeed sometimes so hidden that the same mistake is made more than once.

There is increasing pressure from organisations such as the US National Institutes of Health (NIH) and the FDA for companies to release more of the 'failure data' generated during animal testing and clinical trials so that the industry as a whole (and indeed the public) can learn for its collective mistakes.

The FDA for example has created a database which pools toxicity data gathered from a group of compounds that were found to be carcinogenic in rats and in humans. They are using a variety of rule- and statistics-based techniques to correlate known drug chemical structure features with biological activity (QSAR) so that they can create tools to say predict whether a new compound will be carcinogenic.

Some companies such as [GeneLogic](#), [Iconix](#), [Cerep](#) and [MDS Pharma Services](#) who act essentially as contract research service providers have begun to create databases of their own content plus additional proprietary information, albeit after anonymising these latter data so that no intellectual property will be revealed to a third party. And others, such as [InPharmatica](#), [Ingenuity](#), [GeneGo](#) and [Rosetta](#) are building hybrid products which combine data mined from publications and public access databanks with their own proprietary data and computational software. Interestingly some of the major health IT and health care providers are beginning to collaborate, e.g. GE Healthcare and GeneLogic, and Massachusetts General Hospital and MDS Pharma, to integrate these sophisticated tools and data sets into the clinical workflow.

To err is human, but not this frequently

According to the 1999 Institute of Medicine Report *To Err is Human*, many medication errors result in preventable adverse drug events (ADEs), of which approximately 20% are life threatening. ADEs contribute 7000 deaths per year in the US – one of leading causes of mortality (more than road accidents, breast cancer or AIDS).

The US Institute for Safe Medication Practices has observed that pharmacists make over 150 million calls each year to physicians for clarification of illegible prescriptions and that electronic prescribing can reduce follow-up calls between pharmacists and physicians by over 50 percent.

The costs are out of control and the quality dreadful

According to the US National Coalition on Health Care, in 2004, employer health insurance premiums increased by 11.2 percent - nearly four times the rate of inflation. The annual premium for an employer health plan covering a family of four averaged nearly \$10,000.

In June 2005, The Guardian newspaper reported that hospital mortality rates in some parts of England are 50% lower than in others, according to a new health index showing huge variations in patient satisfaction, quality of care and equality of access.

And the drugs don't work; worse, they poison you

Dr. Allen Roses, worldwide vice-president of genetics at GlaxoSmithKline (GSK), Britain's giant pharmaceutical company, acknowledged at a scientific meeting in London in 2003 that fewer than half of the patients prescribed some of the most expensive drugs actually derived any benefit from them. 'The vast majority of drugs - more than 90 per cent - only work in 30 or 50 per cent of the people', he said.

In June 2005, the New York Times reported that a top federal drug official had told a medical advisory board that the nation's drug safety system had 'pretty much broken down' and that there was room for 'a lot of improvement' in the government's approach to uncovering dangers in drugs already on the market. The official, Dr. Janet Woodcock, deputy commissioner of operations at the Food and Drug Administration, made her remarks before a committee of experts at the Institute of Medicine, which had been asked by the agency to suggest safety improvements after a year of well-publicized troubles, including the withdrawal of two big-selling painkillers Vioxx and Bextra.

But help is coming: US government legislation

A number of high profile national initiatives have been enacted to accelerate the development of better decision support systems.

The Medicare Modernization Act of 2003 includes provisions for electronic prescribing (e-prescriptions) and clinical decision support systems (CDS). This includes the Medicare Health Support program designed to deliver 10 new evidence-based disease management care regimens.

An Office of the National Coordinator for Health Information (ONCHIT) was created in 2004 to coordinate the national development of a healthcare information technology infrastructure. The office, part of the US Health and Human Services Department will be responsible for coordinating the development of information exchange standards.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was designed to improve portability and continuity of health insurance but also was the key piece of legislation

allowing the re-use of information in electronic medical records (EMRs) after the data has been anonymised.

And in the UK

In the UK, the publication of the Wanless Report in 2002 convinced the Department of Health that ‘without a major advance in the effective use of information and communications technology, the health service [would] find it increasingly difficult to deliver the efficient high quality of service’. The National Program for Information Technology (NPfIT) means an investment of \$11bn over a 10 year program creating a basic EMR for 50m patients and providing clinical decision support.

In both the US and the UK, it is fair to add that these investments will take some time to have significant effect. The Department of Health has admitted that not a single primary care trust in England is likely to be in a position to meet its target for the implementation of an electronic referral system and will be relying on paper solutions to deliver its flagship policy. However, top flight hospital consortia such as [Partners Healthcare System Inc](#) (which includes the Massachusetts General Hospital, Brigham and Woman’s Hospital and the Duke University Medical System) are well advanced in implementing some of the more sophisticated systems and demonstrating a positive ROI on their investments.

Current status of healthcare IT

Progress is most notable to date within the US, particularly within the top tiers of the healthcare spectrum. The reasons are two-fold. Implementation of IT infrastructures was already more advanced and the management of change has been handled more effectively. For example, physicians started to use PDAs (and to a lesser extent Tablet PCs) as portable sources of reference material several years ago and so there was already a dedicated PDA user group when hospital networks went wireless.

