

*CambridgeSoft Solutions*

# Implementing an Enterprise E-Notebook

## Lessons & Legal Aspects

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**Desktop Software  
Enterprise Solutions**

**Research & Discovery  
Applied Bioinformatics**

**Knowledge Management  
Chemical Databases**

**CambridgeSoft**  
Life Science Enterprise Solutions

# *Issues Facing Discovery Organizations*

- **Recording Data Electronically**
- **Managing Individual Research Data**
- **Sharing Data Between Researchers**
- **Retrieving Information Rapidly**
- **Handling Large Quantities of Screening Data**
- **Recognizing Uniqueness**
- **Locating/Tracking Products/Supplies**
- **Ordering Reagents for Timely Delivery**
- **Coordinating Efforts of Different Groups**
- **Rapidly Expanding Workforces**
- **Increasing Role of Outsourcing and Collaboration**
- **Maintaining Adequate Security**

# *Outline*

- **CambridgeSoft Introduction**
- **E-Notebooks Defined**
- **Adoption and ROI**
- **Legal Framework**
- **Case Studies**
- **Conclusion(s)**

# **CambridgeSoft Company Profile**

- **Established 1986**
- **Headquarter in Cambridge, MA**
  - Worldwide sales and services offices
- **\$20M in annual revenue with consistent annual growth in software sales and services**
- **Leading Provider of Scientific Software**
  - > 250,000 product licenses in use globally
- **100+ employees in US, Europe & Japan**
  - 10% of employees based in Europe (and rising)



# *The CambridgeSoft Mission*

- **Make scientists more productive by giving them the best tools possible for generating, analyzing, using and communicating scientific information.**

# Selected Customers

## PHARMACEUTICAL



## BIOTECHNOLOGY



## CHEMICALS



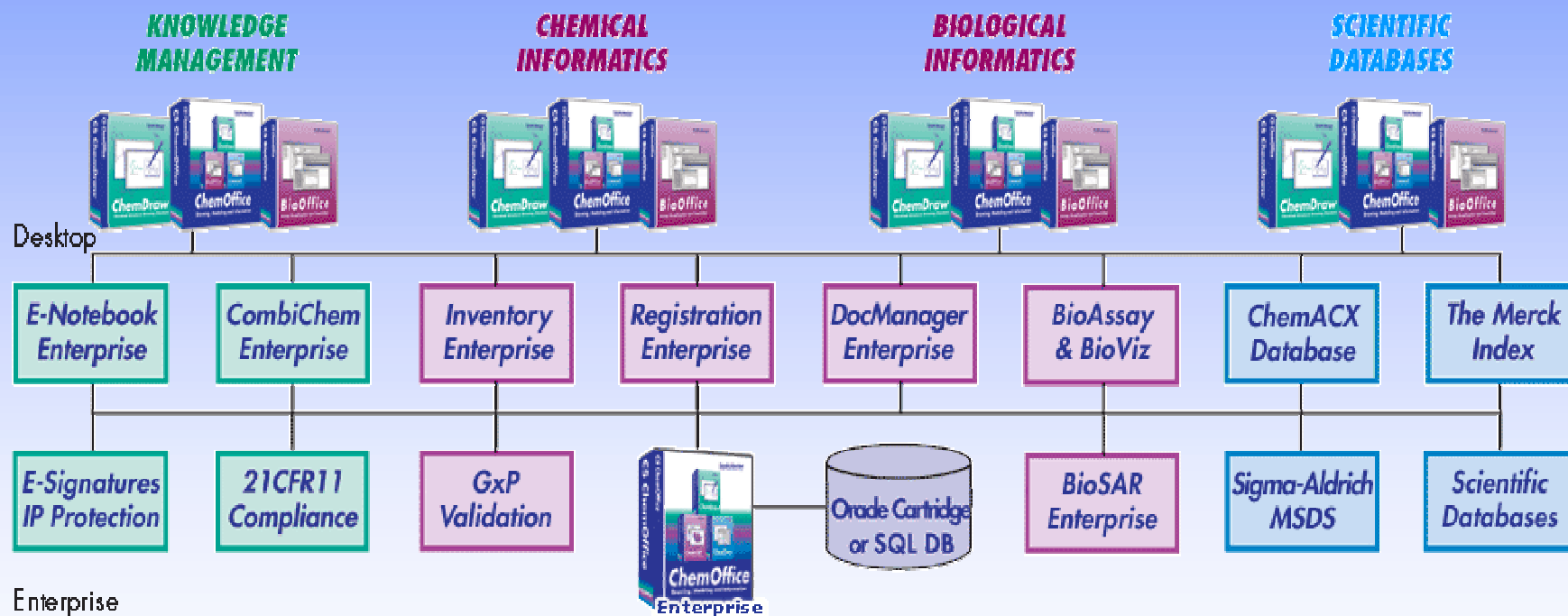
**CambridgeSoft**

# *System Architecture*

- **Web-based applications where ease of distribution is key**
- **Thick-client, 3-tier applications where local processing speed is important**
- **Full middle-tier API's via web services for automation and integration**
- **Fully audit-trailed Oracle database back-end**
- **GmP validated and 21CFR Part 11/37CFR compliant**
  - Including e-Signatures for all IP and regulatory records

