# PharmaVision

## The Business Problem

Time to market is becoming an increasingly important competitive factor for all modern industries. Many have successfully investigated solutions such as Concurrent Engineering, and Computer Integrated Manufacturing. For the pharmaceutical industry, however, companies consider as prime candidate, the automation of the regulatory environment.

## The Business Need

The trend in the industry is towards electronic assembly and eventually submission of new drug approval dossiers (NDAs). Many companies have invested significant ressources in attempting to employ image systems; these are known as CANDA (Computer Assisted New Drug Approval) systems.

Companies are looking for systems which preserve the important expenditures of their information automation plan while providing a significant competitive edge. Hence these systems must be :

- seemlessly integrated into their multi-platform information systems environment,
- tailored to their multi-national organisational and multi-company procedural environments,
- adapted to their multi-line and multi-national strategic programs,
- progressively and smoothly extended to other automation areas such as medical library, record management, or clinical trials functions.

## State of the Art

We have identified two major and opposite approaches to CANDA systems respectively called *day zero* and *day n*..

The ‘day zero’ approach manages the entire life cycle of a NDA dossier, from the first day of discovery research, throughout the approval process. A data repository is opened and made available throughout the contributing departments of the enterprise. The NDA dossier is created on-line and in real-time. In theory, this is the good global response for technical information management. However, it has severe drawbacks and critical constraints, since it:

- dictates the computing environment of both the company and its partners,
- imposes working procedures and tools with little or no concern for the existing environment,
- disregards backlog data and documents
- does not consider all the vital external information sources (e.g. specialized revues and bulletins) and databases (e.g. MEDLINE) which are frequently used by R&D staff.

The 'day n' approach tackles the problem from the other end by enabling the compilation of the NDA dossier at the end of the process line when the project is in the hands of the companies Regulatory Department. Current attemps at implementing this approach have serious drawbacks, too :

- they are small standalone prototypes which can only serve feasability testing and not full scale distributed implementation,
- they provide technical solutions not business solutions by focusing on the enabling technologies rather than on the system's business objectives.

The most critical issue noticed in all CANDA related activities so far is the concept of *all electronic.* It is assumed that most, if not all, information created from today onwards, will be in a computer-readable form, and, hence, processable by conventional computer programs. This goes against all current previsions of the importance of paper today and tomorrow:

- the amount of paper handled in companies has doubled in the last two decades and is expected to double in the next six years,
- 95% of a company's information and documents are on paper,
- on average each document is photocopied 20 times,
- while the IT spendings of European companies represents on average 3% of their revenues, paper handling alone still absorbs 7%.

At a time of worldwide information networks, time-honored but inefficient paper handling remains a major issue. FDA's statement of all electronic submissions by 1995 is not far off and companies must find a technology partner which will help them make them step from evaluation prototypes to full-scale operational systems.

## How Can IA Corp. Help ?

Invited over a year ago by a major pharmaceutical company to explore the technical feasability of a CANDA program and to design a business solution, IA Corporation has developped a standard solution architecture: PharmaVision.

DESCRIBE CREDIBILITY OF TECHNOLOGY BASE OF PHARMAVISION

We have opted for a day n system that will allow you to automate the assembly and printing of one, several or all your drug programs. Using an open architecture that uses distributed client-server equipment, we enable a phased and progressive migration to a complete day zero system completely blended into your IT automation plan. This is PharmaVision's major asset: we provide a short term business solution as part of a systematic approach to the integration of design, submission, production and related processes which consider all aspects of a drug's life-cycle.

PharmaVision relies on a Drug Information Repository (DIR) containing the company's entire know-how. This repository is achieved by adding to your existing information systems and databases the capacity of handling paper and compound documents. Service Modules use this repository to provide specific functions, such as the automated assembly and printing of NDAs. We deliver standard and industry specific functions while you can develop company tailored functions.

PharmaVision hence offers a progressive, flexible, adaptable and long term solution to the automation of the entire drug process. Further, PharmaVision enables stragic planning while relying on a solid, fully tested and widespread technology base.

