

The Emerging Role of Translational Science as Part of a Model Based Drug Development Paradigm: Building an Infrastructure for the Future

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Presentation Topics for Today

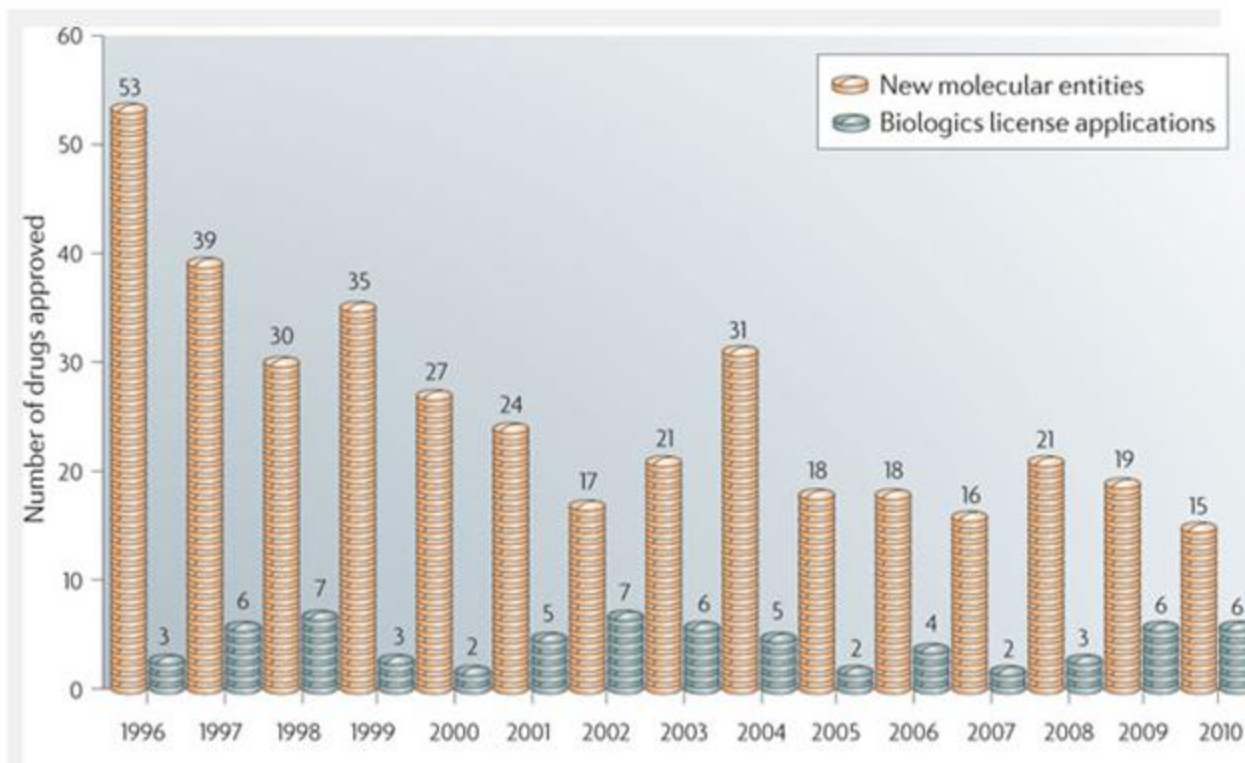
1. Background - The business case for model based drug development
2. Translational Science
3. Criteria for a successful informatics infrastructure
4. Implementation Issues and conclusions



Only 21 New Drugs Were Approved by the FDA in 2010, and Only A Few of These Were First in Class or Represented A Significant Therapeutic Advance

“The US Food and Drug Administration’s (FDA’s) Center for Drug Evaluation and Research (CDER) approved 15 new molecular entities and 6 new biologics in 2010. The total of 21 new products falls below the 25 approved in 2009 and the 24 in 2008.”

Here’s a graphic of the overall trend since 1996:



Only 1 in 10,000+ molecules gets approved, and of that small percentage, only 30% of drugs that are approved have a positive ROI

Ref: Mullard , A. (2011) Nature Reviews Drug Discovery, 10(2)



The Lack of Consistent Success is Adversely Affecting Pharmaceutical Stock Prices

Pharmaceutical Index (^DRG)

This capitalization-weighted index is designed to represent a cross-section of widely held, highly capitalized companies involved in various phases of the pharmaceutical industry.





Companies are Trying to Cope In Part By Raising Prices

Home U.S. World Politics **Business** Sports Entertainment Health Tech

U.S. business on msnbc.com

U.S. branded drug prices soar as generic pressure rises

Pharmaceutical industry nervously eyeing the future of healthcare reform

Latest market data x
 DJIA ↓ -28.91

Below: Discussion Related Tweet 6 Recommend 2



MEL EVANS / AP

Forty-milligram tablets of Lipitor are shown. According to MarketScan, payments for Pfizer's cholesterol drug rose 11.4 percent last year, compared with 5 percent annually from 2005 to 2010.

By Deena Beasley
 REUTERS



But Price Controls Will Eventually Occur in the U.S.

FiercePharma

Published on FiercePharma (<http://www.fiercepharma.com>)

MedPAC: Are new drugs worth higher prices?

By tracy

Created Jun 16 2009 - 10:18am

Here's a hint at how drug prices might suffer even in advance of actual comparative effectiveness research. Call it 'no better until proven better' or 'no costlier unless proven worth it.' The Medicare Payment Advisory Commission is suggesting that reimbursement for new drugs should be set at the same rate as older meds unless drugmakers have evidence proving that the new meds are more effective than the old ones.



A Perfect Storm ...

Source: BioIT World

By Bill Frezza

June 29, 2009 | If ever there was an industry at risk of being sunk by not one but three hurricanes, it's the pharmaceutical industry. Whether it's on the political, economic, or scientific front, this major contributor to our nation's financial and physical well being is headed for wrenching transformations.

Politically, Big Pharma is at the mercy of all three branches of an increasingly hostile government. The executive branch, through its regulatory agencies, has raised the cost of product development to astronomical heights. The judicial branch, through its class action machinery, has made the penalty for delivering anything short of zero-defects untenable. And the legislative branch, on its way to becoming the industry's monopsony purchasing agent, is hell bent to drive prices down to the marginal cost of production.