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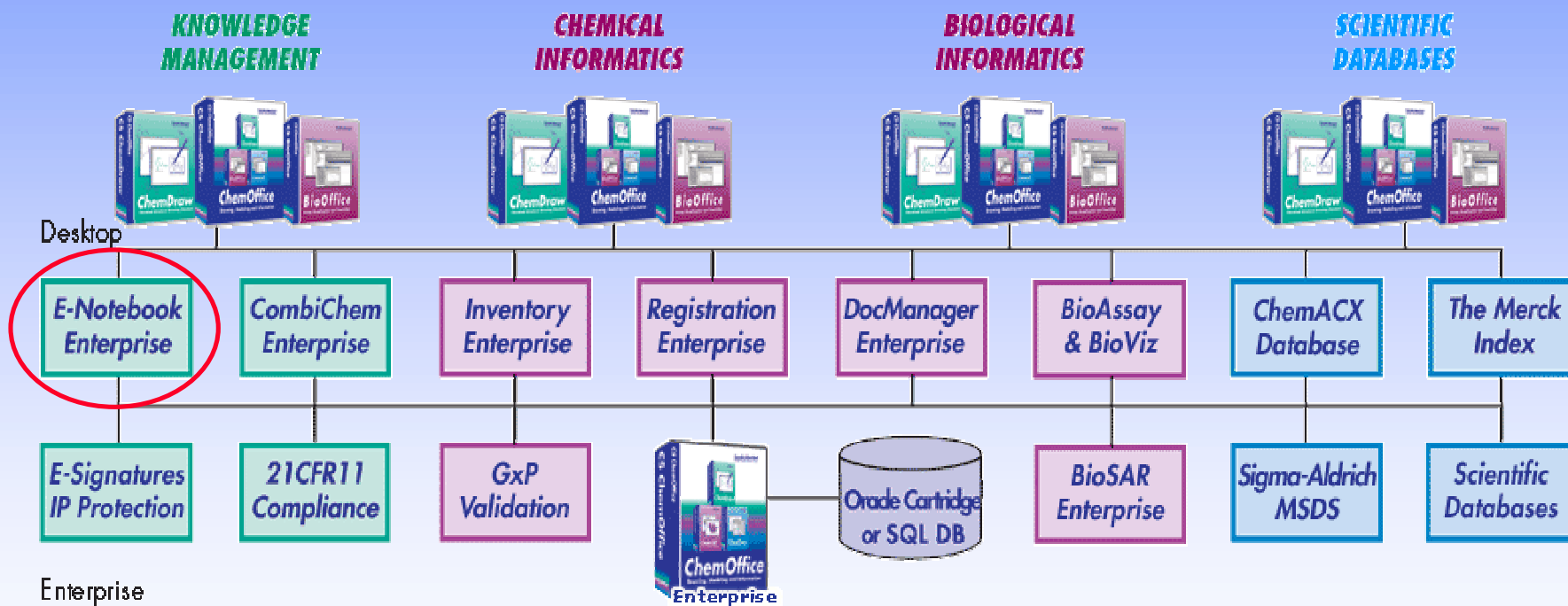
## *Integrated Desktop to Enterprise Solutions & Databases*





# CambridgeSoft

## *Integrated Desktop to Enterprise Solutions & Databases*





# **E-Notebook Overview**

*Desktop Software  
Enterprise Solutions*

*Research & Discovery  
Applied Bioinformatics*

*Knowledge Management  
Chemical Databases*

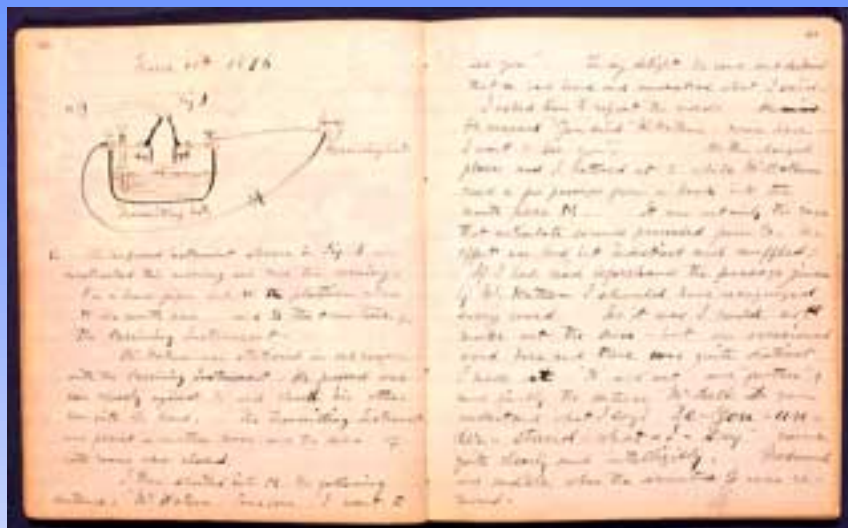
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# *E-Notebook Definition*

## What is an E-Notebook?

- A. Simple, yet complete replacement for traditional paper Laboratory Notebook**
- B. Knowledge Management system for capturing and enabling re-use of IP and know-how**
- C. Complete laboratory workflow support system**
- D. All of the above?**

# Paper Notebook



Jan 22 1979 135

The reaction scheme shows a complex bicyclic carbamate derivative reacting with  $CF_3SO_3H$  to form a bicyclic amine derivative. The starting material has a carbamate group and a hydroxyl group. The product has a secondary amine group and a hydroxyl group.

KCR-7-134-3

~60 mg of the carbamate was dissolved in ~1.0 ml of  $CF_3SO_3H$  in an NMR tube. Given the NMR spectrum were very broad and it was difficult to observe the two diastereoisomers in the NMR. About half the carbamate was gelled in the NMR tube and half left to stir overnight at room temp. The NMR tube was heated at ~40° for 30 min and TLC after acid base workup showed TLC #1. Material that stood O.N. showed TLC #2. The major spot was the same in  $Et_2O$ , 20/10/1 and  $EtOAc$ /hexane as silica. IR, NMR & MS were taken in the major spot after purification by prep TLC. These were essentially identical with material purified from dihydrothebaine from p. 137.

KCR-7-135-1

major spot

← KCR-7-135-1 dihydrothebaine

← TLC #2

← IR

← from dihydrothebaine see p. 137

← TLC #1

# Electronic Notebook

The screenshot displays the CS Notebook software interface. The main window shows a chemical reaction scheme for the synthesis of N-isopropyl-2-(N-isopropylisopropionamide)-3-methylbutanamide. The reaction involves the following reagents: propionic acid, isobutylamine, isobutyraldehyde, and isobutyronitrile.