From the beginning, the priority has been safety, rather than the development of a new IT infrastructure per se. Most errors involve the administration of the wrong drug, overdoses, overlooked drug-drug interactions and allergies, illegible handwriting and decimal point mistakes are the most common sources. So prescribing behaviour was an early focus.

At its simplest, ePrescribing is the two way electronic communication between physicians and pharmacies involving new prescriptions, refill authorizations, change requests, cancelled prescriptions, and prescription fill messages to track patient compliance.

Not only does ePrescribing reduce time and error at input, it can also be used to manage the overall expenditure budget for the hospital as a whole. Usually the choice of alternative drugs is restricted by the extent of the hospital’s formulary. There may also be limitations imposed by the patient’s level of health insurance. All of this information can be used to streamline the prescription process.

The potential savings benefits will actually be most visible in the UK because the National Health Service is effectively the pharma industry's sole customer. Here the National Institute of Clinical Excellence (NICE) issues guidance and recommendations on the use of all new and existing drugs, effectively controlling the pharma industry's access to the market.

Computer-assisted physician order entry (COPE) takes the process of integration one step further by enabling a broader range of actions such as a request of a lab test or medication details to interact with patient information within their EMR. Orders can be checked for potential errors or problems, for example, the possibility of a personal drug interaction, allergy or an overdose. At Boston's Brigham's and Women's Hospital, studies have shown that CPOE reduces errors by 55% as reported by the [Leapfrog Group](#), an independent body promoting improved patient safety in the US.

One step further still, Clinical Decision Support Systems (CDS) effectively integrate a variety of database resources organised so that problems can be addressed and solved at the point-of-care (POC). Initially these might include reference to content sources such as the Cochrane Database of Systematic Reviews – a series of detailed, structured reviews which allow clinicians to get fast 'bottom line' answers to their most commonly-asked questions, a drug reference such as the PDA version of Thomson's PDR (Physician's Desk Reference), and access to Medline. Increasingly though, content suppliers are turning to rule- and phrase-based syntheses of medical knowledge that are more effective in driving decision making.

Finally, the concept of Clinical Pathways was introduced in the early 1990s in the UK and the USA, and is being increasingly used throughout the world. Clinical Pathways are structured, multi-disciplinary plans of care designed to support the implementation of clinical guidelines and protocols. They support clinical management, clinical and non-clinical resource management, clinical audit and also financial management. They also provide detailed guidance for each stage in the management of a patient (treatments, interventions etc.) with a specific condition over a given time period, and include progress and outcome details. Clinical Pathways can now be integrated into PDA-driven decision making and will form the basis for the evidence-based disease management program of the future. An example might be the use of patient-specific HIV viral titres to drive the management of a cocktail of anti-retroviral drugs.

IT support communities

As these implementations become more sophisticated, so the commercial ecosystems supporting them grow more complex and differentiated.

For example [Cerner](#) is a leader in the development of healthcare IT solutions, but it is also a content provider. Its platform, Cerner Millennium integrates workflows around a centralised database of EMRs and through its subsidiary [Cerner Multum](#) it sells databases that support these CDS systems. Lexicon, for example, is Cerner's foundational source of drug product and disease nomenclature information and

addVantageRx is an application that links drug reference information to the electronic medical record to provide patient-specific drug information, for example personalised dosing.

[PatientKeeper](#) is a developer of platform and linking technologies to integrate wireless content sources for PDAs. It partners with Cerner, but also Cingular (wireless data services), DrFirst (comprehensive e-prescribing application), ePocrates (comprehensive drug, disease, formulary reference for PDAs), GE Healthcare (imaging and diagnostics), IBM, Lexi-Comp (drug reference content), MedQuist (medical transcription), Micromedex (content), Park City Solutions (integration platform for information solutions), Sci Systems (scheduling applications), Skyscape (adapts licensed content for PDA applications), Sprint (wireless communication services), and Symbol Technologies (bar code scanning applications).

Overall, PatientKeeper provides access to clinical references, such as drug guides, dictionaries, drug interaction guides, evidence-based medicine modules, clinical guidelines, and calculators, combining patient information with the wealth of clinical knowledge available through third parties. For the time being, it occupies a very sweet spot on the content value chain.

Currently each ecosystem of suppliers surrounding the major IT integrator players is different, and with over a dozen providers of traditional drug reference information it is difficult to imagine all of these players surviving as the major IT providers begin to dominate their markets.

Drug database providers

A survey of PDA-based databases conducted in 2004 listed 17 products from over a dozen of the major suppliers – only First Databank was absent (Clauson et al, *Am J. Health-Syst Pharm* 61, pp1015-1024). At that time products from Lexi-Corp (Lexi-Drugs Platinum), ePocrates (ePocrates Rx Pro), Gold Standard Multimedia (Clinical Pharmacology OnHand) and Tarascon (Pocket Pharmacopoeia) were highly rated. Products from Wolters Kluwer, Thomson and the American Society for Health System Pharmacists were also included. A comparative survey of the non-abridged sources can be found at http://www.library.utoronto.ca/gerstein/subjectguides/drug_ch art.html.