When Profits Go Down ...

1. There are three basic ways to address this
2. Mergers and acquisitions - e.g., Pfizer (Wyeth), Merck (Schering Plough, many others). These are rarely synergistic and “value” comes from eliminating redundant expenses. By most measures while having some short term positive impact they never really add value to the organization long term
3. Reduce costs (e.g. Pfizer most recent closing of their Sandwich site and other expense cuts)
4. Increase revenues via increasing productivity in R&D

My premise is the industry has focused on improving profitability via #'s 1 and 2 above, with limited or no success. It's time to address #3.



A Major Problem is that "Bad" Drugs Need to Fail Sooner

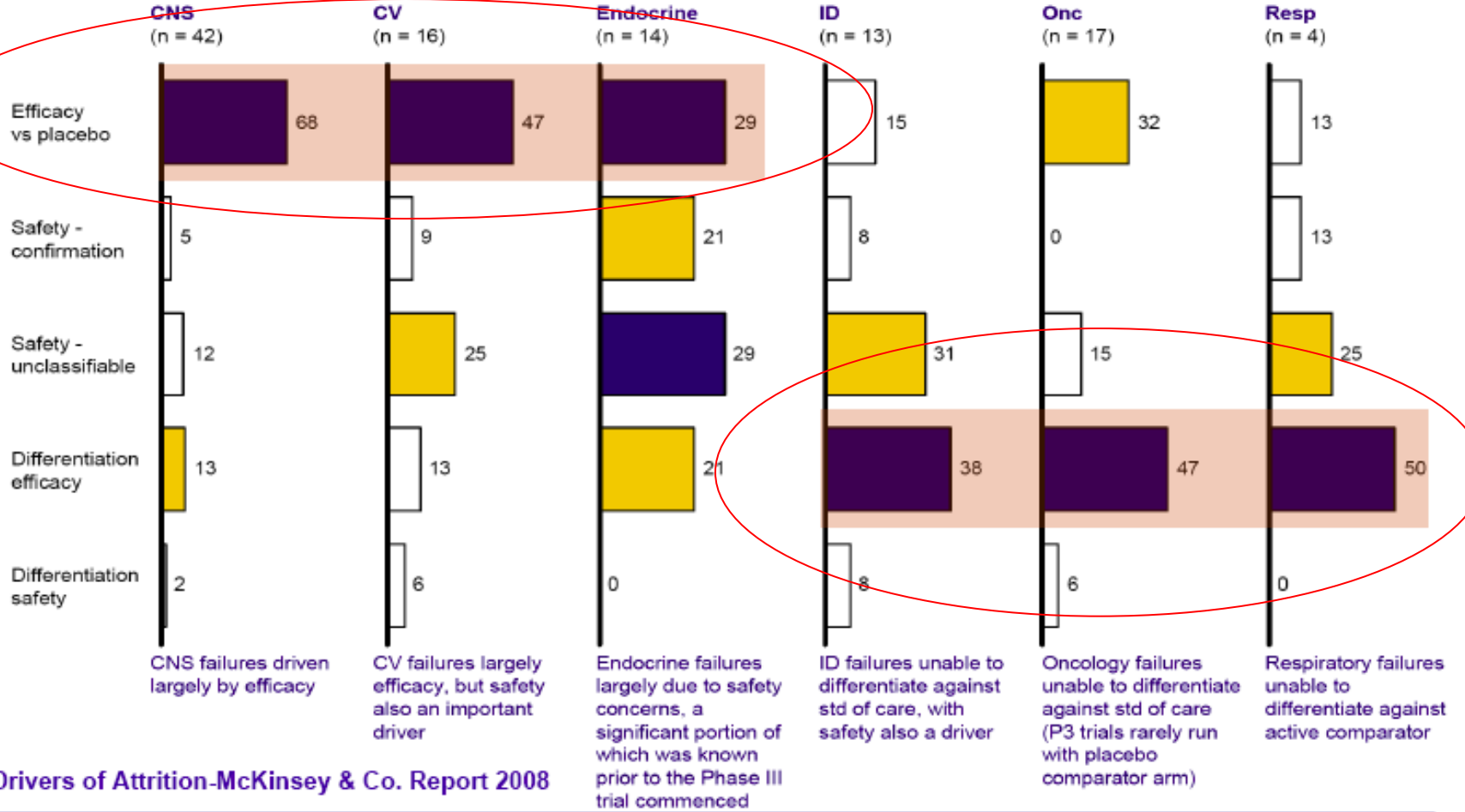
Failure rate is **50%** in phase 3 for drugs completing phase 2B

Failure to demonstrate efficacy is a leading reason for phase III attrition

Presented at Kitasato-Harvard Conference, Sept. 2008

Phase III failures 1990 – 2007
Percent

■ Primary driver
■ Secondary driver



Drivers of Attrition-McKinsey & Co. Report 2008



The Prior Slides Beg the Question...

Why are these drugs failing so late in development (as opposed to earlier in development)?

Are these (late stage) failures occurring because of

- Poor formulations?
- Unexpected toxicity?
- Unacceptable benefit/risk ratio?
- Inability to determine an optimal dose or regimen?
- Other?

What can be done to make better decisions earlier?



Comments on Historical Approaches

Challenges

- What Biomarkers could have predicted efficacy and safety issues earlier?
 - Can we learn this from current experiments?
- What are the population variables with this therapeutic issue?
 - Safety, Efficacy, Dosing regimen
 - Which clinical trial population? which target market?
- Why are we failing late stage compounds for the same reasons over and again?
 - Why can't late stage development benefit from early phase knowledge?
 - Why can't early stage research benefit from late stage knowledge

We Need a Strong Data Sharing,
Collaborative Mechanism to Address These
Issues



Motivation for Change

The current Pharma model, which is fraught with increasing costs year on year while approvals are declining, is not sustainable.

Consensus: Companies need to develop better lead candidates (molecules) while at the same time reducing the risk of developing them.

