



Pharmaceutical Analysis



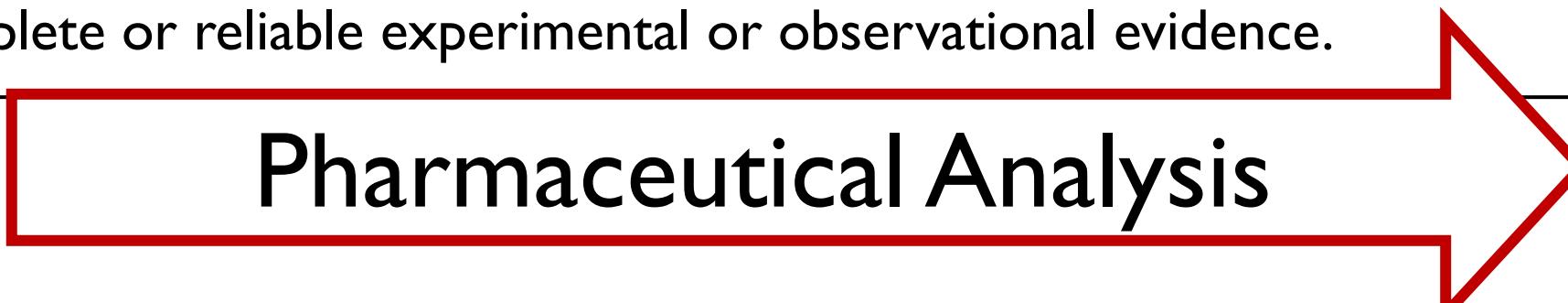
Introductory Lecture 2023
Course (#8002)

Driving Science!

► According to the American Physics Society

Science is the systematic enterprise of gathering knowledge about the universe and organizing and condensing that knowledge into testable laws and theories. The success and credibility of science are anchored in the willingness of scientists to:

- Expose their ideas and results to independent testing and replication by others. This requires the open exchange of data, procedures and materials.
- Abandon or modify previously accepted conclusions when confronted with more complete or reliable experimental or observational evidence.



Pharmaceutical Analysis

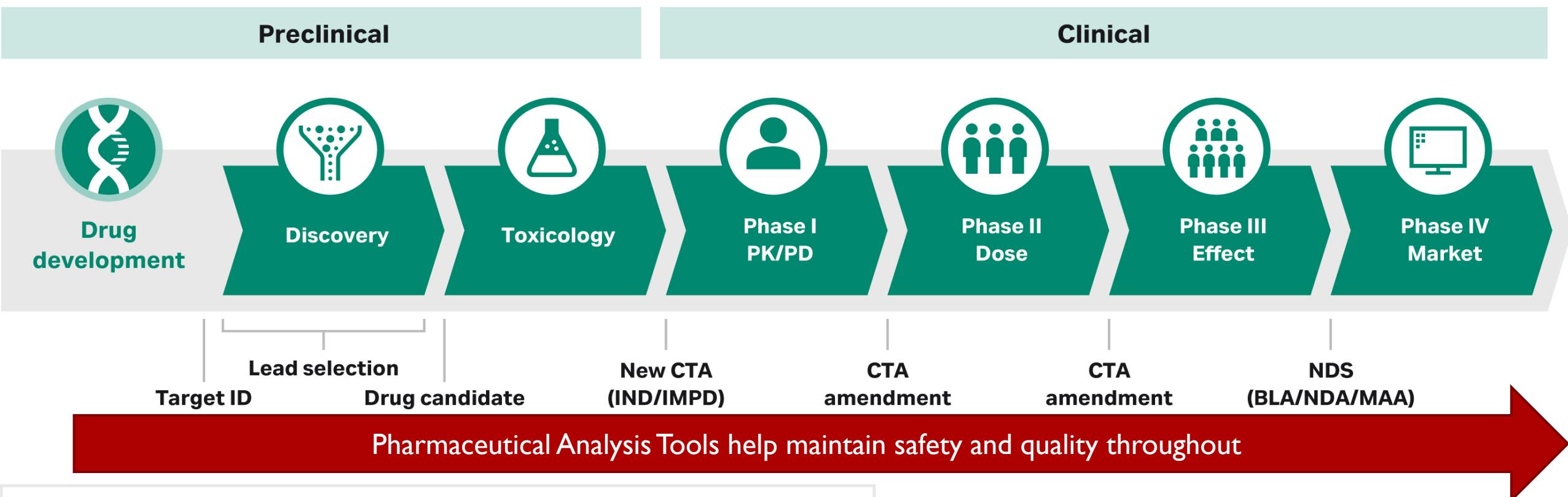


Pharmaceutical Analysis

- ▶ **Introduction:**
 - ▶ Quality Control (QC)
 - ▶ Physical Chemical Properties of Drug Molecules
 - ▶ General Compendial Methods and Regulatory Influences on Analytical Development
- ▶ **Why should YOU care?**
 - ▶ Pharmaceutical analysis is the practices used to ensure medicines and devices are delivered to patients with the utmost safety.
 - ▶ We are going to focus on “Active Pharmaceutical Products (API)” that can either be small molecule ($MW < 1500$) or large molecules (proteins, antibodies).
 - ▶ Leveraging state of the art analytical technology the medicines are characterized to ensure:
 - Identity of API
 - Appropriate API concentration
 - Purity of API
 - Bioavailability of API
 - ▶ Grades ☺

Challenge: Removing Uncertainty

- ▶ Worlds most complex bioreactor: Homosapien
- ▶ Step wise process to help reduce uncertainty and risks as a function of time



BLA – Biologics License Application (USA)

CTA – Clinical Trial Application

IMPD – Investigational Medicinal Product Dossier (EU)

IND – Investigational New Drug Application (USA)

MAA – Marketing Authorisation Application (EU)

