

# CURRENT STATUS AND FUTURE PERSPECTIVES OF DRUG INFORMATION SYSTEMS

Tervonen, Tommi, Faculty of Economics and Business, University of Groningen, PO Box 800, 9700 AV Groningen, The Netherlands, t.p.tervonen@rug.nl

de Brock, Bert, Faculty of Economics and Business, University of Groningen, PO Box 800, 9700 AV Groningen, The Netherlands, e.o.de.brock@rug.nl

de Graeff, Pieter A., Department of Internal Medicine/Clinical Pharmacology, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands, p.a.de.graeff@int.umcg.nl

Hillege, Hans L., Department of Epidemiology/Cardiology, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands, j.l.hillege@tcc.umcg.nl

## Abstract

*The information lifecycle of a drug starts already during the drug discovery phase and continues far into the future in prescription- and adverse-effect databases. In this paper, we describe the past literature and existing technology of Drug Information Systems (DIS). We develop a mapping of DIS to the phased drug lifecycle taking into account the system information contents. The mapping shows that currently there is a lack of DIS providing efficacy- and safety data in a suitable format. This lack severely hinders the possibility of physicians, researchers, as well as regulatory authorities and the pharmaceutical industry, to make quantitative analyses of efficacy and safety over a wide range of drugs.*

*Keywords: health information systems, regulation/deregulation, function-based analysis, decision making.*

## 1 INTRODUCTION

Drug development, testing and administration are information-intensive areas with varying computing needs. These range from storing a single drug's labeling information to complex algorithms for analyzing quantitative structure-activity relationships in the drug discovery process. In this paper we use the term Drug Information System (DIS) to describe the systems that store data related to some phase(s) of the drug lifecycle, and that process it into user relevant information. DISs have various uses in, for example, recording clinical trial results, disseminating findings of adverse drug reactions, and operational support in a hospital environment. Although the amount of clinical health research is growing rapidly, the supporting operational systems have only recently received comparable effort in research (Leape et al. 2005).

The past few years have seen a rise in the amount of research in DISs, but the majority of health information systems literature seems to concentrate on DISs as a tool to improve drug prescription processes and focus on health care safety in a clinical environment (Littlejohns et al. 2003; Haux 2006; LeapFrog 2008). However, in order to support clinical pharmacological decision making and to access and aggregate information from the complete drug lifecycle, it is crucial to have an overview of existing DISs.

A clear overview of existing DISs enables processes dealing with information gaps between discovery, development, regulatory approval, and pharmacovigilance stages. The main motivation to fill these gaps is the need for a reform of the regulatory process recently brought into discussion by regulatory bodies, academia, and industry (Bjerrum 2000; Ray et al. 2006; Garrison et al. 2007; Lesko 2007; EMEA 2008). In order to improve management of drug information, we need an overview of DISs nowadays available and contributing to the drug lifecycle. More structured information will lead to improved transparency in the decision making process of regulatory authorities. There exists evidence that even published clinical trial results have had statistical evidence interpreted incorrectly in order to appear positive (Turner 2004). Transparency of the process could help to find such incorrect analyses as the original studies would be linked with the aggregated results, and finally, with the marketing authorization decisions that (in principle) take into account all relevant clinical data.

This survey considers the existing literature and DISs from a perspective that is, up to our best knowledge, new in the area. We review the existing technology and DISs from a functional point of view, providing an overview of the current state of the technology. Although we briefly present drug discovery systems, we concentrate on clinical data from drug development. The review is followed by a mapping of the existing systems to the various phases of the drug lifecycle. The mapping allows finding possible integration points between DISs of different phases, which can eventually lead to information re-use, improved communication, and following this, to shortened drug development cycles.

## 2 CURRENT STATE OF DRUG INFORMATION SYSTEMS

The drug lifecycle consists of the disjunct phases of discovery, development, launch, and marketing. The discovery phase ends with starting the pre-clinical trials. Together with Phase I-III clinical trials these span the development phase. After the development phase, selected trial information is carried over to the launch-phase, consisting of marketing authorization and labelling. Marketing includes Phase IV trials and the pharmacovigilance process follows launch. These phases are supported by various types of DISs described in the following sections. Figure 1 illustrates the phased drug lifecycle and the related DIS types. Other aspects of Figure 1 will be discussed in Section 3.