To achieve this goal companies need to better utilize and manage information across all phases of drug development.

Collaboration and sharing of information to make better decisions is the key.

We Need a Strong Data Sharing,
Collaborative Mechanism to Address These
Issues that Crosses all Phases of Dev.



Model Based Drug Development - Is a Prerequisite for Improvement



FDA's characterization: the development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and available clinical data to improve drug development knowledge management and decision making.

If implemented, this facilitates the ability to base important decisions on quantitative inputs, which is a cornerstone of model base drug development (MBDD).

Comment: it is my opinion that many companies have interpreted MBDD to primarily apply to doing in-silico studies to optimize the likelihood of getting the dose and regime "right" in clinical trials. While this is clearly of value, it is not enough. Case in point – Pfizer arguable has one of the largest groups of Pharmacotricians working in this area in the industry, yet Pfizer is still struggling with profitability problems and has had to reduce expenses in a big way.

We need to rethink our approach ...



Increasing Reliance on Biotech to Drive Growth

FiercePharma

Published on FiercePharma (<http://www.fiercepharma.com>)

Biologics to top pharma sales by 2014

By tracy

Created Jun 18 2009 - 10:21am

What will the pharma landscape look like after all those big, traditional drugs drop off the patent cliff? Here's a hint: Big Pharma might consider changing its name to Big Biotech.

By 2014, the biggest-selling meds will be biologics, according to an analysis from Evaluate Pharma. Taking the place of Pfizer's gargantuan drug Lipitor [1] will be Roche's Avastin [2], a cancer med expected to account for \$9.23 billion in 2014 sales. (Even when you factor in the recent trial disappointments.) The next five top sellers, in order, are expected to be Humira [3] (Abbott Labs), Rituxan [4] (Roche), Enbrel [5] (Wyeth/Amen), Lantus (Sanofi-Aventis), and Herceptin [6] (also Roche). Notice Roche claims three of the top six spots--with drugs developed by the recently-acquired Genentech.

Evaluate also predicts that half of the top 100 drugs in 2014 will be biotech meds--a huge change from last year's level of 28 percent and 11 percent in 2000. No wonder Big Pharma has been chasing biotech so hard lately.



The Translational Science Imperative

Fully loaded cost for developing a single novel therapeutic with “blockbuster potential” > \$800M (the number is ~ double this if you include amortized failures)

A major component of estimated expenditure is the cost of failure

- > 90% chance that an agent that enters clinical development will fail despite preclinical “evidence” of efficacy and safety (did we get the molecule wrong or get the dose and regimen wrong?)

The Translational Medicine Imperative is to improve prediction of the efficacy and safety attributes of a therapeutic agent as early as possible

- This may be achieved by jointly improving:
 - Discovery, preclinical and clinical experimental methods and materials
 - Collaboration to facilitate integration and joint analysis of discovery, preclinical and clinical data



What is Translational Science?

It means different things to different people.

Most definitions involve the translation of science to clinical practice.

In common use it has been applied to everything from drug discovery, to preclinical (e.g., allometric scaling) to medical treatment (patient individualization of dosing). It also involves feedback systems or loops to be effective (more on this later).

All views and definitions of Translational Science have a common theme. That is, improved collaboration to facilitate making better decisions.



Need for Improved Collaboration Reinforced ...

Clinical and Translational Science: A New Discipline to Catalyze the Transfer of Information. Arthur M. Feldman, MD, PhD ¹ ¹ Editor-in-Chief, CTS.
[Volume 1, Issue 1, 2008.](#)

... This concept of "translating" novel discoveries found at the laboratory bench into the clinical investigation of new technologies and methodologies to both diagnose and treat human disease at the bedside gained increasing focus over the past decade as an explosion of innovative technology supported scientific advances in numerous fields, including genomics, proteomics, gene transfer, stem cell biology, structural biology, and imaging. As these new fields of biology leapt onto the scientific stage, scientists became increasingly aware that the road from the bench to the bedside was not a single lane roadway, but rather a multilane highway that could be traversed in either direction. Indeed, some of the most important discoveries of the past decade have come from observations that were made by investigators in the clinical arena that then stimulated research at the laboratory bench. **It was this recognition of the need for a bidirectional linkage between the bench and the bedside that led to the development of a new moniker for this type of research: clinical and translational science.**



What Does it Involve?

Clinical and Translational Science: A New Discipline to Catalyze the Transfer of Information. Arthur M. Feldman, MD, PhD ¹ ¹ Editor-in-Chief, CTS. [Volume 1, Issue 1, 2008.](#)

...

Furthermore, a variety of impediments, including ... the need to integrate clinical and translational science across multiple departments and schools, the increasing barriers to performing clinical research, and a paucity of well-trained multi- and inter-disciplinary investigative teams, have limited the ability of translational researchers to effectively apply new knowledge and techniques to clinical practice.

Many companies have reorganized along translational lines, but lack the IT infrastructure to carry out the vision for the organization. People need to collaborate, share data, and leverage data into knowledge (via models).



Translational vs. Clinical Pharmacology Approaches

Clinical Pharmacology

The primary focus is the drug.

Translational Science/Medicine

The primary focus is the disease, and how to target drugs to alter the natural progression of the disease.



Translational Science Takes Root

Translational Medicine groups have been established both in academia and industry with the mandate of improving the *translation* of the wealth of new data into new *medicines* for the treatment of human disease.