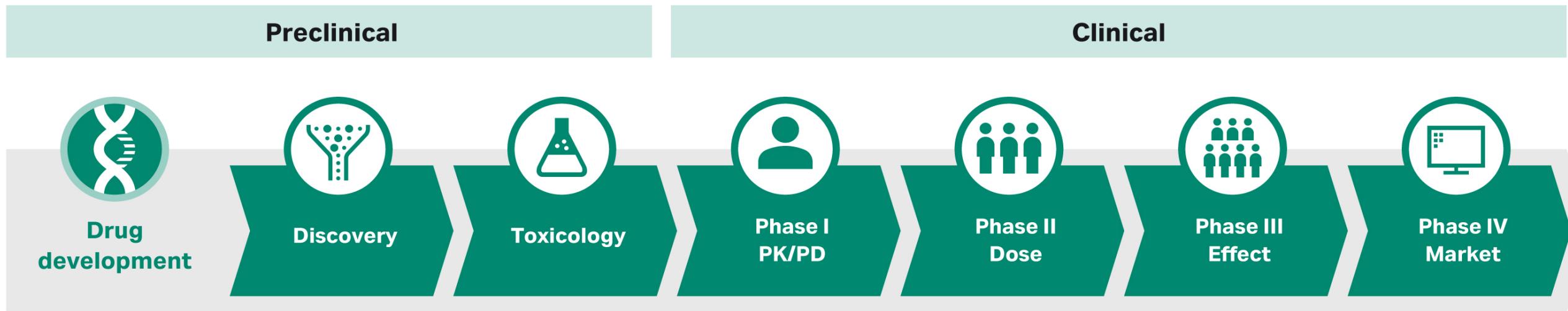
NDA – New Drug Application (USA)

NDS – New Drug Submission

PK/PD – pharmacokinetic/pharmacodynamic

Solution: Control Strategy

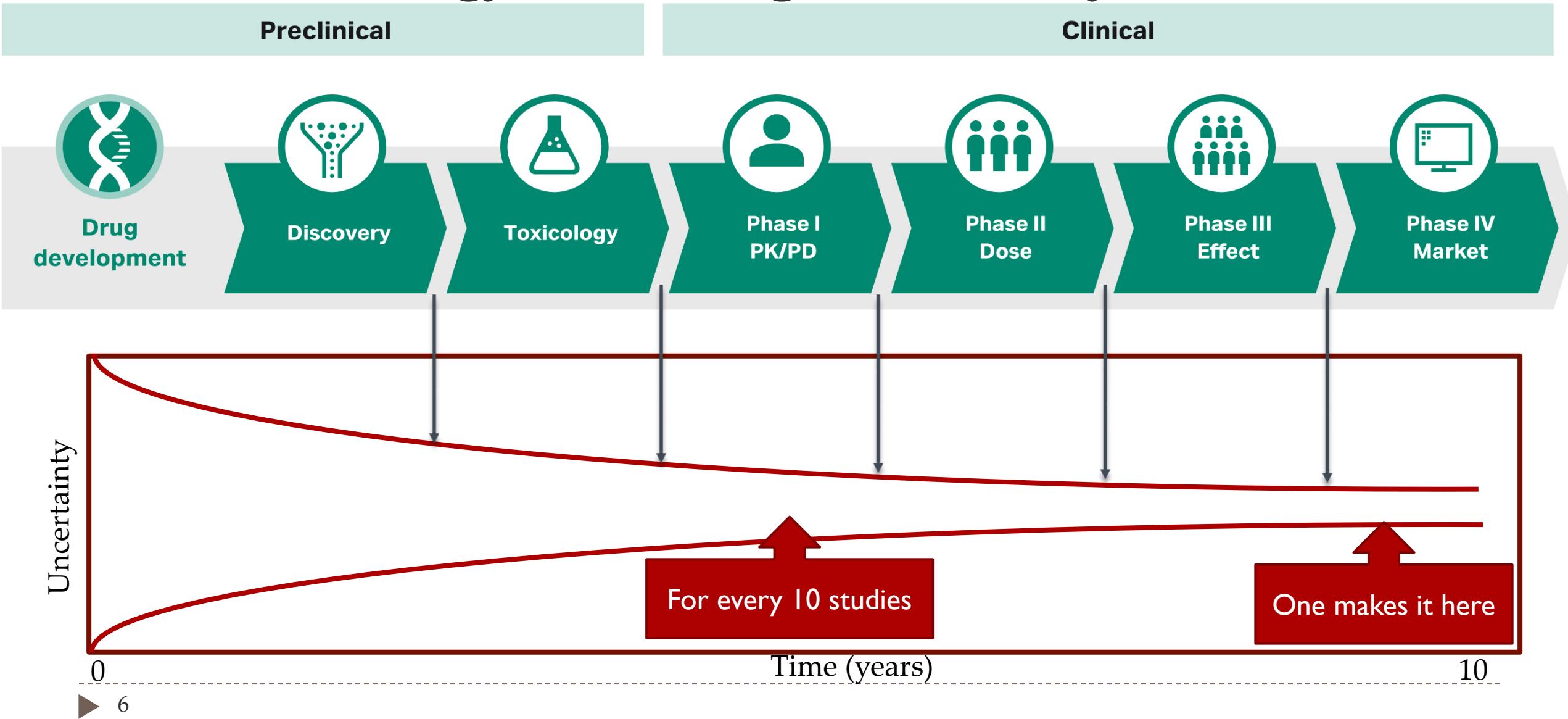
- ▶ Worlds most complex bioreactor: Homosapien
 - ▶ Step wise process to help reduce uncertainty and risks as a function of time



Control Strategy

Reducing Risks and Demonstration of Control as a Function of Time

Control Strategy: Removing Uncertainty



Quality Control

- ▶ Development and Deployment of quality control methods that ensure the API quality throughout the supply chain
 - ▶ Raw material methods, Intermediate control points, Final product testing
- ▶ Scientific + Regulatory Approach
 - ▶ Through the combination and knowledge throughout the process the Quality of a medicine can be assured
 - ▶ Defining regulations that all corporations must follow can help ensure the level of quality across the INDUSTRY is maintained
- ▶ Partnerships
 - ▶ Understanding interrelationships between sectors (e.g., internal {development, clinical/discovery} and external {FDA, EMA}) is a complex, multivariate problem