## PharmaVision Primer

••• give example of planned modules and sell IA's perennity and financial stability here

••• make diagram of PharmaVision concept

••• describe enabling technologies: workflow, SGML or tagged database (xref, data type independancy, standard, accessibility and evolutivity), compound documents, information capture (segmentation, ICR, neural networks for automatic keyword extraction)

(eof)

while incorporating the myriad information sources of their tentacular and multi-continent organization. Further, they are seeking systems with sufficient embedded intelligence to cope with

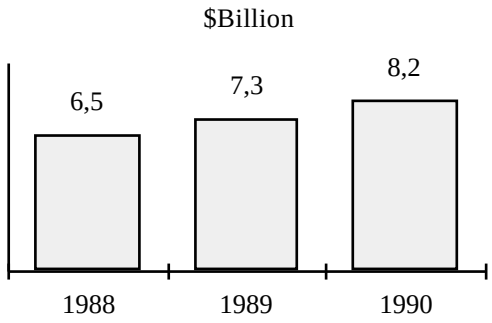


***Figure 1. Escalating R&D Investments.***

Escalating R&D investments are being accompanied by growing risk. A company can expect to lose 35% of market share, the first year a product goes off patent, 50% the second year. About 17 generics enter the market within a couple of years after a patent expires (patents are granted for 10 years).

The number of patients participating in anti-microbial clinical trial in 1979, averaged 1,500. In 1990 a similar trial involved 10,000 patients. The figure doubles every four to six years. Also, diseases remaining unconquered today such as AIDS, cancer diabetes, arthritis, and Alzheimer's, are too slow, degenerative diseases, which require many years of clinical trials to prove efficacy of therapies.

Clinical lab tests double every two years. Case report forms per NDA double every one and half years. Eli Lilly's latest NDA for Pindac (pinacidil) contained 470,000 pages. ICI Pharmaceuticals Group submits four million pages of regulatory filings a year. Glaxo's approval paper work for Zantac (ranitidine) in 100 nations weighed about 16 tons, which is about 128 acres of forest. The average size of a NDA dossier is of 200,000 to 300,000 pages for a new drug and of 50,000 pages for a generic.

The average pharmaceutical company increased the size of its pre-clinical and clinical databases from two gigabytes to about sixty gigabytes over the past five years; that figure is doubling every two years.

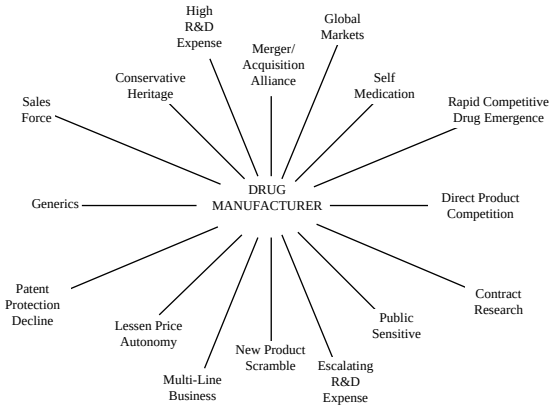


***Figure 2. Pharmaceutical Industry Dynamics.***

## Case Study

Europe Pharmaceuticals Company (EPC) is a $1,2 billion Ireland-based manufacturer of ethical drugs. The industry as a whole has sales in Europe of almost $30 billion, with approximately 125 companies that undertake primary drug development.

EPC currently depends on the antibiotic's market place for 70% of its revenues; $500 million is derived from sales of Elecyclyoneziatran, a general antibiotic that has been on the market for more than five years. Although profits on this drug exceed $200 million, final sales are now flat and other companies are due to release new competitive products within the next two years.

EPC has recognized the internationalization of its industry and although less than 25% of its sales are made outside Europe, it is determined to compete more effectively both in the US and in the Third World.

Pricing strategies have been progressive in the Third World, and sales have increased from $100 million to $150 million. Sales of existing products will not achieve a higher level without changing price policies. This may lead to gray market products appearing in Europe or in the US.

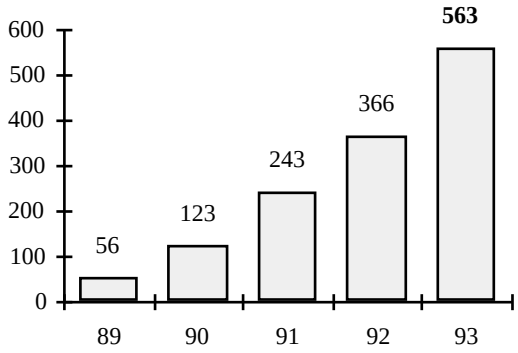


***Figure 3. Pharmaceutical image systems sales projection.***

EPC has acquired France First SA, a Paris-based manufacturer of home testing products for such conditions as high blood pressure and pregnancy. In addition France First is nearing completion of a medication designed to address abnormal heart rhythms. Communications with its French subsidiary have been hampered by incompatible office automation environments and language problems.