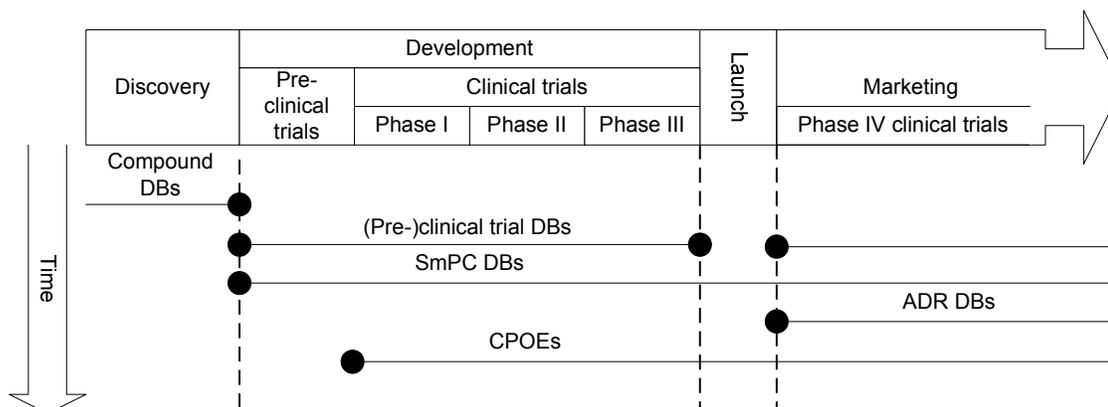


Figure 1: Phased lifecycle of a drug and the related DIS types. SmPC is an abbreviation for Summary of Product Characteristics, ADR for Adverse Drug Reaction, and CPOE for Computerized Physician Order Entry.

## 2.1 Compound databases

Modern drug discovery begins by identifying cellular and genetic factors that play a role in target disease or condition. The search begins *in silico* with identification of chemical compounds possessing drug-like effects. Computational methods are used to predict or simulate how a particular compound interacts with a given protein target. These methods can be used to assist in building hypotheses about desirable chemical properties when designing the drug, and to refine and modify drug candidates. *Compound databases* provide the physico-chemical structural data for the computational drug discovery methods used in component screening and profiling. These methods include Quantitative Structure-Activity Relationship (QSAR) modelling, molecular docking, and pharmacophore mapping (Barnum et al. 1996; Sprague et al. 1997; Shoichet et al. 2002; Tong et al. 2002; Wolber et al. 2005; Ekins et al. 2007). By generating and optimizing leads with the help of compound databases, they generate the first information contents within the drug lifecycle, see for example the Cambridge Structural Database (<http://www.ccdc.cam.ac.uk/products/csd>) or the NCI DIS 3D database ([http://www.dtp.nci.nih.gov/docs/3d\\_database/dis3d.html](http://www.dtp.nci.nih.gov/docs/3d_database/dis3d.html)). However, their focus is on drug discovery and on algorithmic functionality, not on data processing for the later phases of the drug lifecycle.

## 2.2 Clinical trial databases

Clinical trials are pivotal to assess drug efficacy and safety. However, although all trials contribute towards common knowledge, there exists a bias in selective publication of positive results (Dickersin 1997; Chan et al. 2004). Public trial databases help to overcome this problem by providing easy access to the trials with negative results not published in top medical journals. The editors of top medical journals have acknowledged this need, and since 2005 most of such journals require published results have corresponding clinical trials recorded in a public database that meets certain criteria (De Angelis et al. 2004).

In collaboration with the US National Institute of Health, FDA has mounted an open clinical trials web-repository (<http://www.clinicaltrials.gov>). However, although the repository includes functionality for storing results data, most of the studies report only meta data (such as trial settings and objectives). Since 2004 EMEA has EudraCT, a clinical trial registration database established in accordance to the EU Directive 2001/20/EC (<http://eudract.emea.europa.eu>). EMEA does not have a publicly accessible DIS for clinical trials. The FDA clinical trial repository provides a valuable

resource for existing and ongoing trials, but the missing trials and limited amount of trial results cause it to be of limited use.

The Pharmaceutical Research and Manufacturers of America (PhRMA) have a repository where member companies can upload results of clinical trials (<http://www.clinicalstudyresults.org>). They allow open access and to search studies according to drug, indication, or manufacturing company. Even though their clinical trial database reveals details for individual trials, due to the aggregated nature of the data, it is not easy to quantitatively compare safety, efficiency, or efficacy of drugs. As such, the repository is only suitable for obtaining trial results related to a single compound.