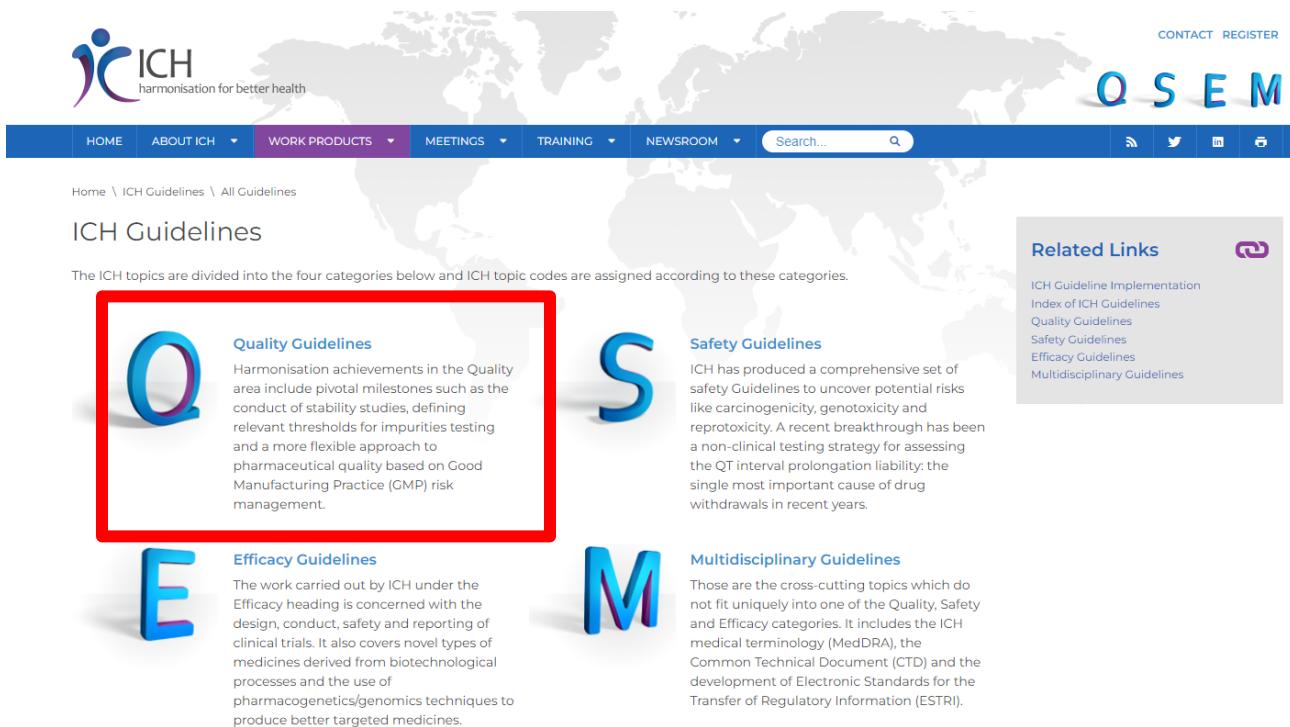
Successful partnerships across these sectors will help ensure your success in developing a quality control strategy for your medicines

Developing a Control Strategy



International Conference on Harmonization (ICH)

- ▶ ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration
- ▶ <http://www.ich.org>



The ICH topics are divided into the four categories below and ICH topic codes are assigned according to these categories.

Q Quality Guidelines
Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

S Safety Guidelines
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

E Efficacy Guidelines
The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

M Multidisciplinary Guidelines
Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

Q S E M

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Quality Guidelines

/ [ICH Guidelines](#) / [Work Products](#) /

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

[Q1A - Q1F Stability](#)



[Q2 Analytical Validation](#)



[Q3A - Q3D Impurities](#)



[Q4 - Q4B Pharmacopoeias](#)



[Q5A - Q5E Quality of Biotechnological Products](#)



[Q6A- Q6B Specifications](#)



[Q7 Good Manufacturing Practice](#)



[Q8 Pharmaceutical Development](#)



[Q9 Quality Risk Management](#)



[Q10 Pharmaceutical Quality System](#)



[Q11 Development and Manufacture of Drug Substances](#)



[Q12 Lifecycle Management](#)



[Q13 Continuous Manufacturing of Drug Substances and Drug Products](#)



[Q14 Analytical Procedure Development](#)



ICH Quality Guidelines

- Provide good external guidelines to develop expectations for each activity

Q1	Stability
Q2	Analytical Validation
Q3	Impurities
Q4	Pharmacopoeias
Q5	Quality of Biotechnological Products
Q6	Specifications
Q7	Good Manufacturing Practices
Q8	Pharmaceutical Development
Q9	Quality Risk Management
Q10	Pharmaceutical Quality Systems
Q11	Development and Manufacture of Drug Substances
Q12	Lifecycle Management
Q13	Continuous Manufacturing of Drug Substances and Drug Products
Q14	Analytical Procedure Development

ICH Q1A

- ▶ “Stability Testing of New Drug Substances and Products”
 - ▶ Guideline defines the stability package for a new drug substance or drug product.
 - ▶ Defines the core stability package for a new drug substance and product
 - ▶ Alternative approaches are acceptable if scientifically justifiable
- ▶ Purpose
 - ▶ The purpose of **stability testing** is to provide evidence on how the quality of a drug substance or drug product varies with **time** under the influence of a variety of environmental factors such as **temperature, humidity, and light**
 - ▶ Leveraging scientific understanding of the drug substance and drug product a re-test period for the drug substance or a shelf life for the drug product can be established along with recommended storage conditions
- ▶ Challenge
 - ▶ The process by which the drug substance and drug product are manufactured, vary as a function of development time. Hence the impurity and stability profile can change, forcing the re-evaluation of your “scientific understanding”
 - ▶ Key is to maintain a **systematic approach** to the Stability Program
 - ▶ When everything is changing around you, standardize your stability approach

What is the Difference of Forced Degradation Studies and Accelerated Stability Studies?

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Stability Study Classifications

- ▶ Accelerated Stability Testing
 - ▶ Formal Studies (ICH Q1A)
 - ▶ Traditional stress testing as outlined in the ICH guidelines

- ▶ Forced Degradation Studies – Research & Development
 - ▶ Higher temperature (i.e., >50C) to help provide faster screening times on stability methods development samples as well as fundamental stability
 - ▶ If No Reaction at Higher Temperatures – safe to say lower temperatures would be fine
 - ▶ If Reaction at Higher Temperatures – need to confirm at lower “Formal” traditional study approaches