- At least 50 pharma and biotech companies have established at least some formal accountability for “translational medicine”

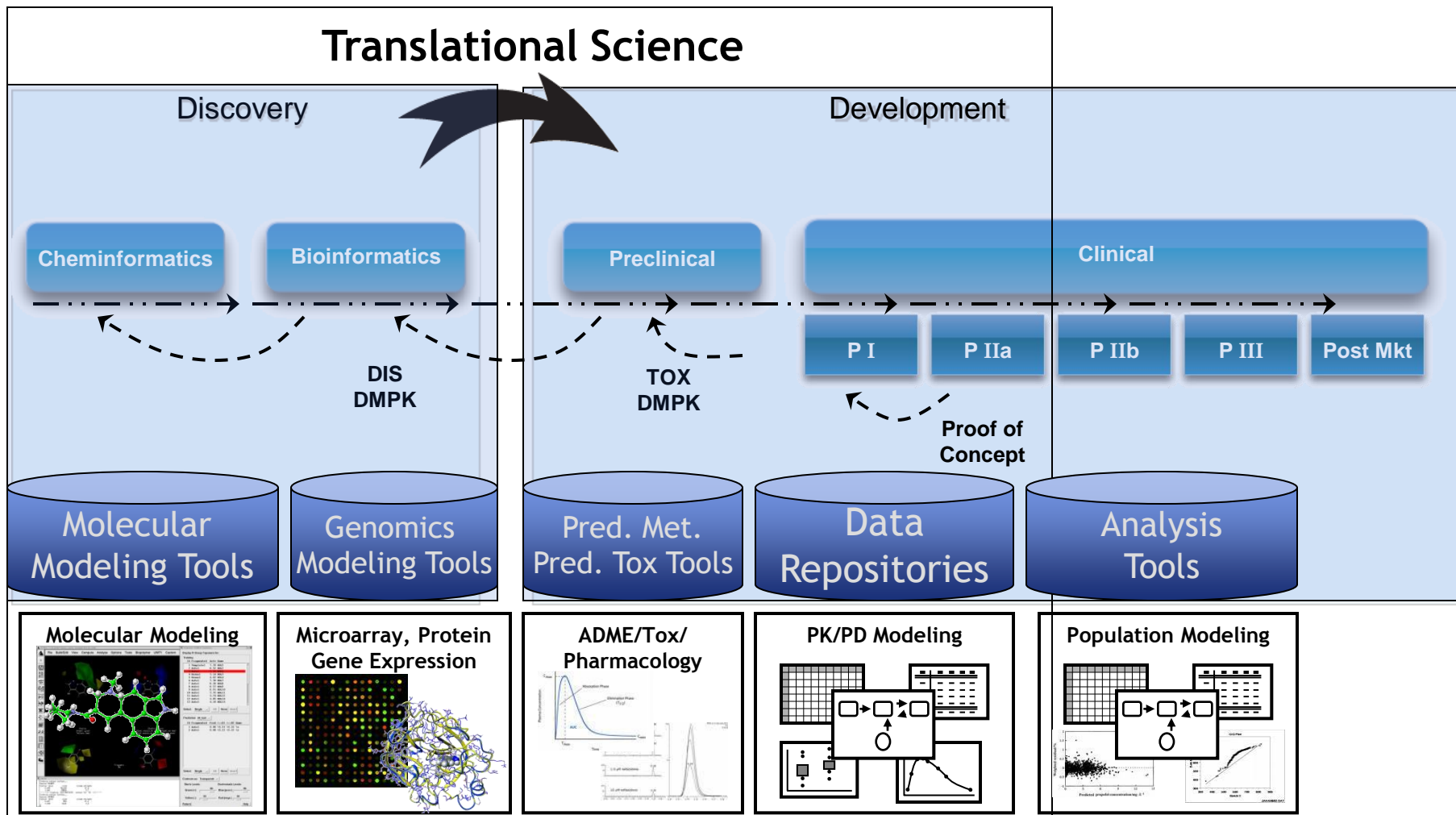
| | | |
|------------------|-------------------|--------------------|
| Abbott | Celgene | NiCox |
| Alexion | Centocor | Novartis |
| Alkermes | Chiron | Oncomed |
| Amgen | Daiichi Sankyo | Ortho Biotech |
| Amplimmune | Eisai | Pfizer |
| Anaphore | Eli Lilly | Phenomix |
| Apocell | Enzon | Regeneron |
| Archemix | Exelixis | Roche |
| Array Biopharma | Gruenenthal | sanofi-aventis |
| Astellas | GSK | Schering Plough |
| Astex | Incyte | Shire |
| AstraZeneca | Intrexon | Solvay |
| Aveo | JnJ | Takeda |
| Bayer Healthcare | Lundbeck | Talon Therapeutics |
| Biocept | Medimmune | Targacept |
| Biogen Idec | Medivation | Vax Onco |
| Biomarin | MGI Pharma | Wyeth |
| BMS | Neurotherapeutics | Xoma |

Based on informal survey conducted by Pharsight Corp.