Below the reaction scheme, there are two tables: 'Reactants & Products' and 'Product'.

Reactant	MF	Unit?	MW	Eq	Units	Sample Mass	Vol	Molarity	d	% wt	FM	Reactant Mass
1 propionic acid	C3H6O2	<input checked="" type="checkbox"/>	74.08	1.000	28 mmol	1.462 g	1.347 ml		1.1 g/ml		74.08	1.462 g
2 propan-2-amine	C3H9N	<input type="checkbox"/>	59.11	1.000	28.00 mmol	1.662 g	1.391 ml		0.85 g/ml		59.11	1.662 g
3 isobutyraldehyde	C4H8O	<input type="checkbox"/>	72.11	1.000	28.00 mmol	19.08 ml		1.25 molar			72.11	1.442 g
4 isobutyronitrile	C4H7N	<input type="checkbox"/>	69.11	1.000	28.00 mmol	1.302 g	2.128 ml		0.65 g/ml		69.11	1.302 g

Product	MF	Actual Mass	Actual Mol	Yield	Purity	MW	Eq	Theo Mol	Theo Mass	FM
1 N-isopropyl-2-(N-isopropylisopropionamide)-3-methylbutanamide	C14H25NO2	4.8 g	19.73 mmol	64 %	98 %	258.36	1.000	20.00 mmol	5.13 g	258.36

The 'Product' table also includes a section for 'Solvent' with the following data:

Solvent	Mol	Volume
1 DMF	1.000	1.838 ml
2 DMSO	1.000	1.838 ml

Below the tables, there is a 'Notes' section with the following text:

In a 400 mL round-bottomed flask, propan-2-amine (1.391 ml, 28.00 mmol) and isobutyraldehyde (19.08 ml, 28.00 mmol) were dissolved in DMSO (1.838 ml) and DMF (1.838 ml) to give a solution.

Then isobutyronitrile (1.302 ml, 28.00 mmol) was added and the reaction mixture stirred and refluxed for 3 hours.

Finally propionic acid (1.347 ml, 28 mmol) was added to give a final solution, which was refluxed for 1 hour and then separated as a standard HPLC column to give N-isopropyl-2-(N-isopropylisopropionamide)-3-methylbutanamide (4.8 g, 19.73 mmol, 64 % yield).

# Benefits for IP Management

**Better quality of evidence:  
more legible, durable**

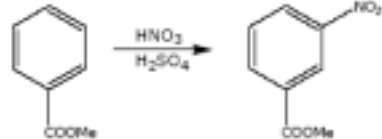
**Improved compliance  
make it easier, and enable  
management monitoring**

**More accessible data  
reduce time to gather  
relevant data for patent  
submission and litigation**

File: SOP-01-001  
Date: 23/07/2004

Created: SUNCO, February 25, 2004 11:01 AM PST -0800  
Printed: SUNCO, February 25, 2004 11:02 AM PST -0800  
Status: Open

### Reaction



**Reaction Properties:**  
Temperature: 15 °C

**Reactants:**

Name	Wt	Limit	Sample Rate	SNV	Vol (mmol)	Eq	M (molar)	Vol (ml)	D (g/ml)
1. Nitric Acid	HNO3	100	100	136.128	125	1.30			
2. Nitric Acid	HNO3	NO	175	65.913	1000	1.31	39.68	125	1.42
3. Sulfuric Acid	H2SO4	NO	100	98.079	1000	1.37		125	1.84

**Products:**

Name	Wt	Theo Mass (g)	Actual Mass (g)	Yield	Purity	SNV	Actual Vol (mmol)	Eq
1. Methyl m-nitrobenzoate	C8H7NO4	271	230	84.7%	100.0%	181.145	1270	1.00

**Preparation:**  
Into a 2-l. round-bottomed flask fitted with a mechanical stirrer are placed 400 cc. of concentrated sulfuric acid cooled to 0° and 204 g. (1.5 moles) of pure methyl benzoate. The mixture is cooled by means of an ice bath to 0–10° and then, with stirring, there is added gradually, by means of a dropping funnel, a mixture of 125 cc. (1.96 moles) of concentrated nitric acid (sp. gr. 1.42) and 125 cc. of concentrated sulfuric acid. During the addition of the nitrating acid, which requires about one hour, the temperature of the reaction mixture should be kept within the range 5–15°.

After the nitric acid has been added, stirring is continued for fifteen minutes longer; the mixture is then poured upon 1500 g. of cracked ice. The crude methyl m-nitrobenzoate separates as a solid and is filtered off by means of suction and washed with water. The product is placed in a flask and agitated with 200 cc. of ice-cold methyl alcohol in order to remove a small amount of o-nitrobenzoic ester and other impurities that are present. The cooled mixture is then filtered by means of suction, washed with another 100-cc. portion of cold methyl alcohol, and the solid dried. The yield is 220–230 g. (81–85 per cent of the theoretical amount) of an almost colorless product melting at 74–76°. In order to obtain a product of maximum purity, which melts at 78°, it is advisable to recrystallize the ester from an equal weight of methyl alcohol.



# E-Notebook vs. P-Notebook

- **Paper Notebook is:**
  - Familiar
  - Portable
  - Flexible
  - Accepted for IP purposes
- **E- Notebook is:**
  - Shareable
  - Able to automate repetitive processes
  - Searchable
  - Flexible
  - Accepted for IP purposes
- **Paper Notebook is not:**
  - Searchable
  - Able to automate repetitive processes
  - Shareable
- **E- Notebook is not:**
  - Familiar to all
  - Quite so portable\*