In the print world there was considerable scope for breadth and currency of coverage to play a role in pricing, but in a digital world these features are expected as standard and the basic content is in danger of becoming commoditised. PDA-deliverable versions provide an additional source of sales (most of the products cited here cost significantly less than \$100), but ultimately integrating the content into site-licensed server-based decision-support tools is the direction publishers will have to move in.

Strategies of major publishers

A brief survey of Thomson's drug-related assets

Thomson is the dominant player in the provision of integrated information solutions across the scientific and healthcare verticals. Through acquisition and internal platform development it is well on the way to providing a seamless suite of applications to satisfy the needs of academic researchers, information professionals, pharmabiotech management, physicians and clinicians, and healthcare management.

With over 20 information brands contributing to its activities in the STM sector, a strategy which makes copious use of the words, 'workflow', 'solution' and 'integrated', Thomson is well placed to take the dominant position in drug information. For corporate customers, much of this content can be accessed through a single platform Thomson Pharma.

Key brands to watch include:

- [Centerwatch](#) provides clinical research and trial information services to patients, pharmaceutical, biotechnology and medical device companies, CROs and research centres. In particular, Centerwatch's drug intelligence databases help pharmaceutical professional track competitive activity, pinpoint trends in therapeutic category development and identify drugs nearing FDA submission. Core resources include the Directory of Drugs in Clinical Trials.
- [Current Drugs](#). The main product is the Investigational Drug database (IDdb) which provides validated, integrated and evaluated information about the R&D portfolios of more than 17,000 companies and institutes involved in drug development including information about more than 92,000 therapeutic patents (with optional links to the full text of the original patent), pipeline status of more than 21,000 investigational drugs, with comprehensive drug reports, development histories, bibliographies and expert commentary on the most promising candidates with all chemical data fully substructure searchable.
- [Derwent](#), [Micropatent](#) and [Current Patents](#). According to their respective web sites, Thomson Derwent is 'the world's leading patent and scientific information provider', MicroPatent is 'the world's leading source for online patent and trademark information' whereas Current Patents is the 'fastest patent alerting service available'. As patent information becomes more easily available via the Web expect these brands to coalesce and the final uber-brand to differentiate by adding more value via advanced text-mining and analysis features.
- [Liquent](#) provides regulatory software solutions, information products and related services for the life sciences industry. Liquent's software and service offerings help to ensure that clients meet the strict standards set by regulatory authorities across the world, helping them achieve quality, accuracy, and data integrity to deliver regulatory reports and submissions reliably and on time. In addition to technology and services, Liquent's IDRAC database service provides intelligence in the life science regulatory environment in 39 of the largest markets in the world.
- [Medstat](#) information solutions assist to strengthen healthcare policy and management decision-making across the whole of the healthcare industry, e.g. cost control and budget management, fraud and abuse, program management and evaluation, policy and legislature support. Medstat Advantage is a decision support tool linked to an in-depth integrated warehouse of medical claims and encounter data, pharmacy drug utilization, medical complication details, eligibility information, and performance measures. The product provides a performance measure catalogue, and produces reports to maximize productivity and facilitate information distribution.
- [MicroMedex](#) – see next page.
- [Newport](#) has developed a series of databases in the pharmaceutical industry on worldwide active pharmaceutical ingredient manufacturing (API). API development is an early and increasingly accurate predictor of generic competition for major brands.

- [PDR](#). PDR.net is the online home of the Physicians Desk Reference (PDR) offering integrated medical information and education tools to physicians, nurses, and other clinical practitioners. The site contains the drug information and resources needed daily by its prescriber user base arranged together in one site for convenience and ease-of-use. Its companion site PDRhealth is written in lay terms and is based on the FDA-approved drug information found in the PDR. It gives consumers plain-English explanations for the safe and effective use of prescription and nonprescription drugs – explanations that are consistent with the information professionals are referencing in the PDR.
- [Scientific Connexions](#) is a medical communications company providing strategic and tactical publishing services to the pharma industry.

Focus on: Thomson MicroMedex

[Micromedex](#) content management systems have undergone a major transformation in order to place context and content specific information directly into clinicians' workflow. MicroMedex's drug information resources include *DrugDex* - peer-reviewed, form-based documents about all FDA-approved or -investigational prescription and non-prescription drugs, plus data on dosage, pharmacokinetics, cautions, interactions, clinical applications, adverse events, and *DiseaseDex*, which supports diagnosis and treatment decisions, preventing medical errors and improving outcomes. Both content sources are endorsed by the medical communities at Stanford, Harvard and Oxford Universities and Micromedex itself is the only commercial source of drug information endorsed by the US Congress.