Arrhenius Equation

- Basis for accelerated (temperature > room temp) stability studies is:
 - Rate constants are a function of temperature

$$k = A e^{-\frac{E_A}{RT}}$$

activation energy

E_A

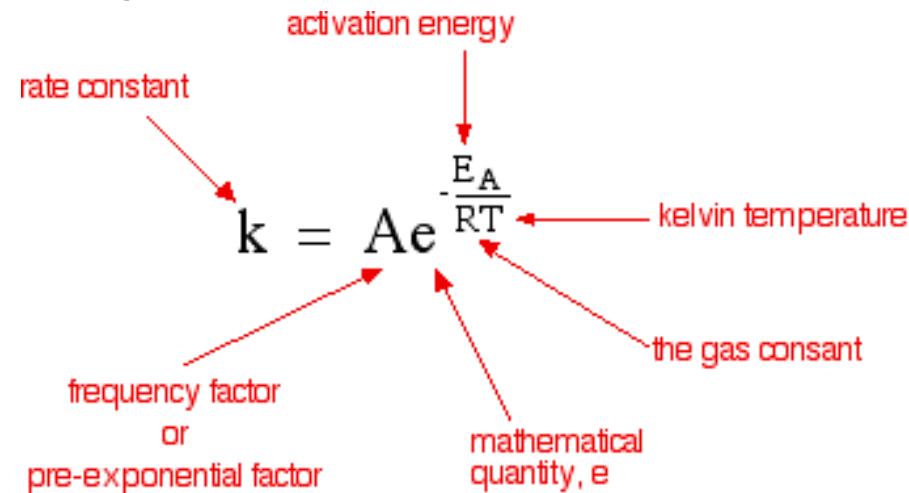
rate constant

kelvin temperature

the gas constant

frequency factor or pre-exponential factor

mathematical quantity, e



```

    graph TD
      AE[activation energy] --> EA[E_A]
      EA --> EXP[-EA/RT]
      EXP --> K["k = Ae-E_A/RT"]
      K --- A[A]
      K --- RT["R T"]
      K --- e["emathematical quantity, e"]
      K --- FPF["frequency factor or pre-exponential factor"]
  
```

- $e^{-(E_A / RT)}$
 - this expression counts the fraction of the molecules present which have energies equal to or in excess of activation energy at a particular temperature.
- A is a term which includes factors like the frequency of collisions and their orientation.



ICH Q1A: Accelerated Stability Testing

- ▶ Stress testing is the process of subjecting either the drug substance and/or drug product to elevated storage conditions that can expedite chemical and physical transformations

Environment	Initial	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo	36 mo
25°C/60%RH	X	X	X	X	X	X	X	X
40°C/75%RH	X	X	X					
30°C/65%RH	X	(X)	(X)	(X)	(X)			

Also evaluate stability of one batch exposed to light: ICH Q1B – Photostability Testing of New Drug Substances and Products

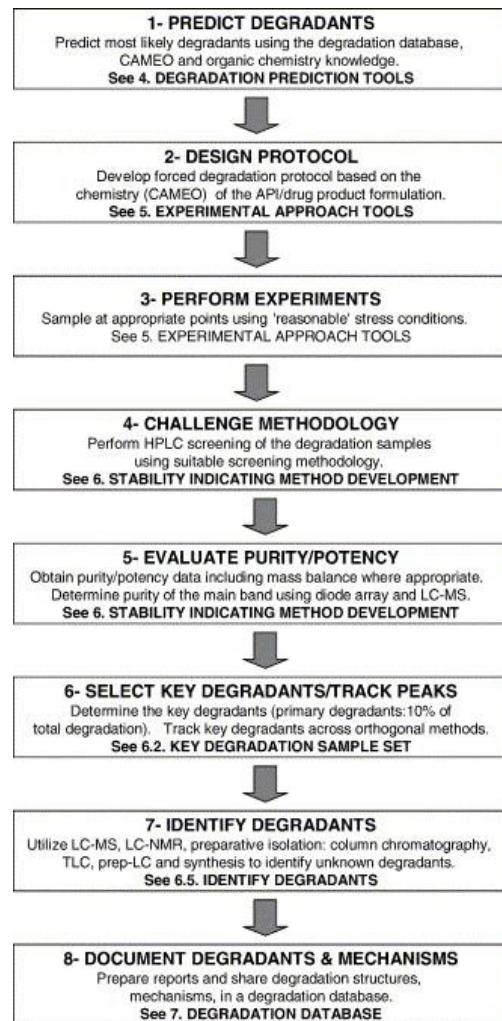
- ▶ Advantage: Provides insight and forecasting of likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.
- ▶ Disadvantage: Some chemical and physical transformations observed at higher temperatures may not occur at normal storage conditions due to the activation energies of the process

Basics Implemented

- ▶ Rate of a reaction will double every 10°C
 - ▶ Can elevate temperature to get real data and samples to develop methods
 - ▶ When marketing a formulation, 2 year shelf life is optimal/expected. To ensure we are able to meet these goals without the need to wait for 2 years, higher stressing temperatures is often employed.
 - ▶ To that end, 80C at 2 weeks ~ 2 years at room temperature when you take into consideration that the rate typically doubles every 10C.
 - ▶ Given that consideration and the fact that you want to balance this speed out with reasonable/relevant stressing conditions and gradient of conditions is setup in the table below. It provides early read on the status but also the long term read on the samples.

Stress Temperature		20	30	40	50	60	70	80
Time to Achieve 2 year equivalent		128	64	32	16	8	4	2
Level	Solid State Stressing Temp (C)	1st Pull Time (Wks)	2nd Pull Time (Wks)	3rd Pull Time (Wks)	4th Pull Time (Wks)			
7 (Forced)	80	0.5	1	1.5	2			
6 (Forced)	70	1	2	3	4			
5 (Forced)	60/75% RH	2	4	6	8			
4 (Forced)	50	4	8	12	16			
3 (Accelerated)	40/75% RH	4	8	16	24			
2	25/60% RH	16	24	52	104			
1	4	16	24	52	104			

Ideal Process Flow



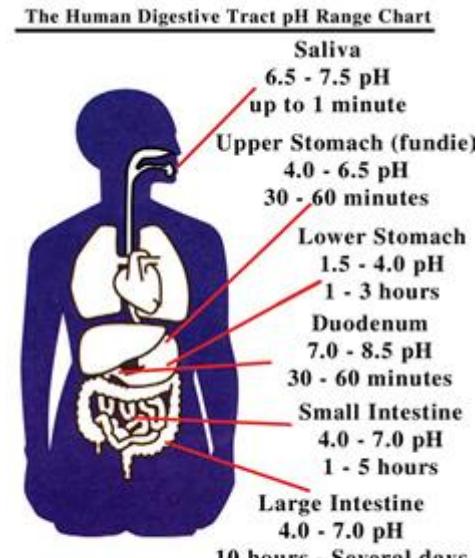
- ▶ Prediction
- ▶ Input for design
- ▶ Perform experiments
- ▶ Challenge methods
- ▶ Mass balance confirmations
- ▶ Determine key degradants (first 10%)
- ▶ Identify degradants
- ▶ Document degradants and mechanisms