The FDA has acknowledged the lack of a centralized, public, and open repository providing raw clinical trial data. They are currently building Janus, a standards-based clinical data repository that utilizes the open source data model (<http://crix.nci.nih.gov/projects/janus>). When operational, Janus stores clinical trial data in raw format through the CDISC Study Data Tabulation Model (Kubick et al. 2007). However, the sheer size of raw trial data might render it practically useless for other than statistical purposes. The requirements for regulatory data will be discussed further in Section 3.

The Cochrane Library (<http://www.cochrane.org>), maintained by the non-commercial Cochrane Collaboration, provides reviews of effects of healthcare interventions through one of its core components, the Cochrane Database of Systematic Reviews (Starr et al. 2003). These have been regarded on average to be of better quality than the corresponding studies published in traditional journals (Jadad et al. 1998). The main innovation of the Cochrane is the possibility to conduct meta-analytic studies through aggregation of results of various studies using software developed especially for that purpose (Brozek et al. 2008). Compared with the traditional journal publications that usually provide data as tables or figures, the Cochrane Reviews incorporate exact descriptions and results of the original studies, and the software allows to form odds-ratio diagrams that can also include the newest studies. These meta-analyses can detect rare adverse reactions that are undetectable in individual studies (see e.g. Nissen et al. 2007).

Evidence-based medicine is aimed to apply the best available evidence gained from the scientific method to medical decision making (Sinclair 2004), and the relevance and impact of the Cochrane Database within this context should not be under-estimated (Grimshaw et al. 2006). However, reviews of the Cochrane Library still can contain biases because, for example, studies demonstrating positive results have higher possibility of getting published than those with negative results (Egger et al. 1998). Further disadvantage is that the reviews are of selected topics rather than systematically covering all areas. Also, although being relevant in evidence-based medicine, the Cochrane Database provides the original study results in a textual format, which makes the results unsuited for application in other analyses.

### **2.3 SmPC Databases**

The drug development process is the basis for the Summary of Product Characteristics (SmPC). SmPC is the source of information visible to non-professionals through drug labelling and package inserts. The information is originally stored in the annex for marketing approval as governed by the regulatory authorities (EMA 2005). In Europe, the SmPC belongs to the European Public Assessment Report (EPAR). The EPAR contains all trial information, but it is completely textual, without semantic structure. All EPARs are publicly available through the web (<http://www.emea.europa.eu/htms/human/epar/a.htm>). It has to be noted that the EMA-based information of EPARs and SmPCs is far from complete from a medicinal product perspective because it concerns only products given a Marketing Authorization via the Centralised Procedure. Although most of the data contained within the SmPC originates from Phase I-III trials, the labelling might change on basis of new information like Periodic Safety Update Reports (EMA 1997) or Phase IV clinical trials. Post registration drug profiling studies might lead to different safety instructions for patient subgroups, such as children.

There have been initiatives for a more structured SmPC from both EMEA and FDA. From EMEA this is in the form of Quality Review of Documents (QRD) and the Product Information Management (PIM) standard. The QRD annotated template provides a loose verbal structure that has to be followed by SmPCs (<http://www.emea.europa.eu/htms/human/grd/docs/Hannotatedtemplate.pdf>). PIM is a standard for submitting data in a structure given through a Document Type Definition (<http://pim.emea.europa.eu/des/docs.html>). Both QRD and the more advanced PIM are designed for transferring and updating information in a structured format that facilitates translating the product information to official languages of all EU member states. FDA has a Structured Product Labeling (SPL) standard similar to the PIM (<http://www.fda.gov/oc/datacouncil/SPL.html>). FDA provides content of labeling information in SPL format. This content can be browsed in a user-friendly format on the DailyMed site (<http://dailymed.nlm.nih.gov/dailymed>) of the National Library of Medicine. However, none of QRD, PIM, or SPL imposes semantics to the quantitative data visible in the SmPC. Some non-profit organizations provide condition-specific drug labeling and/or trial information. For example, the Saskatchewan Lung Association for lung diseases (<http://www.sk.lung.ca/drugs>), or the US National Cancer Institute for different types of cancer (<http://www.cancer.gov/drugdictionary>).