But good content, Thomson believes, is only half of the solution. So Micromedex partners with a number of leading technology providers to deliver enterprise-wide clinical knowledge, patient education, and decision support at the point-of-care. Current partners include:

- Bond Technologies (electronic medical record management software);
- Bridge Medical (patient safety, prevention of medical errors, recently acquired by Cerner);
- CapMed (electronic medical record technology);
- Epic (leading supplier of healthcare IT solutions);
- GE Health Medical Systems (medical imaging, diagnostics and information technologies);
- Health Language (management of controlled vocabularies);
- M2 (systems integration);
- Meditech (systems integration);
- PatientKeeper (mobile computing content integration platform);
- QuadraMed (systems integration);
- RX Link (pharmacy inventory management); and
- Theradoc (expert systems for clinical decision support).

The selection of this range of companies and the patterns of cross-partnership will mean that Thomson content is prominent in many hospital implementations. How will it contribute to the development of additional features and functionality?

By combining these products with some of the flexible technologies listed above, MicroMedex databases and tools can enable clinicians to prevent adverse events, promote the best

clinical practices, and help reduce the overall cost of care from diagnosis to aftercare. The new InfoButton feature, for example, is designed to give users quick access to abbreviated clinical content plus the ability to link to detailed, comprehensive clinical references and patient education information from within an EMR.

That said, there is little else for MicroMedex to leverage against with in the overall Thomson health portfolio. Unlike the pharmaceutical market, here there are few natural synergies between the brands, and little opportunity to try and take the lead in building an overall platform equivalent in comprehensiveness to, say, Thomson Pharma.

A brief survey of Wolters Kluwer's drug information assets

Wolters Kluwer Health comprises four divisions - Clinical Tools, Medical Research, Professional & Education and Pharma Solutions - straddled by eight brands. The branded services include:

- [Adis](#) provides total communications solutions for the pharmaceutical industry worldwide through peer-reviewed journals, decision-making tools and customized communications solutions.
- [Clineguide](#) is a point-of-care decision support system that can be integrated with electronic medical records or used on a stand-alone basis. Clin-eguide Clinical Reference presents a synthesis of the best available evidence on diagnosis, management, and treatment of high-cost problems occurring in inpatient, outpatient and emergency department settings. Clin-eguide Order Sets provides standardized orders for a wide array of high-volume inpatient and outpatient clinical conditions, supported by links to the medical evidence.
- [Facts & Comparisons](#) provides its drug information library of more than 40 publications via hand-held applications, CD-ROM, internet and intranet applications and integrated databases, in addition to the bound publications and updated loose-leaf references that have been the accepted standard for many years.
- [ifi Claims Patents Service](#) has built a solid reputation as the pre-eminent producer of patent databases, from the most rigorous U.S. assignee name standardization process in the industry, to continual class code updates, and comprehensive indexing for chemical patents. ifi claim to be the most comprehensive indexers of the Markoush structures found in chemical patents.
- [Lippincott, Williams & Wilkins](#) publishes more than 275 journals and newsletter products in specialty fields for physicians, and clinicians.
- [Medi-Span Knowledge Bases](#) (databases for screening and reviewing drug-drug interactions, drug-lab conflicts, drug indications and adverse drug effects). Increasingly these are integrated directly into the information systems used by clinicians in inpatient, ambulatory and operating room settings, as well as pharmacy dispensing applications.
- [Ovid Technologies](#) provides online information services for hospitals and medical schools worldwide and is the primary online source for all Wolters Kluwer Health content.
- [Skolar MD](#) is an online provider of clinical information and gives clinicians immediate answers to detailed clinical questions at the point of care by rapidly searching multiple sources of highly regarded medical information, such as textbooks, journals, evidence-based guides and pharmaceutical references. It is the first program approved by the American Medical Association that enables physicians to earn continuing medical credits.

Focus on: Wolters Kluwer

[Wolters Kluwer](#) is also gradually forming partnerships with some of the leading IT and informatics providers in the healthcare market.

In February 2004 a strategic alliance was announced with [Eclipsys Corporation](#). Eclipsys will use medical content from Skolar and LWW to expand the clinical knowledge embedded within Eclipsys' SunriseXA clinical decision support solution.

Later that year agreements were announced involving the integration of medical and drug content from Medi-Span, Clin-eguide and Skolar with both [Epic System Corporation](#)'s health information and clinical applications, and with [Cerner Corp](#) to enhance their Millennium clinical knowledge system.

The most recent announcement – March 2005 – is that Wolters Kluwer will use [Apelon](#)'s terminology knowledge base to crosslink content with key national ontology standards such as SNOMED CT, LOINC and ICD-9. This will ensure that WK Health content can be used across a number of additional healthcare information providers.

Some of Wolters Kluwers' most recent management recruits to its Medical Research Unit, such as CEO Gary Foster (ex-CEO of PatientKeeper, ex-GE Medical Systems), Linda Holder, Vice President and Chief Financial Officer (ex-Hewlett Packard, Compaq), Neil L. Schmidt, Vice President of Operations (ex-GE Medical Systems) and Dr. Paul Weislogel, Executive Vice President of LWW Journal Publishing (ex-Elsevier) indicate a strong commitment to continue to add value to clinically relevant content delivered by technologically sophisticated platforms. But will they succeed?