\* Offline facility provides improved portability

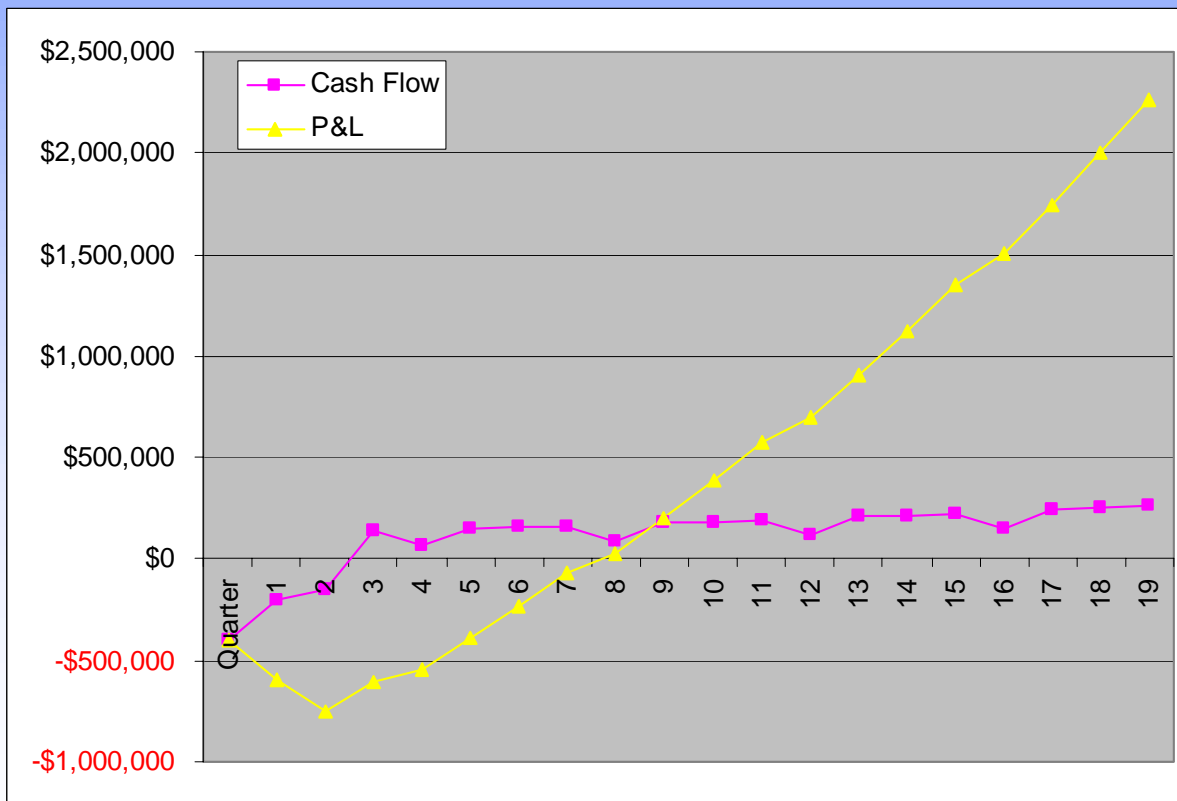
# ***ELN Justifications***

- **“Can’t afford not to”**
  - Failure to protect IP correctly could finish a company
  - Regulatory compliance is critical for market success
- **Cost Savings**
  - Eliminate duplication of experiments
  - The “paperless” laboratory
- **Productivity enhancement**
  - Errors reduced & time saved by removing duplication of data entry
  - Time saved by automation of processes
  - Children at nursery school should be cutting out and sticking in; scientists should be doing science
  - Potential to remove large percentage of the human witnessing requirements
- **Knowledge source**
  - Future-looking investment in building rich knowledge store
  - Value of retroactive loading of paper notebook contents?
- **Collaborative tool**
  - ELN can replace PowerPoint/acetates in project meetings
  - Reduce risk of duplicate experiments in different labs
  - Great way to share research data between labs, locations and external collaborators



# Direct ROI Example

- Based on averaged data from 3 companies
  - DIRECT savings = 10% of OVERHEADS from Q3 onwards
  - Based on reduction in consumables through elimination of duplicate experiments