Common Routes of Degradation

- ▶ Hydrolysis
- ▶ Oxidation (light, radical, chemical)
- ▶ Rearrangements
- ▶ Decarboxylation
- ▶ Dimerization, polymerization
- ▶ Reaction with excipients (inactive ingredients)
- ▶ Polymorph conversion, racemization
- ▶ Solution phase
- ▶ Solid state reactions
- ▶ Apparent Degradation (recovery)

Solution Stability

- Solution stability should be evaluated to determine if any degradation in vivo may occur and to what extent.
- To that end, stability at elevated temperature for 1 week as a function of pH is common practice
 - ▶ pH 2-10 (mimic in vivo conditions)
 - ▶ Strong acid (0.1N HCl)
 - ▶ Strong base (0.1N NaOH)
 - ▶ Oxidation (0.3% peroxide)
- Conditions samples submitted
 - ▶ Heat
 - ▶ Light
- For example, sample days 1, 3, 5, 7 at 40C or 50C will provide good basic understanding



The diagram illustrates the average time food spends in each part of the digestive system along with the average pH.

Remember What is Required

- Balancing a design space around what is required and what you do internally is critical
- As per Guidelines: Minimal Requirements for submission

Study	Storage condition	Minimum time period covered by data at submission
Long term*	$25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$	12 months
Intermediate**	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$	6 months
Accelerated	$40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$	6 months

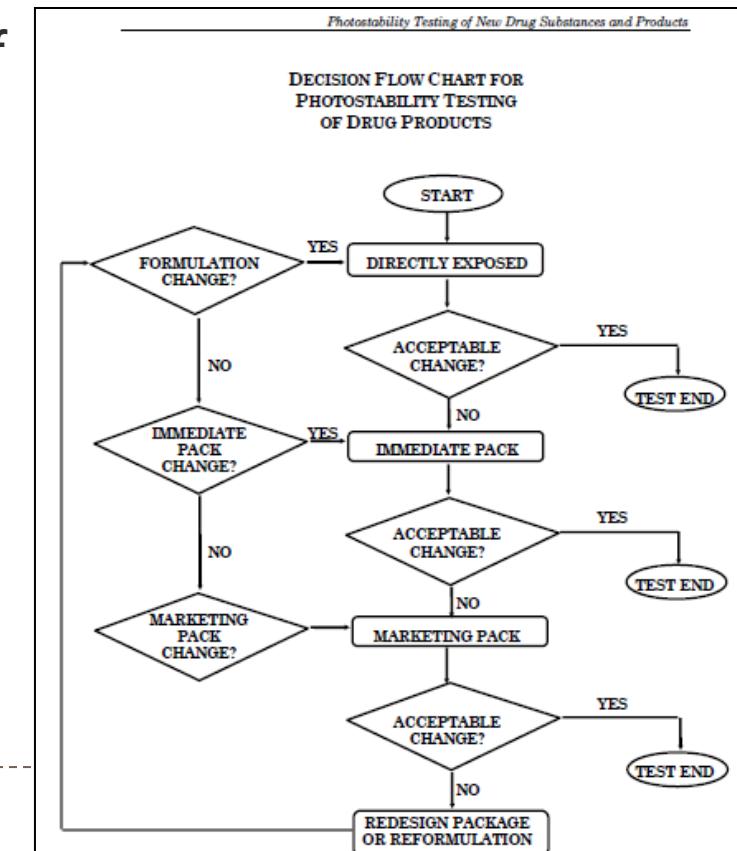
*It is up to the applicant to decide whether long term stability studies are performed at $25 \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$.

**If $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ is the long-term condition, there is no intermediate condition.

- Accelerated and forced stability testing is used to help quickly explore new formulations and processing conditions
 - ▶ If you do NOT see degradation at a higher stress level, justification of methods and shelf life specifications at lower temperatures is scientifically relevant

ICH Q1 B

- ▶ “Photostability testing of new drug substances and products”
- ▶ The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected
- ▶ Basic Flow Chart demonstrates that most of the stability problems can be fixed via packaging
- ▶ During manufacturing and/or analytical testing the samples can also be exposed to light and hence careful consideration as per the handling during production may be warranted



ICH Q1 C

▶ “Stability Testing for New Dosage Forms”

- ▶ A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.
- ▶ Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).
- ▶ Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases.
- ▶ Note: Vague guidelines which lead a lot to be interpreted by both the agencies and the industry
 - ▶ Partner with internal experts (regulatory + Analytical/Formulators) to come up with a strategy

ICH Q1 D

- ▶ “Bracketing and matrixing designs for stability testing of new drug substances and products”
 - ▶ A full study design is one in which samples for every combination of all design factors are tested at all time points.
 - ▶ A reduced design is one in which samples for every factor combination are not all tested at all time points.
 - ▶ A reduced design can be a suitable alternative to a full design when multiple design factors are involved.
 - ▶ Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified.
- ▶ Formulators often perform “Bracketing” and “Matrix” designs in the formulation development ... these samples can feed nicely into your stability program.
 - ▶ Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

ICH Q1 D

► Design Factors

- ▶ Strength – again – if formulator uses a “common blend” and simply changes dosage size (tablet size or solution volume) to adjust dose – you can leverage their bracketing into your stability testing;
- ▶ Other examples:
 - capsules of different strengths made with different fill plug sizes from the same powder blend
 - tablets of different strengths manufactured by compressing varying amounts of the same granulation
 - oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colourants, flavourings).
- ▶ Container Closure Sizes and/or Fills
 - ▶ Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapour permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate.
 - ▶ Leverage your forced degradation work to support any packaging study (e.g., API does not undergo oxidation or is not light sensitive).

ICH Q1 D

► Example Study

Table 1: Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

- More sophisticated statistical designed methods also applicable, but must have appropriate justification

ICH Q1 E

- “Evaluation for stability data”
 - ▶ The purpose of a **stability study** is to establish, based on testing a **minimum of three batches** of the drug substance or product, a **retest period** or shelf life and **label storage instructions** applicable to **all future batches manufactured and packaged under similar circumstances**. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.
 - ▶ A **systematic approach** should be adopted in the presentation and evaluation of the stability information.
 - ▶ The stability information should include results from
 - Physical
 - Chemical
 - Biological/microbiological tests
 - including those related to particular attributes of the dosage form
 - dissolution rate for solid oral dosage forms
 - ▶ Where the long-term data and **accelerated data** for an attribute **show little or no change over time** and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed retest period or shelf life. **In these circumstances, a statistical analysis is normally considered unnecessary** but justification for the omission should be provided.