Wolters Kluwer certainly has a clear vision of the emerging shape of the drug information market place, but as others have commented, can they manage within the complexity of the organisation they have created? And, perhaps most importantly, Apelon aside, where is the investment in added functionality going to come from?

Enter, stage right - IMS Health

IMS acquires pharmaceutical sales data and healthcare trend information in over 100 countries and from hundreds of thousands of sources, principally manufacturers, wholesalers, pharmacies, hospitals, doctors and mail-order pharmacies. It checks, cleans and formats the data and analyses it to provide total drug market projections and market sizes. This information is then sold on to pharmaceutical and biotech companies, insurance and managed care organisations, governments and investment banks. With a turnover of \$1.6bn (60% from outside the US), a growth rate of 14%, and 5,900 employees, IMS dominates its marketplace.

As David Carlucci (CEO, ex-IBM) explained to the audience at the Goldman Sachs Healthcare Conference this June, IMS' role has evolved from a data aggregator to a provider of innovative decision support tools, emphasising sales force effectiveness

and management tools, portfolio optimisation, launch management, brand management, consumer health and most recently managed healthcare intelligence.

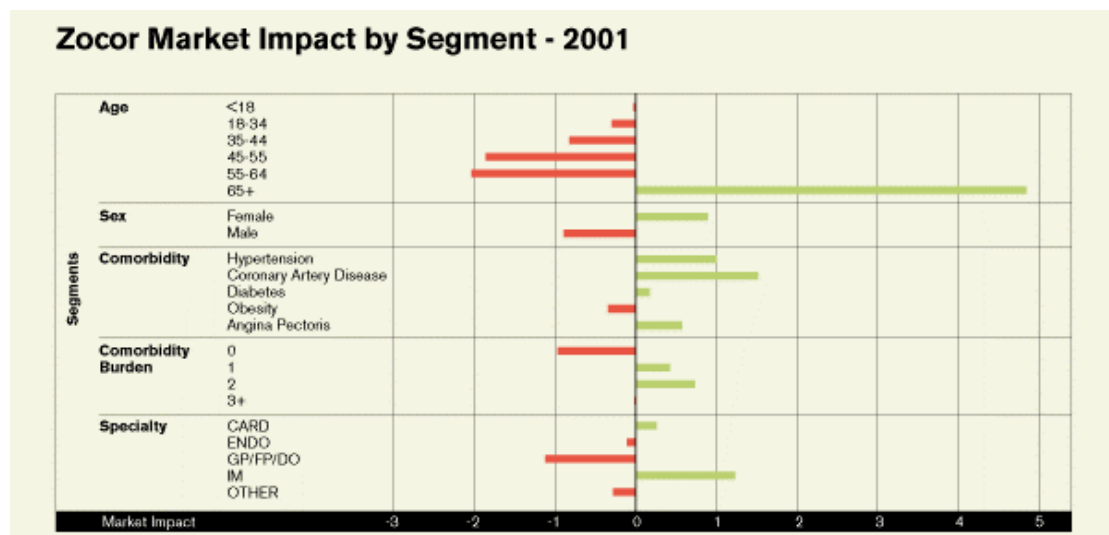
This has meant not only that the company has been able to increase the range and value of the products sold to its traditional customers, but also that it has been able to extend its customer base to include payers, employers, government and researcher physicians. Carlucci estimates that this will grow the total market to around \$5bn.

In June 2005 IMS announced a strategic initiative to address the specialized needs of early-stage biopharmaceutical firms. A new set of IMS offerings - focused on the most prevalent disease states in the early-stage pipeline - will help these clients understand critical market issues, and plan and execute successful commercialization strategies.

Goliath buys David

More significantly, in June they announced a definitive agreement to acquire [PharMetrics](#), the leading US provider of business intelligence utilizing patient-centric integrated claims data with a turnover of about \$20m.

By working with hospital networks, managed care organisation and payers Pharmetrics has built up a database of drug usage which can be used to measure market size and share, but which also contains de-identified information about the patient. In return for ongoing contributions of insurance claims and enrolment data, data suppliers can access national and regional normative data that enable them to compare their performance to regional and national health care cost, utilization and quality outcomes.



Source: Pharmetrics promotional leaflet

Pharmetrics has formed alliances with a number of US hospital consortia and their insurers and now has access to data from over 55m patients (IMS owns a similar company Disease Analyzer, based in Europe, so the overall number will be higher).

This anonymised, patient-centric data can provide information about diagnoses (co-morbidities, adverse events, etc), patient demographics (gender, age), chronology (services provided, prescriptions filled), medical services provided, Health Plan type, charges and payments. The analytical detail far surpasses anything that can be produced from prescription data alone, and clearly has applications that extend beyond market intelligence, to e-detailing, CME and research. They can offer a real time view of medical practice at an unprecedented level of detail and will undoubtedly be used for a variety of other purposes yet to be imagined.