**Payback is  
c. 2 years**

**Investment  
is \$750k in  
Year 1**

**5 Year NPV  
= \$1.5m**

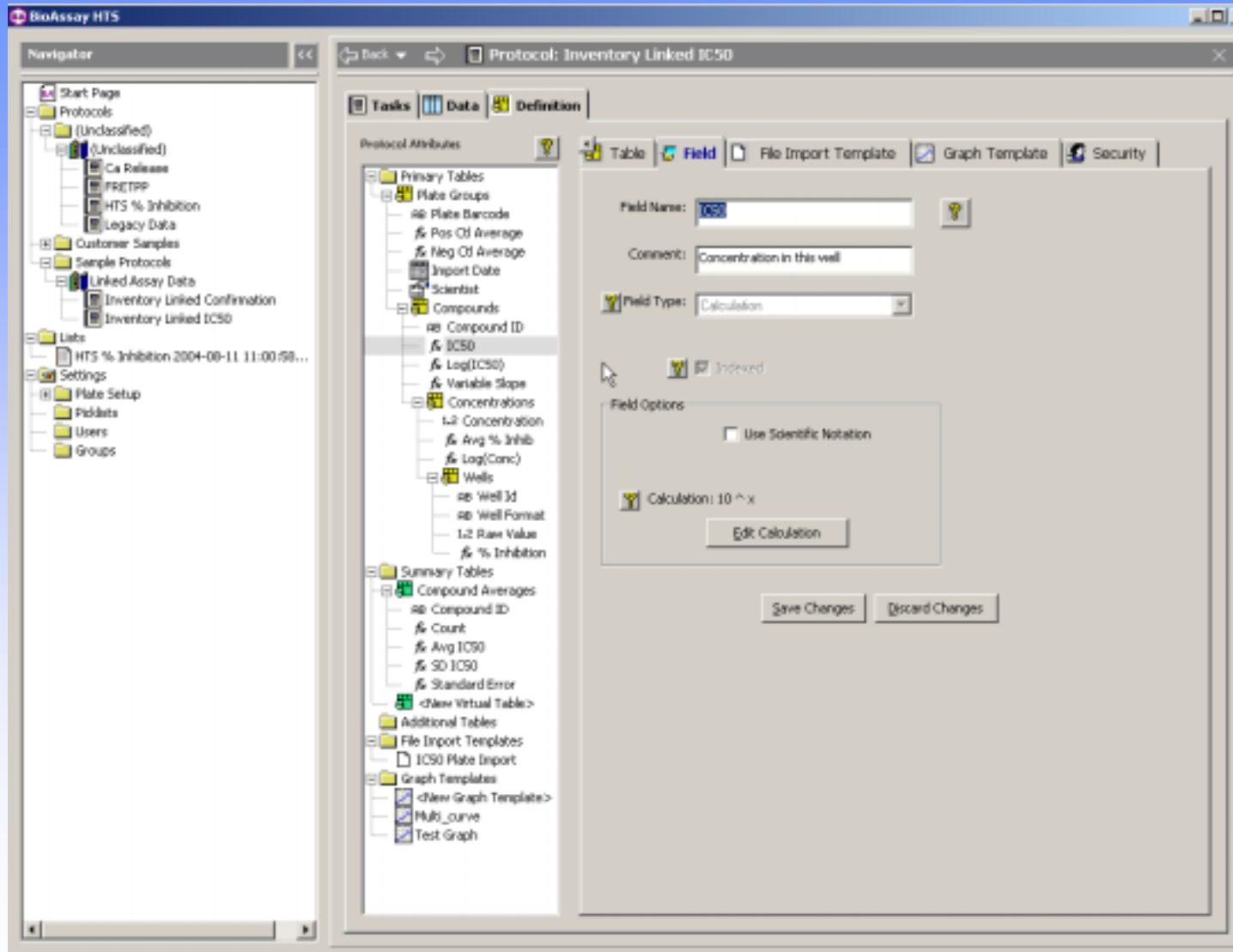
# *E-Notebook Summary*

- **Captures all IP-related information in a consistent and controlled manner**
  - Biology, Chemistry, etc.
- **Provides flexible and configurable system across multiple disciplines and geographies**
  - Configurable security and access rights
  - Configurable data forms
- **Framework for supporting complex experiment lifecycles and workflows**
  - Communication between groups
  - Services requests
  - Collaboration tools

# *Multi-disciplinary ELN*

- **ELN's are not just for Chemistry, and not just for Discovery**
- **Biology**
- **Analytical Chemistry**
- **Process Research and Manufacturing**

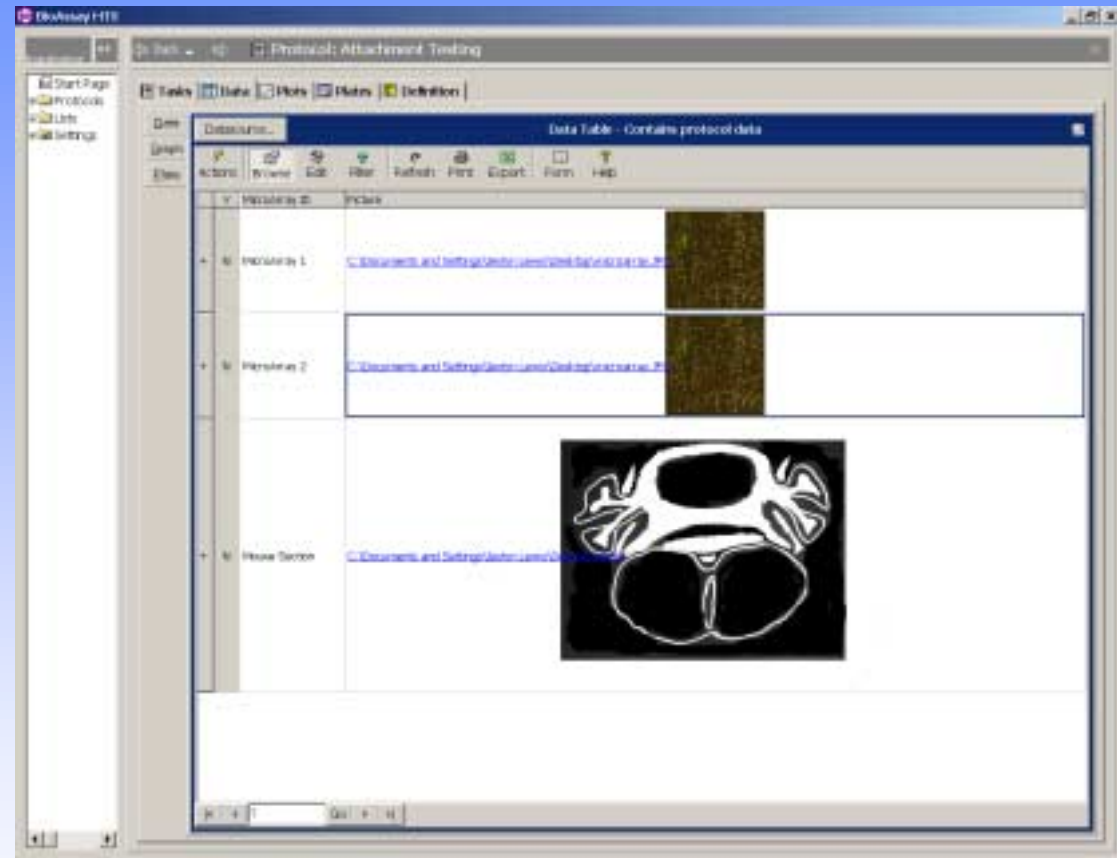
# Biological Assays: Flexible model definition.