## Market Opportunities

Most pharmaceutical companies have invested significant resources in attempting to employ image systems technology in a number of different ways[1]. Half a dozen pharmaceutical companies have started test programs to submit their new drug applications to the Government approval department using optical disk technology.

Companies have bought image systems either for their medical library areas, records management functions, or for the purposes of automating the drug development functions during clinical trials. Some have even gone so far as to give an imaging system to the Government approval department in the hope that this would improve the time lags in the drug approval process[2]. The format and layout of submissions is not imposed; in some countries, the content is not imposed either. Existing guidelines and reglementations only defines the topics which should be addressed. This gives considerable latitude for system design; each company desires a custom system (which they view as a discriminator).

Pharmaceutical companies hence present the perfect client profile: they are big, profitable and healthy.

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| Investigational new ethical drug applications (IND) | 1,337 |
| New ethical drug applications (NDA) | 126 |
| New ethical drug applications approved | 87 |
| New biological drug applications approved | 113 |
| New generic drug applications approved | 265 |

***Table 1. US Pharmaceuticals Industry Activity Volumes for 1990.***

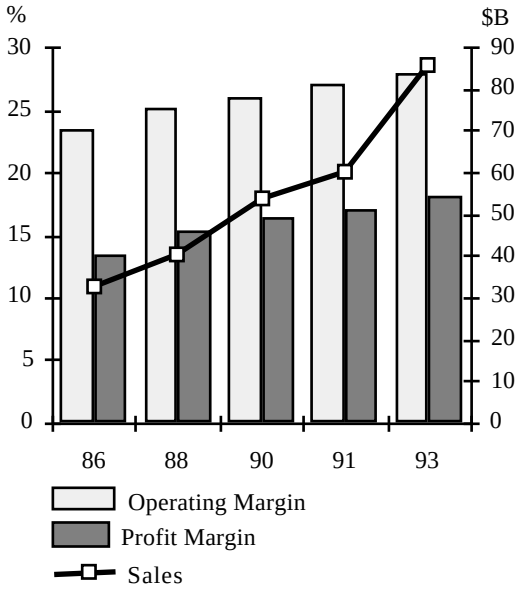


***Figure 4. US Pharmaceutical Industry Sales.***

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1 The US pharmaceuticals industry new investment budget was rated at $400 million for 1990.

2 Current CANDA experiences show that the average approval time of 28 months for the paper applications was cut down to 17 month with the computer assisted applications.

## Typical Grounds for Image Systems

The average research scientist spends almost two hours per day looking for the appropriate documentation. Since a scientist and his/her associated costs total approximately $200,000 per year, the cost for low productivity is of $40,000 per scientist. For a company of 600 scientists, the overall cost for low productivity would be of $24 million: an image system can reduce this time to less than 10 mn per day per scientist. The cost of an image system can be paid back in short order with increased productivity.

## Typical Office Automation Environment

The corporate side of business (e.g, accounting, legal) is often an IBM environment, while the clinical side (e.g. drug development) is primarily Digital. In addition Unix, PC or Macintosh workstations are used by the scientists, Hewlett-Packard systems are used for manufacturing and Wang systems for administrative functions.

The corporate MIS function has an annual budget in the range of $100 million of which the clinical budget for MIS represents over 50% (the manufacturing budget represents approximately 10%).

# Competitive Outlook

Many companies have developed a sales strategy for electronic CANDAs (Computer-Assisted New Drug Applications). Many of which are system integrators as shown in Table 2.

CANDA offerings follow one of two approaches: a ‘day zero’ or a ‘day n’ approach.

The ‘day zero’ approach manages the entire life cycle of a NDA dossier, from the first day of discovery research, until the day the regulatory affairs department submits it to the Government(s) for approval. A data repository is opened and made available throughout the contributing departments of the enterprise. The NDA dossier is created on-line and in real-time. In theory, this is the good global response for technical information management. However, this approach is very constraigning since it dictates the customer’s computing environment, imposes his working procedures and does not integrate his existing specialized applications nor his backlog data and documents. Further, the ‘day zero’ approach supposes that all partners have the same tools. Finally, this approach does not consider all the vital external information sources (e.g. specialized revues and bulletins) and databases (e.g. MEDLINE) which are frequently used by R&D staff.