Although the effort to allow publicly accessible SmPC information seems to have paid off, and both EMEA and FDA have very good SmPC databases, they don't link to any structured clinical trial results databases. Such functionality would be preferable, as it would allow tracing the scientific evidence from a drug in the market to the original clinical trials. Moreover, the drug compendia, that should replicate the SmPC information, have been shown to lack consistency of drug-to-drug interactions due to insufficient standardization of the used terminology (Vitry 2006).

#### **2.4 Adverse drug reaction databases**

The DISs related to adverse drug reactions (ADR) seem to be less sophisticated than the clinical trial ones. Health Canada has its ADR database MedEffect Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff>) that incorporates information about suspected ADRs with both prescription drugs and health products such as non-prescription medicines and natural health products. EMEA does not allow public download of their ADR database, although they do provide an empty Access database for submitting data (<http://eudravigilance.emea.europa.eu>). FDA does not have an online ADR database, but provides access to quarterly ADR reports (<http://www.fda.gov/cder/aers/extract.htm>).

#### **2.5 Computerized physician order entry systems**

In 1999, the USA National Institute of Medicine released a report (Kohn et al. 1999) arguing that Adverse Drug Events (ADEs) are the leading cause of preventable death and disability in American hospitals. They suggested Computerized Physician Order Entry (CPOE) systems to be the main tool in preventing ADEs. CPOEs achieve this by automating the human error-prone parts of the process, especially with regard to drug prescription.

CPOEs in Europe often include internal nationally oriented SmPC databases for drug information. The clinical decision support functionality within a CPOE allows a prescribing physician to rely on the system to do drug-allergy checking, basic dosage guidance, formulary decision support, duplicate therapy checking, drug-drug interaction checking, dosing support for renal insufficiency and geriatric patients, guidance for medication-related laboratory testing, drug-disease contraindication checking, and drug-pregnancy checking (Kuperman et al. 2007). CPOEs have clearly reduced prescription errors (Bates et al. 2003; Kaushal et al. 2003), although studies have indicated, that general CPOEs without clinical decision support functionality achieve only a minor fraction of this decrease (Nebeker et al. 2005). Nevertheless, incorporation of information technology in the prescription process has also introduced new sources of errors (Koppel et al. 2005).

Although the national SmPC database is the core component of a CPOE, the commercial packages seem to use a proprietary SmPC database instead of a public one. The lack of a centralized database

containing more than only national information hinders the interconnectivity of CPOEs with other DISs. CPOEs seem to be the most logical information system for automated reporting of ADRs for pharmacovigilant purposes, but this potential has not been utilized in existing CPOEs.

A future research in CPOEs should aim in building a summarizing functionality that would link to available drug databases with possibly heterogeneous information. It is technically challenging to design drug databases that guarantee backwards compatibility while allowing evolving schemas. To achieve this and to promote external access, the drug databases should provide a versioned API. On the CPOE side of the link, the trust and security of external data sources must be addressed. The recently proposed SANDS, a service-oriented architecture for clinical decision support, has some similar structure (Wright et al. 2008). The strength and limitation is that it links to existing national health databases and provides e.g. drug interaction checking and diagnostic decision support together with a patient interface allowing to query drug interactions between personal medicines. Although important in clinical decision support, SANDS does not seem to provide sufficient integration of clinical trial information for pharmacological uses.

### 3 MAPPING AND DISCUSSION

We have summarized all the DISs reviewed in previous sections in Table 1, and classified them as compound databases (DBs), clinical trial (CT) DBs, SmPC DBs, ADR DBs, and CPOEs. The table also provides information whether the system provides raw and/or aggregated data, whether the data is available in quantitative format, and the estimated start year of the data. Table 1, together with Figure 1, shows that Janus is the only DIS providing quantitative data from the development and marketing phases. However, as Janus is not yet operational, there exists no DIS with data that can be used in automated quantitative (meta-)analyses.

Figure 1 (presented earlier) includes mapping of DISs to different phases denoted by the horizontal lines with dots. The mapping indicates how DISs incorporate data originating from the different phases. The vertical direction (indicated by the Time-arrow) represents chronology of information input regarding a drug, that is, the order in which information most often enters the different DISs. Figure 1 emphasizes the chronological characteristic of DISs: they incorporate information from different phases. This can be explained by workflows supported by DISs; when a certain DIS was designed, its purpose was to support the information processing needs of specific phases. In case of CPOEs and Cochrane DB, this is explicit, as their requirements have been studied intensively and are fairly stable. Other DISs have been more *ad hoc* solutions for coping with practical needs. The phased drug lifecycle presented in Figure 1 can help existing and potential users to scope their current DIS needs by clarifying the information contents carried through the drug lifecycle in various information systems.