ICH Q1 Summary

- ▶ Leverage the guideline to help define your study protocols
- ▶ Ensure systematic approach throughout your program
 - ▶ May cause some “extra” work, but after a 3-5 year development program will be glad you locked in on an approach
 - ▶ Ideally, develop or simply use a standard approach your corporation has developed
- ▶ Remember, product stability can not only lead to patient getting lower dose of API but also degradation products can be linked to side effects
- ▶ Stability program is an evolving story that can be used to help design product as well as develop your analytical methods being used to maintain ultimate product quality

ICH Quality Guidelines

- Provide good external guidelines to develop expectations for each activity

Q1	Stability
Q2	Analytical Validation
Q3	Impurities
Q4	Pharmacopoeias
Q5	Quality of Biotechnological Products
Q6	Specifications
Q7	Good Manufacturing Practices
Q8	Pharmaceutical Development
Q9	Quality Risk Management
Q10	Pharmaceutical Quality Systems
Q11	Development and Manufacture of Drug Substances
Q12	Lifecycle Management
Q13	Continuous Manufacturing of Drug Substances and Drug Products
Q14	Analytical Procedure Development

ICH Q2

- ▶ “Analytical Validation”
 - ▶ Guideline defines the validation of an analytical procedure
 - ▶ Goal is to demonstrate that it is suitable for its intended purpose.
 - ▶ A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included.
- ▶ Types of Analytical Procedures to be Validated
 - ▶ Identification tests
 - ▶ Quantitative tests for impurities' content
 - ▶ Limit tests for the control of impurities
 - ▶ Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.
- ▶ Challenge
 - ▶ The process by which the drug substance and drug product are manufactured, vary as a function of development time. Hence the method may need to undergo re-validation depending on the degree of change in the process. A multivariate approach is often recommended to ensure quality (i.e., orthogonal methods)
 - ▶ Key is to maintain a **systematic approach** to the Stability Program
 - ▶ When everything is changing around you, standardize your stability approach

Testing Definitions

- ▶ **Identification tests**
 - ▶ intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard
- ▶ **Testing for impurities**
 - ▶ can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test;
- ▶ **Assay procedures**
 - ▶ are intended to measure the analyte present in a given sample. In the context of Q2, the assay represents a quantitative measurement of the major component(s) in the drug substance.
 - ▶ For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s).
 - ▶ The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

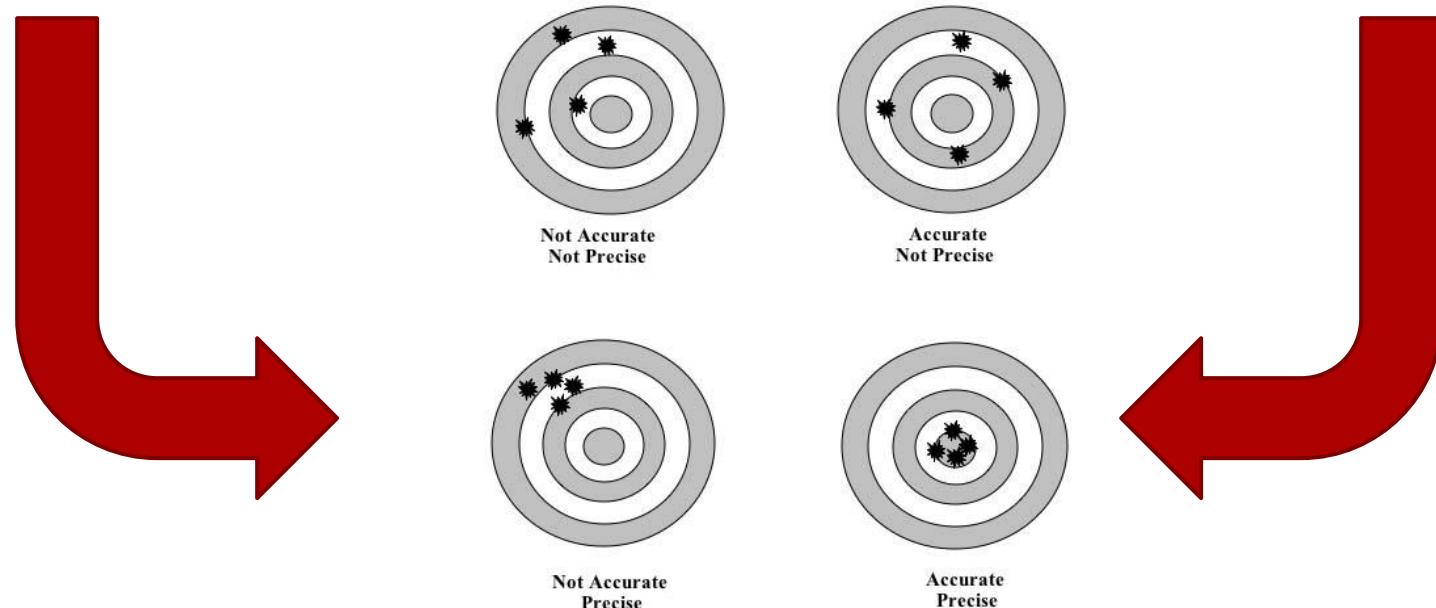
Typical validation characteristics

- ▶ Analytical Figures of merit
 - ▶ Accuracy
 - ▶ Precision
 - ▶ Repeatability
 - ▶ Intermediate Precision
 - ▶ Specificity
 - ▶ Detection Limit
 - ▶ Quantitation Limit
 - ▶ Linearity
 - ▶ Range
- ▶ Definition of each of these factors for a given method will describe the design space under which it can effectively operate and measure quality of your process

Accuracy and Precision

- ▶ **Accuracy**
 - ▶ the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found
- ▶ **Precision**
 - ▶ The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.
- ▶ **Repeatability**
 - ▶ Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision .
- ▶ **Intermediate precision**
 - ▶ Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.
- ▶ **Reproducibility**
 - ▶ Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Accuracy and Precision



Specificity

- ▶ Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present.
- ▶ Typically these might include impurities, degradants, matrix, etc.
- ▶ Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).
- ▶ This definition has the following implications:
 - ▶ Identification: to ensure the identity of an analyte.
 - ▶ Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.
 - ▶ Assay (content or potency):
 - to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