# High-Content / Low-Throughput Screening

Store documents and images:

- Protocol definitions
- High-content assay images
- Raw data files





**Legal and  
Regulatory  
Aspects**

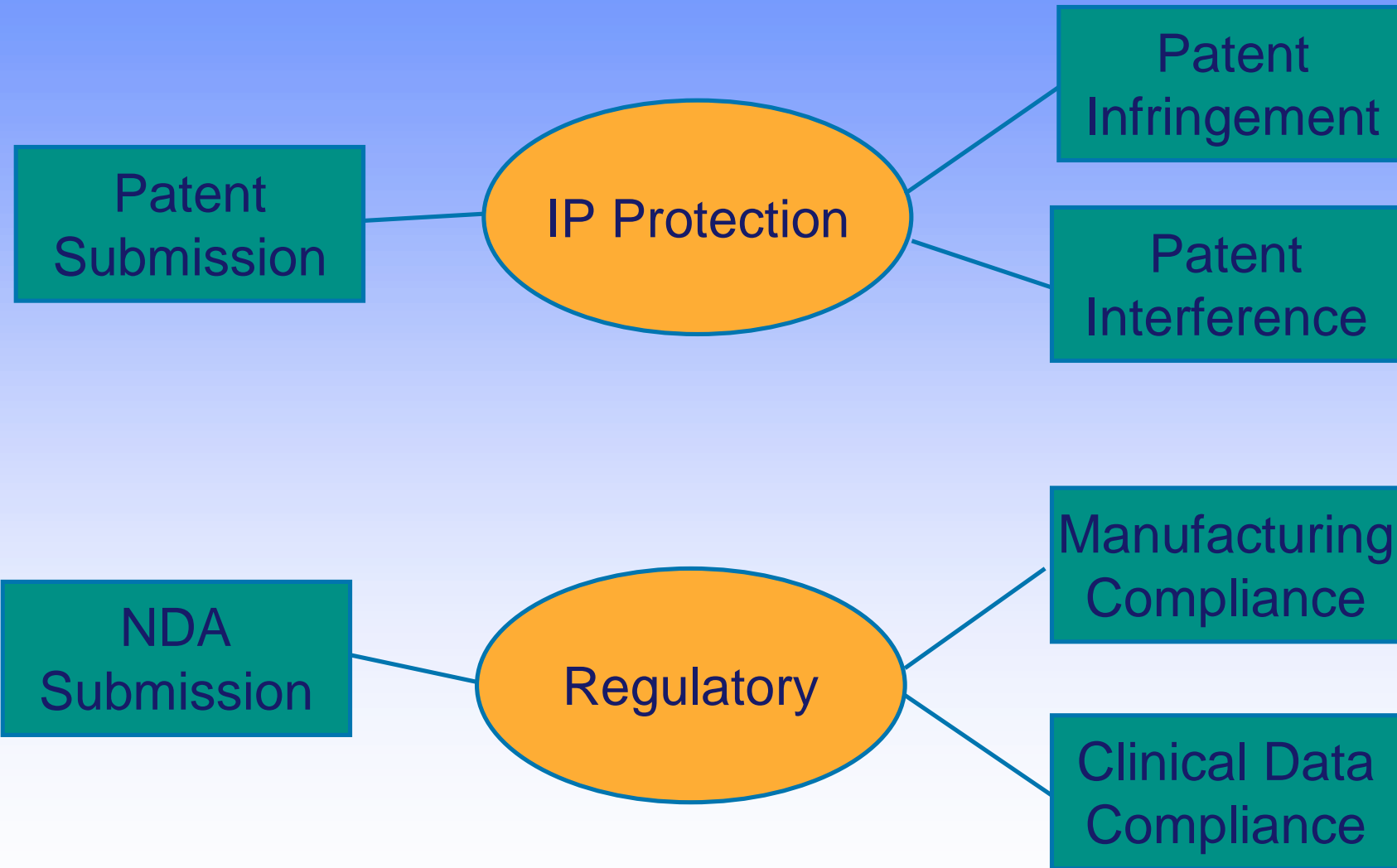
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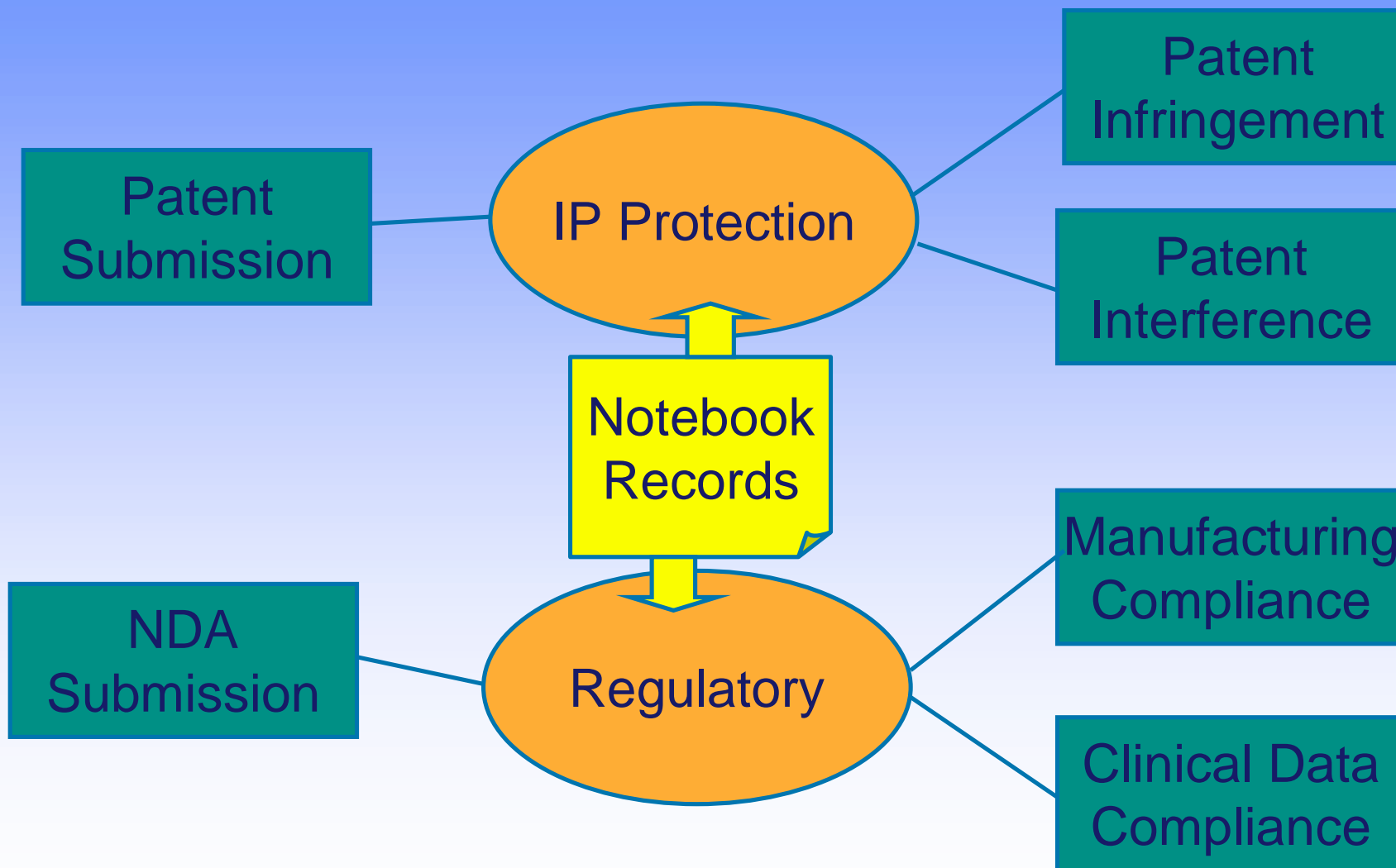
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# Legal Issues – What's at Stake?