Future sources of competition

IMS' competitors include Cegedim, Verispan and until recently NDC. However, in 2004 NDC announced that it planned to divest its European information management operations, leaving IMS without rival in the EU, and then in August 2005 the company was broken up and sold to Wolters Kluwer and Per-Se Technologies Inc, a transactions processing and business services outsourcing company. Wolters Kluwer acquired NDC's pharmaceutical data analysis services.

There is still a huge amount of scope to develop new businesses from this content source. Marc Schiller, CEO of Adherence Tracking, a small US start-up focussed on capturing and analysing longitudinal patient data for pharmacy benefit management companies feels the potential is enormous. This will be an interesting market to watch in future.

The role of the public sector

The core of traditional drug information is effectively created and endorsed by the FDA and a significant proportion of the US healthcare bill is underwritten by the federal government. So it could make sense for government to become more involved in the development of some of these services themselves - and it is.

Mark McClellan, head of the federal Medicare System (and prior to that Commissioner of the FDA) has suggested that Medicare data could be used to drive the FDA's adverse event reporting system. For years the FDA has struggled with medications that they had approved but which later turned out to have rare but serious side effects - the FDA's current system of voluntary reporting (the Adverse Events Reporting System, AERS II) only picks up 10% of the serious reactions and has no way of normalising the data against the total number of patients being prescribed the drug.

To help shrink the gap, McClellan suggests that a patient-claims-driven system could track the safety and effectiveness of medications - much in the way that IMS/Pharmetrics is proposing to do. The Medicare data would cover millions of patients and potentially be far more effective than the FDA's Adverse Event Reporting System of voluntary submissions which most experts believe only scratches the surface of the problem.

Future trends

1. e-Prescribing will reduce the number of drug information vendors

The Medicare Modernization Act requires that all US government health-related agencies establish technical standards that enable providers to share electronic medical records and to electronically prescribe drugs. A main component of an electronic prescribing system is access to accurate, up-to-date information about these drugs based on the FDA-approved labelling information (allowed therapeutic uses, dosage information, side effects, etc).

The Electronic Labelling Rule became effective in June 2004 and required that the content of the labelling should be submitted as a PDF. Currently this is the only electronic format that is accepted for formal reviewing, but this will change later this year when structured product labelling (SPL) becomes the required format. The SPL specification is an HL7-compliant document mark-up standard that specifies the structure and semantics of the content from a regulatory perspective. This will make it far easier to integrate this information directly into clinical support systems.

Much of the information contained in standard drug information reference resources is in the public domain and with over a dozen vendors it is difficult to see how they will be able to differentiate their products in future. A survey of the web sites of the top 20 health IT providers (as defined by the publication *Healthcare Informatics*) revealed that only five content providers received significant mention - First Databank, Cerner Multum, Wolters Kluwer (MediSpan, Skolar, Clin-eguide), Thomson MicroMedex and WebMD – implying that these companies are already taking the lead in content delivery. Given the overlap between these services, even five may be too many for this market in the future.

2. Patient-centric longitudinal data will drive the growth of the drug informatics market

The ability to link drug usage and cost data with patient-centric information such as outcome, adverse reactions, dosage, age, sex and so forth will enable healthcare providers and payers to evolve schemes of best practise for clinical care, prescription choices and cost management.

[Ingenix](#) produces Symmetry EBM Connect which compares the analysis of health claims data with evidence-based clinical guidelines for 20 diseases, including coronary artery disease, diabetes, HIV/AIDS and sickle cell anemia. The gaps in care identified provide specific targets for improving quality and reducing costs.

Several companies are developing the evidence-based clinical guidelines. [DiagnosisOne](#) has developed a comprehensive library of Care Pathways that have diagnostics as a central focus. These care pathways, a road map for physicians, provide succinct information on presentations, patient history, physical examination, lab and radiology tests and clinical conditions all

linked together to provide a comprehensive clinical decision support system.

This knowledge will be used to develop precise programs for evidence-based disease management which in turn will provide a framework for the design of drug formularies with a host of interesting potential impacts on drug marketing activities such as e-detailing and CME.

3. Personalised medicine will enable publishers to add more value to their drug reference databases

It is becoming clear that an individual's genetic profile can dramatically affect drug efficacy and toxicity so several pharmaceutical and biotech companies are working on diagnostic tools to identify responders from non-responders, or people who are likely to suffer a severe adverse reaction to the drug. This is called personalised medicine.

As this information becomes available, it will begin to populate EMRs and claims databases. It will enhance the content of drug information databases by requiring that indications and potential side effects are referenced according to the patient's pharmacogenomic profile. This will provide an opportunity for publishers to add value to their products.

Activity in this field is already evident. [ThereStrat](#) for example, has begun to develop a database, SafeBase, connecting data relevant to the molecular basis of serious ADRs. It covers a complex array of information ranging from chemical structures of parent compounds, metabolites to genetic variations of genes that in combination render individual patients susceptible to serious ADRs.