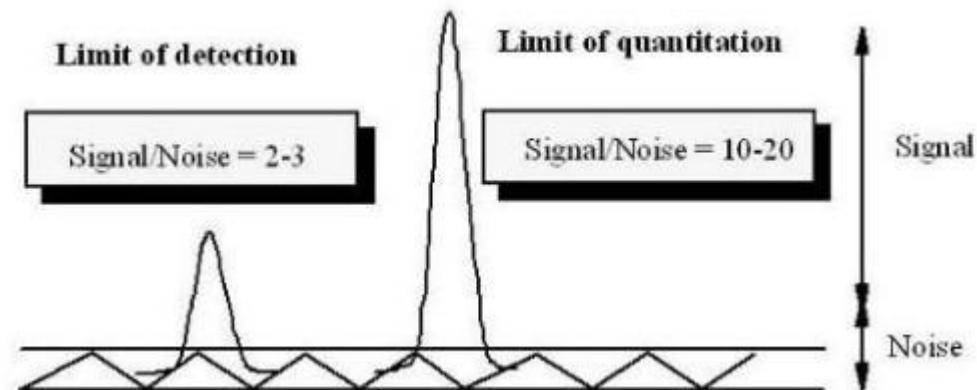
Analysis Limits

▶ Limit of Detection

- ▶ is the lowest concentration level that can be determined to be statistically different from a blank

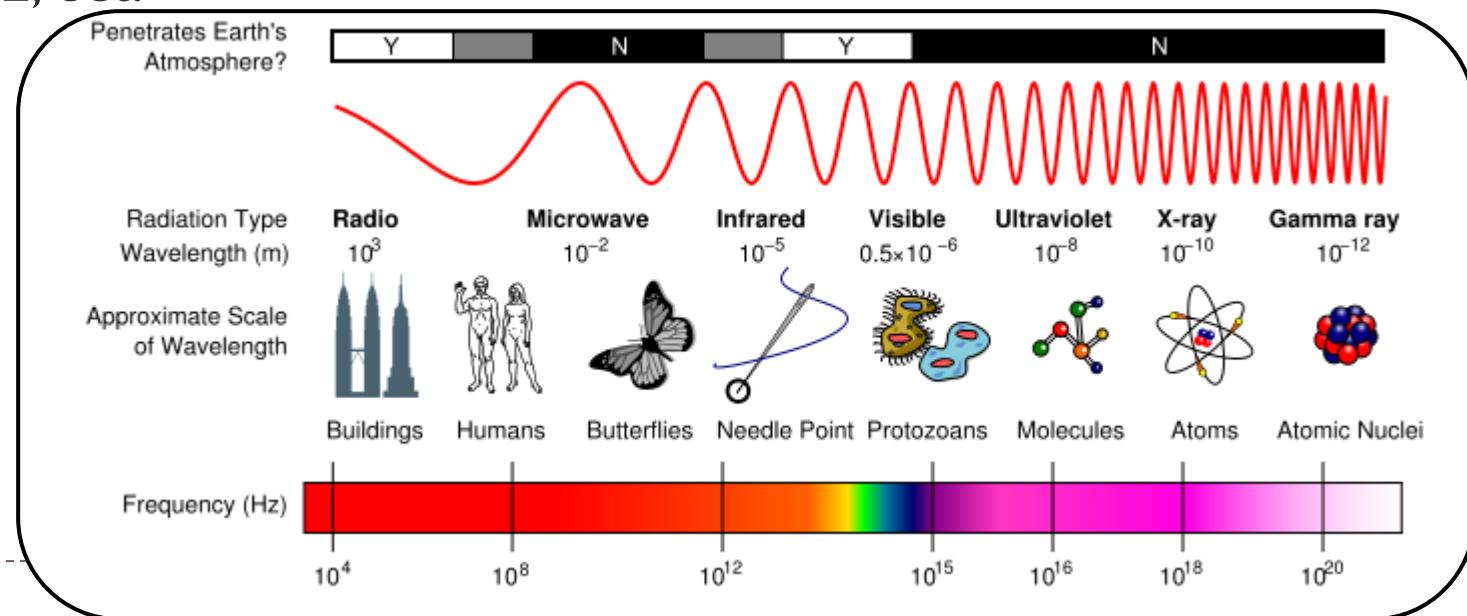
▶ Limit of Quantitation

- ▶ is the level above which quantitative results may be obtained with a specified degree of confidence.



Analytical Methods

- ▶ Leverages the interaction of light and chemical species to accomplish a unit of measure
 - ▶ Direct measures can include NIR, IR, UV, Vis
- ▶ Sample preparation may be required prior to measuring the interaction which includes
 - ▶ TLC, LC, CE, ect.



Classification of Methods

- ▶ **On-Line:** Process Analytical Technology (PAT) used to measure processes in real time
 - ▶ NIR – measures moisture and chemical composition
 - ▶ Raman – chemical composition and polymorphic forms
 - ▶ FBRM – Particle Size
- ▶ **At-Line:** Measured off line, but in the plant. Response time within 5 minutes
 - ▶ Loss on Drying (LOD)
 - ▶ NIR systems to measure tablet uniformity
 - ▶ High Temperature Dissolution – Monitoring controlled release products
- ▶ **Off-Line:** Traditional Quality control laboratories
 - ▶ More intricate complicated methods like:
 - ▶ LC, GC, CE, MS



Goal is to drive quality control methods into the plant (PAT/QbD)

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ICH Q3

- ▶ “**Impurities in new drug substances**”
 - ▶ Guideline outlines how to tabulate results as a function of development
 - ▶ Close interaction with previous two guidelines (Stability and Validation) as these will determine the effects and ability to track any changes in the impurity levels
 - ▶ Toxicity of said impurities is extremely important to understand and evaluate
- ▶ **Classes of Impurities**
 - ▶ Organic impurities (process- and drug-related)
 - ▶ Inorganic impurities
 - ▶ Residual solvents
- ▶ Traditionally, in early development the impurity levels may be a little higher than in later development for 2 reasons:
 - ▶ You don't have enough knowledge around your process to understand how to control it
 - ▶ Can help “tox qualify” the impurities if at higher (i.e., 1% or so) in early development for later development safety