I believe that ‘day zero’ CANDAs can only be supplied by the major computer manufacturers, of which Digital Equipment Corp.[1] is, probably, the only one which can win a significant market share.

The ‘day n’ approach appears as the most practical solution. The NDA dossier is compiled once the project is ready for submission to Regulatory Departments. While ‘day zero’ CANDA systems can be considered as data repository management systems which manipulate diverse data types including compound documents, ‘day n’ CANDA systems are real  and specialized imaging systems. Real systems because they offer the basic functionality of capturing, storing and retrieving mechanical and digital documents; specialized systems because they offer assembly and printing functions which allow to cut and paste all of parts of documents, and compile them into a NDA dossier.

I believe that Integrated Automation Corp. has a real and significant market opportunity: we have the base technology to build such systems, the approach that best suits customers who look for *partners* and *custom* systems and the opportunity, through RPR, to mature and stabilise a standard offering. The only major handicap might be that of sufficient credibility in a market where we still do not have any reference installations; but this handicap could be turned into an advantage by developping partnerships with companies, such as Interleaf, who have a complementary know-hows aznd a large installed base in the pharmaceutical industry.

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1 Digital Equipment Corp. packages a ‘day zero’ CANDA solution named *Computer-Integrated New-Drug Applications* (CINDA).

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|---|---|
| AGS Information Services | Grumman Data Systems |
| Andersen Consulting | Hewlett-Packard Co. |
| AT Kearny | IBM[1] Corp. |
| Cap Gemini | Laser Recording Systems |
| CIMI Corp. | LaserData, Inc. |
| Communications Network Architects Inc. | Plexus Software, Inc.[2] |
| Computer Task Group | Science Applications International Group |
| Coopers & Lybrand | Summit Software Corp. |
| Digital Equipment Corp. | TAB Products Co. |
| FileNet Corp. | ViewStar Corp. |
| | Wang Laboratories, Inc. |

***Table 2. The Competition Tenors.***

# Outline of a CANDA Offering

## Base Functionality

The functional requirements for a CANDA system can be classified in three categories:

◊ Standard imaging functions;
◊ Standard NDA assembly & printing functions,
◊ Custom document and data interchange functions.

Standard imaging functions

These are the vital functions that are always present:

◊ Document and data capture;
◊ Optical storage
◊ Information retrieval and display

Document and data capture must allow to capture mechanical and electronic documents. It is important to capture facsimile transmissions since they are intensively used and to be able to manipulate foreign files using both a native format and an interchange format (e.g. PostScript). It is equally important to provide automatic data recognition and processing through (e.g. optical mark sense, forms recognition, forms segmentation, and flexible data extraction, computer-aided key-entry and editing) since intensive indexing and bibliographic data is to be input into existing databases.

Optical storage must also encompass backup and security procedures including the possibility to share storage farms across several sites.

Information retrieval and display must offer standard imaging features and should include an annotation facility (revision control is not necessary). It should also be possible to automatically load the native format of foreign files when the correct environment is present.

Standard NDA assembly & printing functions

The NDA assembly and printing functions cover areas which require special application software. These are generic and applicable to all customers; they include:

◊ Document creation,
◊ Dossier definition
◊ Dossier assembly
◊ Dossier printing

Document creation is a word processing utility in which raster images can be pasted in order to create new documents which will be stored[3].

Dossier definition functions must allow to create NDA dossier outline templates indicating the topics which should be covered and their order. Such templates only deal with the logical structure of the dossier; there are no layout rules.

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1 IBM has a setup a special 'SolutionHouse' infrastructure called IBM Pharmaceutical Industries Group

2 Plexus Software, Inc. is not an actor as such in this market but is the prime supplier of imaging technology to Hewlett Packard Co. et Grumman Data Systems.

3 Interleaf is a perfect candidate. Tests conducted at MC2 have shown that it is possible to automate an interface with Interleaf to offer such a cut & paste solution for raster images.

Dossier assembly functions allow to manage the assembly of an NDA dossier according to a given template. The assembly consists in associating document references to each logical level of the template. The assembly must be able to support cross-referencing (though this could be accomodated by annotations). Workflow support is probably a necessity. Dossier printing involves the construction of a hard copy document with continuous page and paragraph numbering, date stamping and standard headers and footers.