# Legal Issues – What's at Stake?





# ***Legal Issues***

## ***Patent Submission***

- **37 CFR - Patent Submission Rules – electronic records acceptable as long as they comply with appropriate format requirements**
- **Recent rulings (Sept 2004) confirmed that electronic records will be accorded the same weight as paper records in interference cases**

# Legal Issues

## Patent Interference and Infringement

- **Are E-Notebook records admissible as evidence or are they “Hearsay”**
- **Federal Rules of Evidence – Business Records Exemption Fed. R. Evid. 803(6)**
  - **Records of regularly conducted activity.** A memorandum, report, record, or data compilation, **in any form**, of acts, events, conditions, opinions, or diagnoses, made at or near the time by, or from information transmitted by, a person with knowledge, if kept in the course of a regularly conducted business activity, and if it was the regular practice of that business activity to make the memorandum, report, record, or data compilation, all as shown by the testimony of the custodian or other qualified witness, unless the source of information or the method or circumstances of preparation indicate lack of trustworthiness. The term "business" as used in this paragraph includes business, institution, association, profession, occupation, and calling of every kind, whether or not conducted for profit.

# ***Legal Issues***

## ***Best Evidence Rule***

- **The Federal Rules of Evidence state that**
  - **If data are stored in a computer or similar device, any printout or other output readable by sight, shown to reflect the data accurately, is an "original". Fed. R. Evid. 1001(3).**
- **An accurate printout of computer data always satisfies the best evidence rule.**

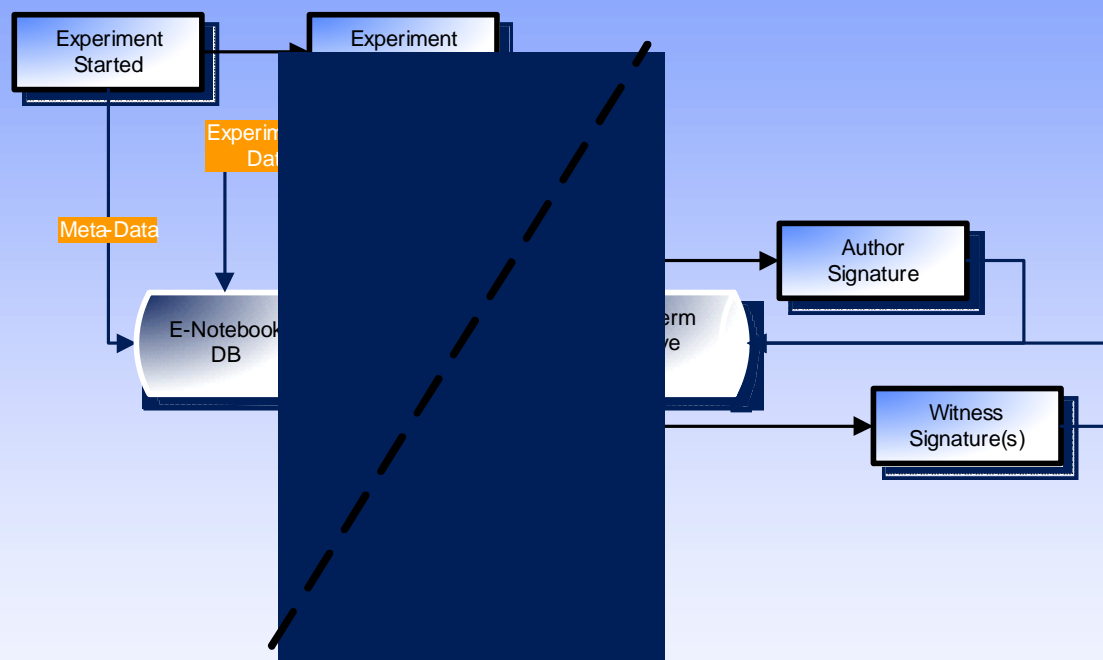
# ***Legal Issues***

## ***Chains of Evidence & Corroboration***

- **The most important aspects of admitting E-Notebook records as evidence is then:**
  - Records are kept as a normal part of business practice – makes them admissible under FRE exceptions
  - Records are properly managed and archived – e-Record Retention Policy, etc.
- **Corroborating evidence provides basis for veracity of paper and electronic notebooks**
  - Chronology of concept → reduction to practice
  - Supporting evidence of experiments carried out as a direct result of this invention/discovery

# Legal Issues

## e-Record Management



Clear distinction between the Authoring of the e-Records  
and their storage/archiving