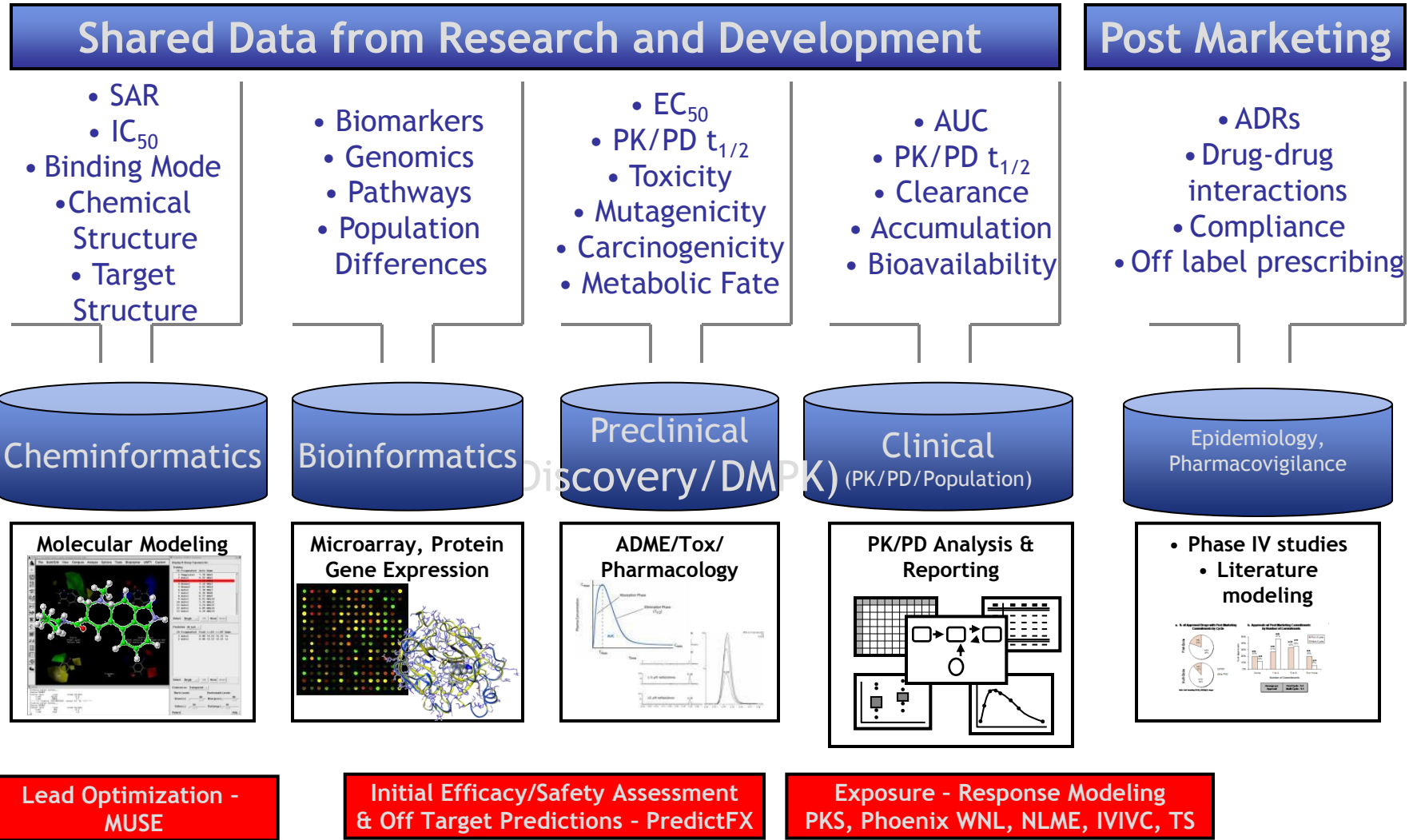
Companies are Starting to Reorganize Along Translational Science Lines, and ...

One concept of Translational Science is to break down the barriers between Discovery and Development. Several companies have reorganized along these lines.





... Need an Informatics Infrastructure to Facilitate Data Sharing and Feedback





Key Barriers to Implementation of Translational Approaches

Organizational—budgets, priorities, reward systems are set by multiple different departmental managers in large organizations. This may lead to sub-optimization of the entire system.

Scientific Silos—scientists see problems from their own perspectives, read different journals, go to different conferences, speak with different jargon, prefer different mental frameworks and tools according to their academic training. This may inhibit communication and knowledge sharing.

Informatics—information does not map from silo to silo and is collected without an overall master plan. Diverse data sets needed for translation must be mapped ad hoc.

IT—data sets are not linked and cannot be easily retrieved and analyzed.

- Much useful analysis is never done (takes too long)
- Ad hoc efforts are hard to re-use, replicate, and teach

Analytics and modeling—the science of extrapolating conclusions from work done in one silo to another, and ultimately from R&D silos to the treated patient in the market, requires special expertise in math, careful judgment, and profound understanding of the limits of inference.



Personal Observations on the Organizational/Silo Issue

Here are two examples of political/control issues getting in the way of making progress in implementing effective translational approaches.

- I know of multiple companies where one M&S team existed with limited success, and the company is trying to add a second Pharmacometrics team without integrating the existing team (due to political/control concerns). As a result, there is little or no incremental improvement in decision making practices.
- In virtually every company I have worked with, “Departments” are hesitant or resistant to allow non-Departmental staff to access “their” data directly for “fear” that it will be misused. This is contrary to the collaboration aspect to Translational Research.

Bottom line? Management has to deal with these issues for the Organization to be able to move forward...

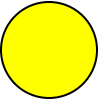
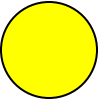


Conquering Barriers to the TM Vision

Organizational Scientific Silos



- Organizational issues can be overcome in 2 years or so by motivated pharma and biotech companies
- Scientific silos will take 5 or more years to break down and implement new approaches
- Move to a Translational based organization needs to be management driven



Informatics

IT

SEND, CDISC, Pistoia, and other informatics standards are of variable maturity, are funded and organized, are tractable, and will mature in the next 2-5 years.

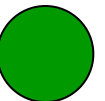


Analytics and modeling

Linking point solutions will solve much of the IT problem leading to faster availability of data, faster results, and faster, more informed decisions.



Newer and more powerful analytic tools are being developed. However, different domains use different tools, and sharing of information is often hampered by this. Newer platforms, such as D360, help address this issue.





Enablers - Standards and Processes

Process Changes

1. Automate and standardize data collection, handling and reporting
2. Establish central proprietary databases (*that are domain specific*)
3. Utilize all available information to generate knowledge and optimize development at compound and portfolio levels