Class	Name	Quantitative data (Yes/No)	Aggregated/Raw data	Start year of data
Compound	Cambridge Structural Database	Y	R	1970
Compound	NCI DIS 3D database	Y	R	1994
CT	Janus	Y	R, A	-
CT	Cochrane	N	A	1988
CT	ClinicalTrials.gov	N	A	2000
CT	EudraCT	N	A	2004
CT	ClinicalStudyResults.org	N	A	2004
CT/SmPC	NCI Drug Dictionary	N	A	1980's
SmPC	DailyMed	N	A	1993
SmPC	EMEA EPAR	N	A	2004
SmPC	Lung Association of Saskatchewan lung disease drug repository	N	A	2006
ADR	MedEffect Canada	N	A	N/A
ADR	EMEA ADR	N	A	2001
ADR	AERS (FDA)	N	A	2004
CPOE	Various	N	A	Various

*Table 1: Reviewed drug information systems.*

Although the current DISs allow to store, retrieve and process data from certain phases of the drug lifecycle, they have not been designed to allow quantitative comparisons in the drug development phase. The Cochrane Database seems to be currently the only one that contains a comparison module for performing meta-analyses, but it does not allow for quantitative comparisons based on pharmacodynamic, pharmacokinetic, and clinical cross-product data. CPOEs contain some decision support capabilities, but they use proprietary databases instead of quantitative data. If a practicing physician wants to use the existing DISs for pharmacological decision support of choosing the medicine to prescribe, (s)he is limited to simple queries and proprietary reasoning rules.

From the regulatory viewpoint, the most important phase in the drug development process is the marketing authorization (launch). The largest regulatory authorities (FDA, EMEA) have rigorous processes to avoid drugs with severe side effects or insufficient benefit-risk ratio to enter the market. These processes explicitly require that sufficient quantitative data needs to be collected in the form of clinical trials. However, current regulatory DISs are incomplete from a medicinal compound perspective and do not store the information in a suitable quantitative format that would allow computerized benefit-risk analyses (see Table 1). Janus is an exception, but not yet operational and in any case will not allow public access. So the current DISs do not provide quantitative regulative data utilizable in automated analyses. For example, a physician cannot use the existing DISs to obtain a list of hypertension drugs suitable for pregnant women, let alone to compare the drugs with respect to robustness of efficacy and safety metrics. To develop a system that handles such metrics is not a straightforward task, because some of the metrics need to be comparable in an automated manner. For example, for a DIS to allow automated benefit-risk analysis of several compounds, the compounds

need studies with the same endpoints or alternatively similar studies and scientifically strictly grounded rules of conversion between measurements of the endpoints.

Recently the drug industry, researchers, and regulatory authorities have raised concerns of reforming the marketing authorization process. Mean total capitalized cost for an approved drug is rising rapidly (DiMasi et al. 2003), while the number of approved drugs is decreasing. One way of lowering these costs is to optimize efficiency of the marketing authorization process. A suitable DIS using quantitative methods could both explicitly force the industry to submit the marketing authorization application in an appropriate format, and also make more certain that all (and only) the required data are submitted. In order to realize this, the future regulatory DISs need to store clinical trial results in a suitable format and provide methods for executing standard inter-study analyses.

It is not a trivial task to design and build a DIS that allows storing drug information in a format suitable for quantitative analysis, marketing authorization, and labelling. On one hand, raw clinical trial data might be required for validating statistical conclusions, but its size and varying schemas make preparation for automatic processing a laborious task. On the other hand, the data should be stored with sufficient granularity for utilizing it in new analyses and for revealing possible biases in existing ones. However, in order to enable quantitative reasoning often sought by practicing physicians and medical researchers, we need data with strict semantics and with the precision currently provided by SmPC databases only in textual format with no semantics.