# *Legal Issues*

## *Formats and IT questions*

- **“Best Practice” today suggests that PDF is an appropriate format for long-term archiving of e-Records**
- **PDF/Archive moving forwards (ISO 19005-1 finalised as of September 2005, work started on ISO 19005-2) as a better current choice**
- **SVG may provide a more “Open” alternative longer term**
- **Key point is that records are kept in a form which is independent of the authoring application and which represents best practice at the time of implementation**

# ***Legal Issues***

## ***Where's the Test Case***

- **A simple numeric analysis shows that a true “Test Case” in the common meaning is unlikely to arise**
  - Very few Patent Interferences and Litigations arise each year
  - 95% of them are settled pre-trial
  - Of the remainder the basis of evidence being an E-Notebook vs. a Paper Notebook is unlikely to be the sole issue
- **There are relevant rulings in other fields...**

# Legal Issues

## *In Re Scott T Jolley – Fed. Cir. 2002*

- **Lubrizol initially granted Patent on new HFC compatible lubricants**
- **Dow granted interference based on prior art (May 20<sup>th</sup> 1988 vs June 2<sup>nd</sup> 1988)**
- **Appeal by Lubrizol denied on basis of email between co-inventors**

The Board in this case found that such a disclosure could be found in an e-mail sent by Ward to co-inventor McGraw and several other Dow employees on May 20, 1988. This e-mail stated:

I suggest that we thoroughly evaluate the possibility of blends of polyglycols with esters as lubricants for refrigerants such as R-134A, even if we discover some specific polyglycol or polyglycol derivatives that work well. If we can show that polyglycol/ester blends exhibit some improvement over a pure polyglycol basestock, we could end up with defacto patent coverage on the basis of our two compressor lubricant patents, which, as you know, each have composition of matter claims separate from the use claims as compressor lubricants.

Due to the present research activities of companies like Union Carbide, ICI, Allied, and DuPont, "generic" patent disclosures on the use of polyglycols for this application have probably already been filed. If polyglycol/ester blends really work better in this application, we could really pull off a coup de grace.

It is undisputed that "our two compressor lubricant patents" referred to two patents assigned to Dow, U.S. Patent No. 4,302,343 to Carswell and McGraw ("Carswell '343") and U.S. Patent No. 4,751,012 to Ward, McGraw, and Appleman ("Ward '012"). Both Carswell '343 and Ward '012 disclose and claim polyglycol/ester blends as lubricants for air compressors. Although the esters disclosed by Ward '012



# *Regulatory Issues*

- **FDA remit is to increase the number of submissions made electronically**
- **Use of accredited User Authentication technology (e.g. SAFE-compliant Smart Card) and 3<sup>rd</sup>-party time stamps**
- **Electronic systems make the process of submission and the process of compliance easier...**
- **...but that is not without cost**



**Case Studies**

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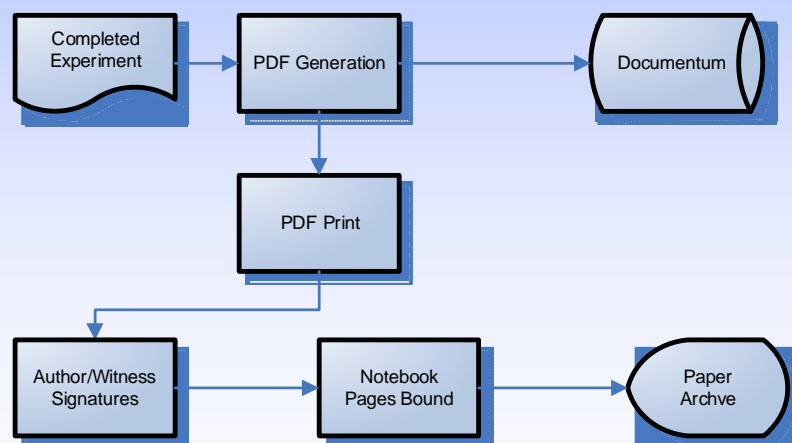
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# ***Case Study - 1***

- **'Top 5' Major Pharma**
- **Deployment to 2,500 scientists globally across whole of R&D**
- **User authentication using SAFE**
- **Fully electronic – no paper anywhere in the system**
- **Senior IP Counsel was key driver for ELN decision**
  - **Past experience with unreliable access to paper notebooks**
  - **Signing/witnessing SOP compliance**
- **LTA is PDF with SAFE-compliant e-Signature**
  - **2-tier system using CambridgeSoft for signing/witnessing workflow and “near-line” storage, Documentum for offline**

## Case Study - 2

- 'Top 5' Major Pharma
- Deployment to 500 scientists globally across Discovery and Development Chemistry
  - Target is to roll out application to all 7,500 scientists across entire organisation
- Hybrid system – e-Records created as PDF
  - PDF is printed to “E-Notebook Paper”
  - PDF also routed to Documentum for storage
- Long-term desire to move to fully electronic
  - Legal situation was less clear at time of deployment decision
  - Business benefits significant enough to warrant a hybrid short-term approach





# Summary and Conclusions

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# Conclusion

- E-Notebooks and their associated Electronic Records can be used for both FDA submission and Patent Purposes
- BUT, there has to be a strong set of IT systems, procedures and rules surrounding the generation, management and storage of these records
- *“The Pharmaceutical Industry is in many ways behind the curve with respect to where the judges, courts and federal regulators have moved forwards with electronic records vs. paper records”* – Kristin H. Neuman – Proskauer Rose LLC

## ***Conclusion - 2***

- **The implementation of an Electronic Notebook system needs to be done in light of the general business practices and particularly in relation to adequate processes for e-Record retention**
- **The benefits of an E-Notebook system are clear and strong – the commonest reason for not implementing, that “they are not legal” is no longer true**
- **Because of the timescales and issues involved though, this is still an emerging market and growth is unlikely to be explosive**



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*Thank You For Your  
Attention*

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