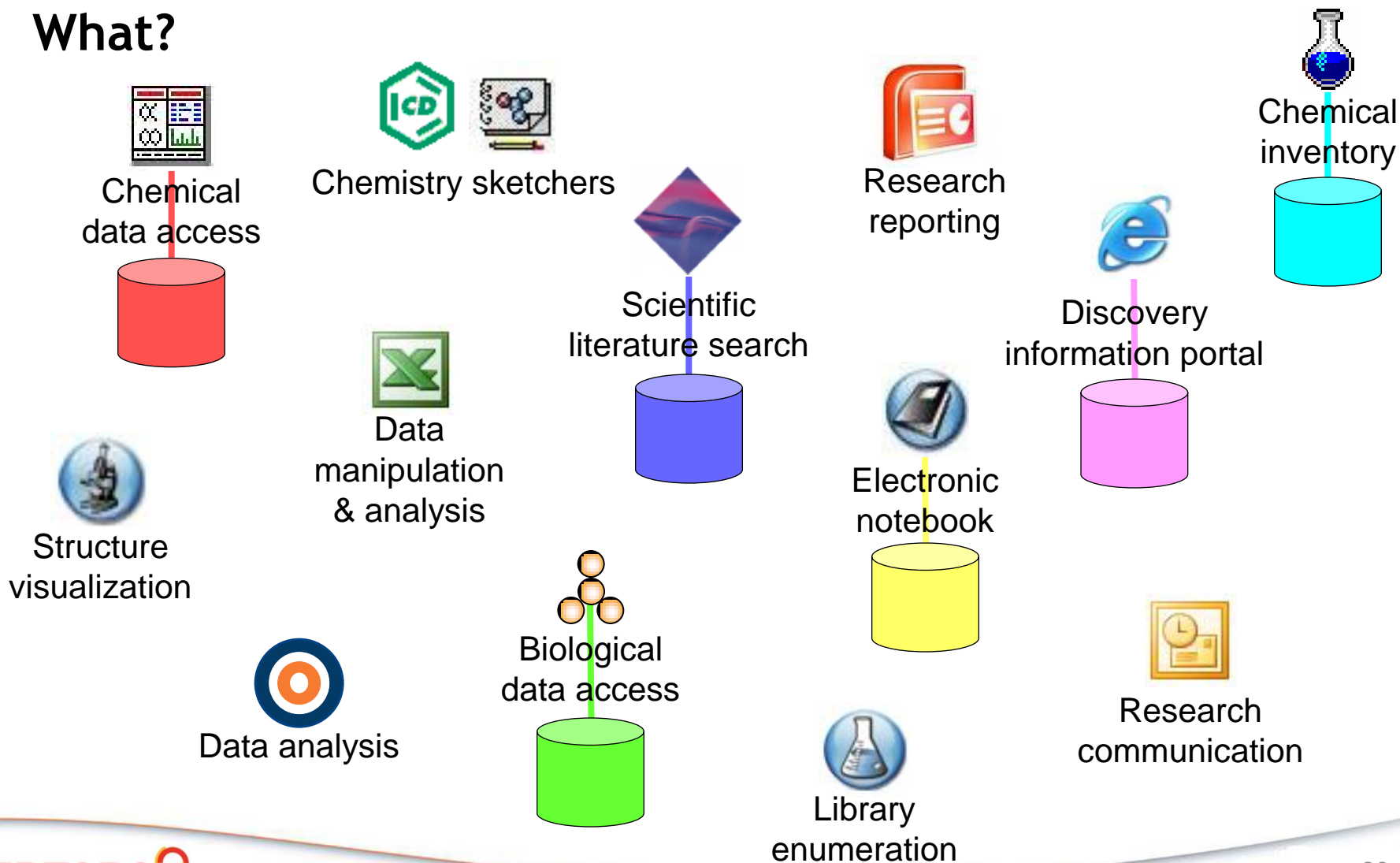
Source: Zhang L, Pfister M, Meibom B. 2008. Presented at ACoP.

If steps 1 and 2 are not in place, it can takes weeks or months to prepare historical / prior collected data for decision making, and the project teams cannot wait for this to be completed



A Typical Researcher's Desktop

Many applications, little integration! Where? How? What?





Effective Translational Approaches Require ...

An informatics infrastructure with 3 key, high level capabilities:

1. Data Access

- Users can ask any question of the data appropriate to their task and understanding
- Data is presented in a manner that the user understands

2. Data Analysis

- Data is transformed on the fly to a user digestible view
- Built in Tools support all common workflows for a wide user base
- The solution needs to integrate with 3rd party tools for specialist use
- Analysis steps should be automated as much as possible

3. Collaboration and Sharing

- Data queries, datasets, list and other user artifacts can be shared through common workspaces
- The solution allows the development of a self sustaining user community which leverages the intellectual assets of the team



Where Should Such a Solution Be Applied?

ALL Phases of Drug Development

Early Drug Discovery

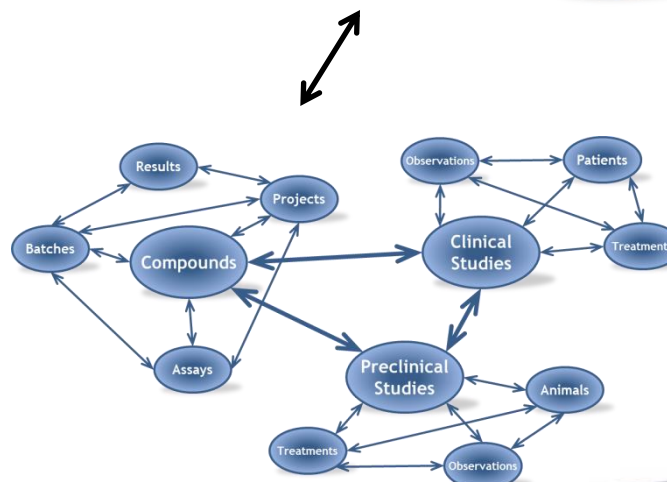
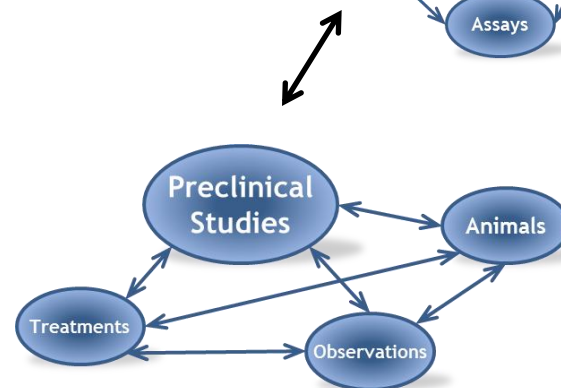
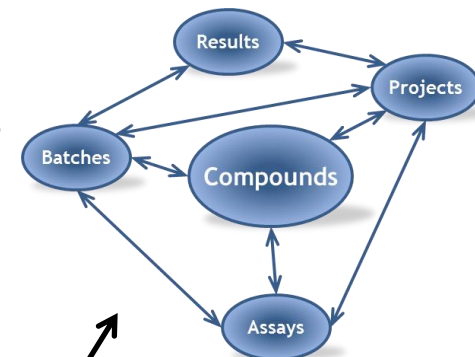
- Standard project data views through complex data mining
- Users from chemistry, biology, management...
- Applicable to both large and small organizations

Preclinical

- Animal PK/PD data
- Safety Data (tox, pharmacology, etc.)