## **4 CONCLUSIONS**

This survey reviewed the existing state of Drug Information Systems (DIS) used to process pharmacological information content carried through the lifecycle of a drug. We mapped the existing systems into the drug lifecycle and pointed out information gaps in the drug development process. The gaps originate from systems that have been designed to support certain workflows, rather than to comprehensively store information related to the complete drug lifecycle. A possible cause for designs carrying poor information coverage in the marketing authorization context is the lack of structure in the submission format.

There is an actual need to fill the gap of provided quantitative data found by this survey. The Cochrane Library has already proved the relevance of evidence-based medicine, as can be seen by the vast amount of published meta-analyses. Top medical journals require published results to be stored in publicly accessible databases. Regulatory authorities have already taken initial steps in allowing marketing authorization data to be submitted in a more structured format. Such advances can eventually help to bring down the cost of drug development, and ultimately, the consumer prices, and to improve drug safety.

The mapping of this survey should be taken as a starting point for information integration across DISs. The most appropriate way of enabling efficient application of DISs may be to make them interoperable instead of aiming for a single integrated enterprise system. This survey did not consider this topic into detail, and future research should investigate whether an integrated system in practice could be built.

The meta-analytical approach as applied in the Cochrane Library seems to be the most appropriate starting point for building the next generation DISs for regulatory uses. The future systems should store all required measurements in a numerical format with strict semantics. For aggregate clinical trial results, we are currently working on building such a system (see <http://www.drugis.org>).

## Acknowledgments

This study was performed in the context of the Escher project (T6-202), which is a project of the Dutch Top Institute Pharma. We thank Kit C.B. Roes (Organon Research Institute) and Daniela Dobre (University Medical Center Groningen) for their valuable comments on the manuscript.

## References

- Barnum, D., J. Greene, A. Smellie and P. Sprague (1996). Identification of common functional configurations among molecules. *Journal of Chemical Information and Computer Sciences*, 36, 563-571.
- Bates, D. W. and A. A. Gawande (2003). Improving safety with information technology. *New England Journal of Medicine*, 348 (25), 2526-2534.
- Bjerrum, O. J. (2000). New safe medicines faster: A proposal for a key action within the European Union's 6th Framework Programme. *Pharmacology & Toxicology*, 86 (Supplement I), 23-26.
- Brozek, J., A. Oxman and H. Schünemann (2008). GRADEpro [computer program]. Version 3.2 for Windows. <http://www.cc-ims.net/gradepr>.
- Chan, A. W., A. Hrobjartsson, M. T. Haahr, P. C. Gotzsche and D. G. Altman (2004). Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to published articles. *Journal of the American Medical Association*, 291, 2457-2465.
- De Angelis, C., J. M. Drazen, F. A. Frizelle, C. Haug, R. Horton, et al. (2004). Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *New England Journal of Medicine*, 351 (12), 1250-1251.
- Dickersin, K. (1997). How important is publication bias? A synthesis of available data. *AIDS Education and Prevention*, 9 (Suppl 1), 15-21.
- DiMasi, J. A., R. W. Hansen and H. G. Grabowski (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 22 (2), 151-185.
- Egger, M. and G. D. Smith (1998). Meta-analysis bias in location and selection of studies. *British Medical Journal*, 316, 61-66.
- Ekins, S., J. Mestres and B. Testa (2007). *In silico* pharmacology for drug discovery: methods for virtual ligand screening and profiling. *British Journal of Pharmacology*, 152, 9-20.
- EMA (1997). ICH Topic E 2 C (R1), Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, Step 5, European Medicines Agency (EMA).
- EMA (2005). A guideline on summary of product characteristics, The rules governing medicinal products in the European Union, EudraLex, Vol. 2C.
- EMA (2008). Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medicinal products for human use, Committee for medicinal products for human use, European Medicines Agency (CHMP-EMA). 2008.
- Garrison, L. P., Jr., A. Towse and B. W. Bresnahan (2007). Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. *Health Affairs*, 26 (3), 684-695.
- Grimshaw, J. M., N. Santesso, M. Cumpston, A. Mayhew and J. McGowan (2006). Knowledge for knowledge translation: the role of the Cochrane Collaboration. *Journal of Continuing Education in the Health Professions*, 26 (1), 55-62.
- Haux, R. (2006). Health information systems - past, presence, future. *International Journal of Medical Informatics*, 75 (3-4), 268-281.
- Jadad, A. R., D. J. Cook, A. Jones, T. P. Klassen, P. Tugwell, et al. (1998). Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. *Journal of the American Medical Association*, 280, 278-280.
- Kaushal, R., K. G. Shojania and D. W. Bates (2003). Effects of computerized physician order entry and clinical decision support systems on medication safety. *Archives of Internal Medicine*, 163 (12), 1409-1416.