Custom document and data interchange functions

Document and data interchange functions allow the seemless integration of the CANDA system in the existing automation environment. They are necessarily custom and allow to receive and send both documents and data.

## Base Technology

The above listed functionality relies on the following base technologies:

◊ High speed A3/A4 scanning;
◊ Group III facsimile capture;
◊ Postscript to Group IV conversion;
◊ Optical character recognition (Omnifont/handprint),
◊ Mark sense detection,
◊ Form and document segmentation,
◊ Multi-layered raster/text imaging,
◊ Workflow management,
◊ High speed A3/A4 printing.
… (not exhaustive)

SGML and DSSSL[1] are contenders to solve the assembly and printing problems. Their standard features allow in particular:

a) documents to be tagged to indicate their position in the dossier,
b) automatic renumbering of the dossier outline (volumes, parts, section, chapters, etc.)
c) definition of headers and footers,
d) automatic page numbering,
e) insertion of cross-references
f) insertion of (last minute) free-text
g) insertion of (encapsulated) foreign files.

We currently have no experience of SGML or DSSSL. This is the main issue (along with the sales strategy).

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|---|---|
| **Partie I** | **Résumé du dossier** |
| Partie I A | Renseignements administratifs |
| Partie I B | Résumé des caractéristiques du produit |
| Partie I C | Rapports d'experts |
| **Partie II** | **Documentation clinique, pharmaceutique et biologique** |
| Partie II A | Composition |
| Partie II B | Méthode de préparation |
| Partie II C | Contrôle des matières premières |
| Partie II D | Contrôle des produits intermédiares |
| Partie II E | Contrôle du produit fini |
| Partie II F | Stabilité |
| Partie II G | Autres informations |
| **Partie III** | **Documentation toxicologique et pharmacologique** |
| Partie III A | Toxicité par administration unique |
| Partie III B | Toxicité par administration réitérée |
| Partie III C | Etudes de reproduction |
| Partie III D | Potentiel mutagène |
| Partie III E | Potentiel carcinogène/oncogène |
| Partie III F | Pharmacodynamie |
| Partie III G | Pharmacocinétique |
| Partie III H | Tolérance locale |
| Partie III Q | Autres informations |
| **Partie IV** | **Documentation clinique** |
| Partie IV A | Pharmacologie humaine |
| Partie IV B | Documentation clinique |
| Partie IV Q | Autres informations |
| **Partie V** | **Renseignements particuliers** |
| Partie V A | Présentation |

[1] DSSSL is not yet a standard but can be considered as a *final draft*.

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| Partie V B | Echantillons |
| Partie V C | Autorisation(s) de fabrication |
| Partie V D | Autorisation(s) de mise sur le marché |
| Partie V E | Déclaration d'expertise ou dispense |
| Partie V F | Fiche destinée aux centres régionaux de pharmacovigilance et aux centres antipoisons |

***Figure 5. Top level outline of a NDA dossier for the European Economic Community.***

## Conclusion

I firmly believe we can adopt a Docuvision III-like approach and deliver Docuvision CANDA. The main technical issue is the SGML/DSSSL integration on which I would like to work. Further, 15 man/days are sufficient to deliver a draft sales kit composed of:

- ◊ an offering description
- ◊ a template study and solution proposal,
- ◊ a module and component catalog (à la DV III).

In parallel Sales & Marketing should concentrate on:

- ◊ the decision process (steps, actors, time scale and purchase influencing factors),
- ◊ the purchase motivations (tied to the industry and the offering),
- ◊ the marketing strategy (technical/symbolic value, level of innovation/development, price magnitude)

As might appear in this document, I am highly motivated by this topic and have been since the end of last year when I finally and clearly understood the problem RPR is tackling. This was early November 1991; date at which RPR told us that, if they did the system, they would do it with us (we've heard a lot of that recently!). Since then the account has practicaly been abandonned and I have seen no prospection (at least on the Old Continent) for new pharmaceutical accounts. Hence the problem is not that the market is already saturated, nor that we don't have sufficient credibility, nor that we don't have an offering, etc.…it simply is that we have no marketing strategy and have not identified the sales effort we are willing to place on this market opportunity. I sincerely hope that this small contribution will help make things change.