[Partners Healthcare](#) in Boston are already using tools like this to screen cancer patients and Iressa (Astra Zeneca) is an example of a drug that is effective on a small proportion of patients whose lung cancers have a particular gene mutation.

Conclusion

The development of sophisticated healthcare IT infrastructures, economics and the rapid expansion of our knowledge about disease processes dictate that the market for drug information will change radically over the next few years. We predict that the market for this information will grow dramatically as a result of access to richer sources of well-indexed information in digital form and the coalescence of markets previously seen as separate. STM publishers will continue to play a significant role in this market place, but they must move quickly to partner with leading IT and informatics providers if they are to secure their place in this future.

Interview:

Jerry Osheroff, Chief Clinical Informatics Officer, Thomson Micromedex

What are the key drivers in the healthcare publishing market?

The changes in the marketplace are being driven by the shift away from a publication or product-centric focus to a greater concentration on user needs. In the past, publishers have been more focused on the content they are producing than on what the issues facing users are and how they might help them address these issues. At Thomson, specifically, we are focused on the important decisions that professionals make all day long; how do we help them make better decisions faster?

In healthcare generally, and drug information particularly, there is intense interest in achieving better outcomes more efficiently. This means looking outside simply offering data on drug doses, interactions and so on. It means focusing on improving overall care outcomes, such as decreasing adverse drug events; increasing appropriate selection, dispensing and administration of medications; and promoting greater cost-effectiveness of medication use. Achieving these enhanced outcomes means looking broadly at the needs of the care team (including patients) at different stages of their individual workflows.

Publishers now need to think in terms of solutions, pulling together the various types of content that are needed and delivering them to the right stakeholder, in the right format, through the right channel at the right stage in workflow. Clearly all this information should be consistent. For example, whether the user is a patient looking at an educational handout on a disease; a physician, nurse or pharmacist looking for drug information to treat that disease; or a clinician presented with an order set or clinical alert pertinent to the patient and imbedded in a clinical information system, the underlying management information should be consistent.

In addition, the content also needs to be current. While this can be a huge challenge for publishers, users have been trained by the web to expect up to date information instantly. Similarly, information must also be based on the best available evidence so that users can be confident that decisions based on the information will do more good than harm. It is this shift in worldview from products to solutions that is currently driving major changes in the publishing world.

The US is far ahead in healthcare markets – where else in the world should we be looking for examples of best practice?

The US is not particularly advanced in some key aspects of the healthcare market, in my opinion. We are way behind where we should be in terms of IT and outcomes, despite spending a lot of money on healthcare. There are many places where use of IT is further advanced, notably in settings where there is more uniformity in how healthcare is paid for and organised, such as the UK and other European countries.

In the US, the recently created Office of the National Coordinator for [Health Information Technology](#) has been charged with co-ordinating healthcare IT strategy across the fragmented market in order to achieve better healthcare outcomes. Dr. David Brailer, the head of this office, is exploring strategies that leverage the strengths of a free market, together with federal enablers and drivers, to accomplish this mission. One component of this strategy currently under review focuses on improving knowledge management as a mechanism for improving outcomes. Healthcare publishers should keep an eye on these developments to optimize their role in supporting the new information realities these activities will bring about in the US.

What are the most exciting healthcare information implementations?

'The future is here, it's just unevenly distributed' is a William Gibson quote that is pertinent here. There is some incredible work being done in taking knowledge and using it to enable better outcomes. Some noteworthy examples in the US include the Regenstrief Institute, Partners Healthcare and Intermountain Health Care (IHC), among others. Most of these

institutions have been working over the past decade or more on sophisticated ways to deliver knowledge to the healthcare team in order to make care safer, higher quality and more cost-effective, e.g. by decreasing adverse drug events. What we are working towards is for the whole world to be able to realise the sort of solutions that are already being deployed in these innovative centres. Advanced implementations have been taking place on a cottage industry basis; what publishers now need to do is provide industrial strength content for clinical decision support that can be easily deployed on a widespread basis, and localized as needed.

What will be the advances in hand-held computers in the US over the next few years? Will users be employing wireless for sophisticated uses?

The technology of various handheld devices is increasingly converging (e.g. phone, PDA, internet, lectures/books), so these devices offer ever richer opportunities to deliver information to members of the care team – including patients. As the technology becomes used more widely in general and in healthcare, publishers will need and want to leverage these channels more fully. For example, when urgent test results are sent wirelessly to a clinician's handheld device, accompanying guidance on appropriately interpreting and responding to the result could also be provided. Additional details about the test also might be delivered to the device for review at a convenient time, for CME credit. Given the current widespread use of these mobile technologies in society at large, they already warrant careful attention by publishers.

Increasingly, information is tied up in IT systems. How will pharma researchers and doctors be able to interact more effectively to make use of the different worlds of information to which each group has access?

Interoperability is key for cutting across different islands of data, from electronic health records with patient data to information from publishers aimed at driving better decisions and outcomes. The global movement toward standards for exchanging data and knowledge among disparate information systems is creating a tremendous opportunity for interplay between different pieces of information and knowledge bases that have traditionally been separate. This will benefit the entire cycle of information use in healthcare. An example of this kind of interoperability is Thomson Pharma, which ties different pieces of key information from diverse sources together in one user-focused solution for pharmaceutical research and development.