Other

- Clinical data informatics
- Healthcare patient data
- Food Science
- ...



A Single Informatics Platform With Domain Specific Analysis Tools Can Facilitate this



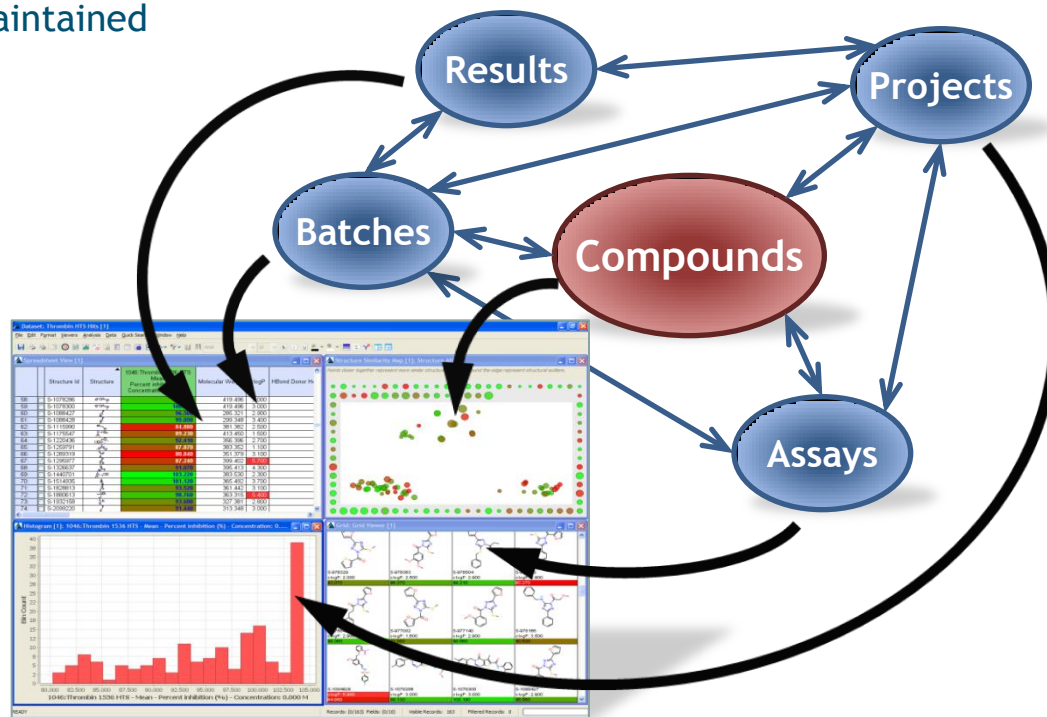
How Should Queries Be Facilitated?

Most companies will want to **keep data sources federated**

- Relational databases, web services, files...
- “Complete” Data warehouse not a requirement

A Queryable Data Network is created through logical data relationships that is comprehensible to users

- The solution is not hard coded to specific kinds of data
- Configured to deal with the data at hand
- Data context is maintained



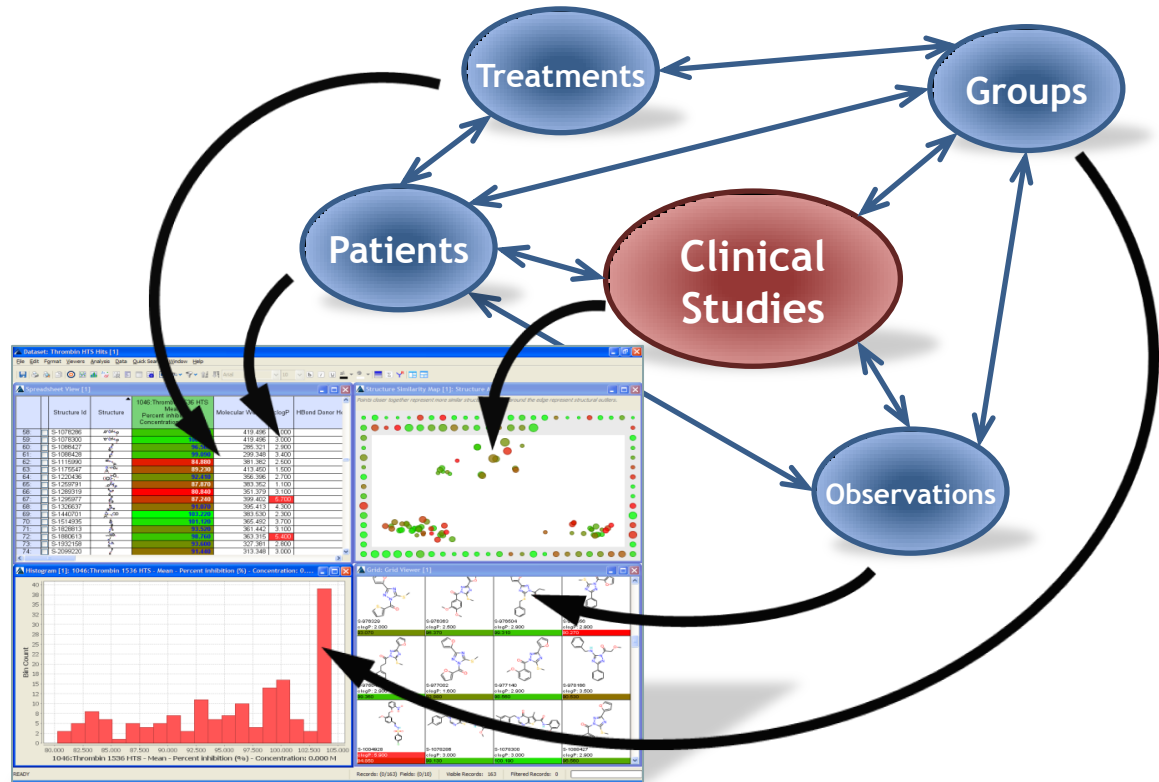


Queryable Data Networks for Safety Data

Clinical/preclinical scientists can use such a solution to perform study or group-centric searches that return related subject, treatment, and observation information