- Kohn, L. T., J. M. Corrigan and M. S. Donaldson, Eds. (1999). *To err is human: Building a safer health system*. Washington, DC: National Academy Press, Committee on Quality of Health Care in America, Institute of Medicine.
- Koppel, R., J. P. Metlay, A. Cohen, B. Abaluck, A. R. Localio, et al. (2005). Role of computerized physician order entry systems in facilitating medication errors. *Journal of the American Medical Association*, 293 (10), 1197-1203.
- Kubick, W. R., S. Ruberg and E. Helton (2007). Towards a comprehensive CDISC submission data standard. *Drug Information Journal*, 41, 373-382.
- Kuperman, G. J., A. Bobb, T. H. Payne, A. J. Avery, T. K. Gandhi, et al. (2007). Medication-related clinical decision support in computerized provider order entry systems: a review. *Journal of the American Medical Informatics Association*, 14, 29-40.
- Leape, L. L. and D. M. Berwick (2005). Five years after *To err is human*. *Journal of the American Medical Association*, 293 (19), 2384-2390.
- LeapFrog. (2008). "Computerized Physician Order Entry Bibliography." Retrieved 11. Dec., 2009, from [http://www.leapfroggroup.org/media/file/cpoe\\_bibliography.pdf](http://www.leapfroggroup.org/media/file/cpoe_bibliography.pdf).
- Lesko, L. J. (2007). Paving the critical path: how can clinical pharmacology help achieve the vision? *Clinical Pharmacology & Therapeutics*, 81 (2), 170-177.
- Littlejohns, P., J. C. Wyatt and L. Garvican (2003). Evaluating computerised health information systems: hard lessons still to be learnt. *British Medical Journal*, 326, 860-863.
- Nebeker, J. R., J. M. Hoffman, C. R. Weir, C. L. Bennett and J. F. Hurdle (2005). High rates of adverse drug events in a highly computerized hospital. *Archives of Internal Medicine*, 165, 1111-1116.
- Nissen, S. E. and K. Wolski (2007). Effect of Rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine*, 356 (24), 2457-2471.
- Ray, W. A. and C. M. Stein (2006). Reform of drug regulation - beyond an independent drug-safety board. *New England Journal of Medicine*, 354 (2), 194-201.
- Shoichet, B. K., S. L. McGovern, B. Wei and J. J. Irwin (2002). Lead discovery using molecular docking. *Current Opinion in Chemical Biology*, 6, 439-446.
- Sinclair, S. (2004). Evidence-based medicine: a new ritual in medical teaching. *British Medical Bulletin*, 69 (1), 179-196.
- Sprague, P. W. and R. Hoffman (1997). CATALYST pharmacophore models and their utility as queries for searching 3D databases. *Computer-Assisted Lead Finding and Optimization*. H. van de Waterbeemd, B. Testa and G. Folkers. Basel, Verlag Helvetica Chimica Acta: 225-240.
- Starr, M. and I. Chalmers. (2003). "The evolution of The Cochrane Library, 1988-2003." Retrieved 21. Oct., 2008, from [www.update-software.com/history/clibhist.htm](http://www.update-software.com/history/clibhist.htm).
- Tong, W., R. Perkins, H. Fang, H. Hong, Q. Xie, et al. (2002). Development of Quantitative Structure-Activity Relationships (QSARs) and Their Use for Priority Setting in the Testing Strategy of Endocrine Disruptors. *Regulatory Research Perspectives*, 1 (3).
- Turner, E. H. (2004). A taxpayer-funded clinical trials registry and results database. *PLoS Medicine*, 1 (3), 180-182, e60.
- Vitry, A. I. (2006). Comparative assessment of four drug interaction compendia. *British Journal of Clinical Pharmacology*, 63 (6), 709-714.
- Wolber, G. and T. Langer (2005). LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. *Journal of Chemical Information and Modeling*, 45, 160-169.
- Wright, A. and D. F. Sittig (2008). SANDS: A service-oriented architecture for clinical decision support in a National Health Information Network. *Journal of Biomedical Informatics*, 41 (6), 962-981.