How will the experience of Merck with Vioxx affect how pharma companies approach their investment in and use of drug information?

Many problems arise from the fragmentation or sub-optimal use of information, and cases like this are an example. If all the available information pertinent to drug development and use were readily available in a useable format to all the various stakeholders, we'd be much better off. The Thomson Pharma solution is a step in this direction. With more fully integrated patient data, it will be possible to learn sooner about problems and dangers associated with medication use. In addition, a seamlessly integrated body of healthcare data and knowledge will enable new information about effective medication use to emerge more quickly and efficiently, e.g. through data mining and outcomes research supported by electronic medical records.

On a related theme, major changes in the use of medications (such as the withdrawal of a medication like Vioxx) require that new information about appropriate clinical management be disseminated rapidly and effectively to both clinicians and patients. Drug information publishers should be prepared with content creation mechanisms to generate this management information and propagate it throughout all their content and formats (e.g. patient information, referential databases, and information system integrated information). Likewise, publishers will need dissemination infrastructure to rapidly distribute this information to patients and clinicians who need it to support proper decisions and actions.

As tools and information and workflow converge, how much consolidation will there be? How many players can we expect to survive?

We are already starting to see consolidation in the HIT market, e.g. as major global companies such as Siemens, GE and Philips penetrate more deeply into healthcare. For the foreseeable future though, I think HIT companies like these (with a focus on managing patient data) will remain separate from companies that create the clinical decision support

content that infuses those systems. This is because the knowledge development process is such a complex and substantial undertaking in itself, requiring very different competencies than data management systems. There will be consolidation on the knowledge side too. However, since providing comprehensive, integrated, current, evidence based decision support information across the continuum of care is such a major undertaking, large global players will likely play a central role here too. However, especially in the US (with its strong spirit of innovation and entrepreneurship) there will always be smaller companies in the market filling niches on both the data and knowledge sides, even if most are ultimately allied in some way with a larger player.

Where does Thomson Healthcare see its drug information business developing in future?

Thomson Healthcare companies such as PDR, Micromedex and continuing medical education businesses have provided widely used and trusted drug information and tools for the healthcare information marketplace for decades. Going forward, a major focus is on providing knowledge solutions that meet user's information needs seamlessly within workflow, and help them deliver the highest quality, most cost-effective care. This includes not just information about drugs themselves, but more comprehensive and integrated knowledge offerings to support disease and patient management – a component of which addresses the appropriate and cost effective use of drugs to optimize health.

All Thomson businesses are driven by a front-end customer strategy that involves getting close to customers, understanding their needs, and learning where we can add value. Each of our individual businesses expends considerable energy spending time with customers, exploring what they do day-to-day, and finding ways to apply our capabilities to help them make better decisions faster. This strategy includes taking a prominent role in shaping the healthcare information marketplace – through both innovative solutions and thought leadership on approaches to harnessing knowledge to improve outcomes.

Over the past four years Thomson Scientific and Healthcare has invested heavily in developing a new content management and delivery system and re-architecting the content development process. This has resulted in a unified, lexicon-based, integrated repository of evidence-based information that is used to deliver just the right content to a broad spectrum of healthcare users, in different formats, to optimally address needs. This also ensures that our content is tied to all the industry-standard vocabularies, e.g., ICD-9, CPT, SNOMED, LOINC, etc., which is critical for deploying actionable knowledge in CPOE and other clinical information systems.

We are delivering products from this repository now through a variety of channels (e.g. handheld, internet, information-system integrated) and formats (e.g. context-sensitive infobuttons, alerts, etc.). With patient management information coming from this central and integrated repository, all users - from patients, to pharmacists, nurses and physicians - are singing from the same song-sheet, i.e. making decisions based on the same trusted information. In addition, this content management system enables rapid responses to changes in healthcare information, such as medication withdrawals noted above.

What is the role of the publisher in a world in which the value of information is increasingly determined by the technology behind it?

Technology is part of the evolution towards meeting user needs, but I see it as an enabler rather than the primary focus. The publishing industry needs to get away from simply putting out databases and instead concentrate on how we can best deliver the right content to the right person at the right time to drive better processes and outcomes of care. Fully utilizing available technologies is a key ingredient for helping us do this.

About David Bousfield

David Bousfield is an independent management consultant and business analyst focussing on describing and predicting the impact of informatics on value in the biotech, pharmaceutical, healthcare and publishing industries. Based in Cambridge UK, David is supported by a network of experts – Ganesha Associates - based in Cambridge and London in the UK and in Boston, Washington and San Francisco in the US.

David has over 30 years experience in the biomedical research, STM publishing and bioinformatics and has worked with many leading companies and brands in these areas to create new products, extend existing businesses and identify new business development opportunities. He can be contacted at david@ganesha-associates.com or on +44(0)1223 324400.

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