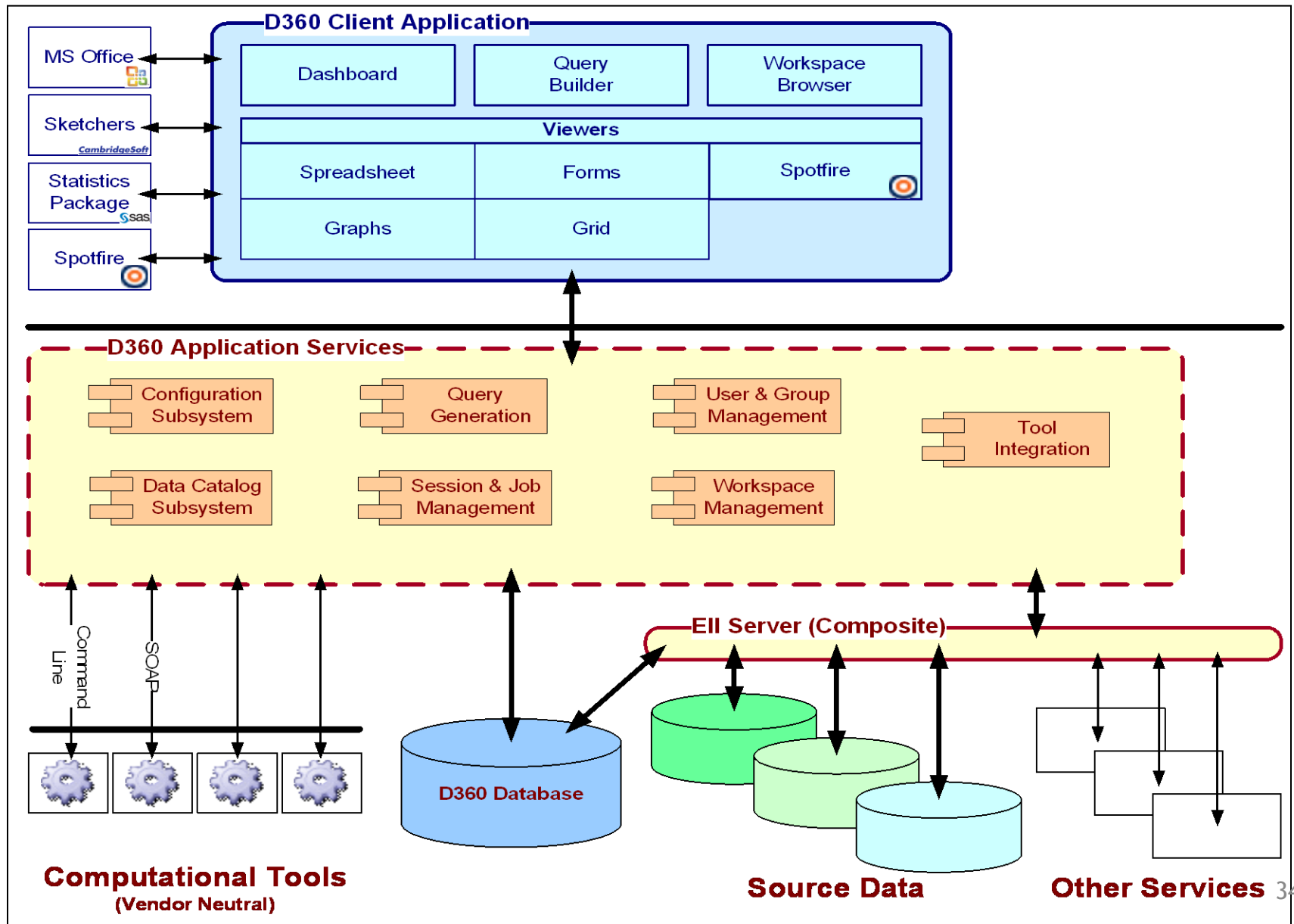
- Queryable data networks relate data in scientifically meaningful ways
- The same data can be searched and analyzed from multiple perspectives

The informatics platform needs to support examination of data from different points of view. Thus supporting different workflows for different groups of users.



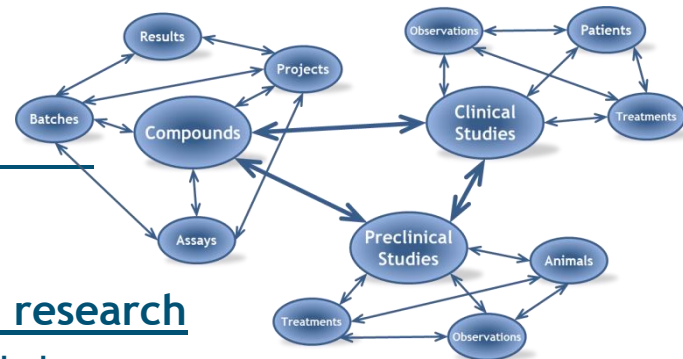


High Level Architecture of TS Solution (D360)





Benefits of a Translation Support Platform



Link data “Islands”

- Provide support for translational approaches to research
- e.g. discovery, non-clinical safety, PK-PD, clinical data

Serve the needs of the scientist: allow the user to easily go from Question -> Action

- Automatically present data in the format the user wants to see it - eliminate manual data transformations
- Present data from multiple perspectives (Studies, Compounds, Subjects...)
- Support multiple levels of user, from basic to expert, within the same application.

Reduce costs of IT Support - increase ROI (Return on Information)

- Users are empowered to build and share queries and analysis, without IT support.
- Self discovery of new data
- Extensive configuration (non coding) capability
- Allow customization (configuration, scripting, coding) through extensive APIs in a multi-tiered architecture



Summary and Conclusions

Companies need to move to a true Translational development model to improve profitability.

- The move to a Translational-based organization needs to be driven top-down.
- Reorganizing is not enough - there needs to be an informatics platform in place to support collaboration across the Translational organization.
- All staff need training to understand their role and the role of the data they collect as part of the Translational paradigm

Certara has created D360 to address these needs