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ICH Q4: Pharmacopoeias

- ▶ A book containing an official list of medicinal drugs together with articles on their preparation and use
- ▶ About ~50 Globally*
 - ▶ Most are branches of the Government
 - ▶ 2 are designed with international scope (EP & Int. Pharm.)
 - ▶ Others are accepted internationally (USP)
 - ▶ All are independent of the compliance sections
 - ▶ 2 supply certification (EP & USP)
 - ▶ All but USP are constrained to include only membership and standards for materials on their market
- ▶ ICH provides guidance when the participating pharmacopoeias do not agree

*http://www.who.int/medicines/publications/pharmacopoeia/WHOPSMQSM2006_2_IndexPharmacopoeiasUpdated.pdf

ICH Q4: Pharmacopoeias

- ▶ The advantage to the drug sponsor is a reduced requirement for validation supporting such methods
 - ▶ the methods themselves are considered validated, and may only require product-specific verification in the particular testing lab
 - ▶ Reviewers are familiar with these methods and how they perform in monitoring quality attributes
- ▶ After all – how many times do we have to explain how to measure pH ☺
- ▶ ICH provides guidance when the participating pharmacopoeias do not agree
 - ▶ Everyone has their standards – ICH helps bridge those standards

ICH Q4: Pharmacopoeias

- Random sampling of ICH Q4 Coverage

1R1	Residue on Ignition
2R1	Test for Extractable Volume of Parenteral Preparations
3R1	Test for Particulate Contamination: Sub-Visible Particles
4AR1	Microbiological Examination of Non-Sterile Products
4BR1	Microbiological Examination of Non-Sterile Products: Tests for specified Micro-organisms
5R1	Disintegration test
6R1	Uniformity of dosage units
7R2	Dissolution
9R1	Tablet Friability
11	Capillary Electrophoresis
12	Analytical Sieving
13	Bulk Density and Tapped Density

ICH Quality Guidelines

- Provide good external guidelines to develop expectations for each activity

Q1	Stability
Q2	Analytical Validation
Q3	Impurities
Q4	Pharmacopoeias
Q5	Quality of Biotechnological Products
Q6	Specifications
Q7	Good Manufacturing Practices
Q8	Pharmaceutical Development
Q9	Quality Risk Management
Q10	Pharmaceutical Quality Systems
Q11	Development and Manufacture of Drug Substances
Q12	Lifecycle Management
Q13	Continuous Manufacturing of Drug Substances and Drug Products
Q14	Analytical Procedure Development

ICH Q5: Examples

Q5A (R1)	Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
Q5B	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
Q5C	Stability Testing of Biotechnological/Biological Products
Q5D	Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
Q5E	Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

1.1 Objectives of the Guideline

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical or clinical strategy. The main emphasis of the document is on quality aspects.

ICH Quality Guidelines

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Q1	Stability
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Q12	Lifecycle Management
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Q14	Analytical Procedure Development

ICH Q6

- ▶ “Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances”
 - ▶ Guideline outlines how and when to set specifications
 - ▶ Includes decision trees
- ▶ What is a specification?
 - ▶ A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.
 - ▶ It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.
 - ▶ "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.
 - ▶ Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.
 - ▶ Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency

Certificate of Analysis (CoA)

- ▶ A CoA is an industrial standard documentation that outlines:
 - ▶ Analytical Tests (which were developed based on Q1, Q2, Q3)
 - ▶ Specifications (defined product criterion under which the quality is met)
 - ▶ Results (actual results for a given batch)
- ▶ Justifications of each basic section required
 - ▶ CoA summarizes this work into a simple document
 - ▶ You have a CoA – you have the quality current control measures for that product

PureBulk
sales@purebulk.com 1-406-251-3270

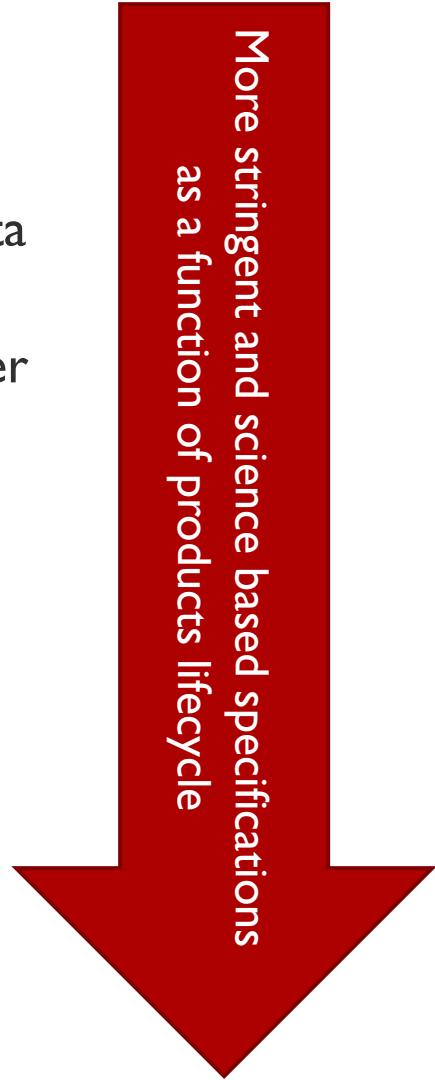
L-Tyrosine
CERTIFICATE OF ANALYSIS

Weight:	1 kilogram (2.2 pounds)	
Synonym:	Beta-(p-hydroxyphenol) Alamine	
Appearance	White crystalline powder	
Molecular weight:	181.0739 grams per mole	
CAS#:	60-18-4	Batch Qty:
Batch Number:	080128	1,000kg
Raw material:	Animal products (non-vegetarian)	
Country of Origin:	China	
Manufacture Date:	2008-01-09	Shelf Life:
Expiration Date:	2011-01-09	3 years
Product Testing:		
Assay:	Limits Results	
Bulk Density:	0.350 ~ 0.450 g/cc	0.398 g/cc
Particle size:	100% thru 20 mesh	Conforms
Loss on drying:	< 0.3%	0.09%
Chloride:	< 0.04%	Conforms
E. coli / Salmonella:	None detected	Conforms
Yeast & Mold:	< 100 cfu/g	Conforms
Total plate count:	< 1000 cfu/g	Conforms
Solubility:	0.045g/100ml	Conforms
Specific rotation:	-9.8° ~ -11.2°	-10.61°
Sulfate:	< 0.04%	Conforms
Conclusion:	Conforms to USP24 Standard	
Storage conditions:	Keep tightly sealed, cool, dry, dark	

Evolution of Specifications

- **Discovery/Early Development**
 - ▶ Fewer batches, Fewer specifications, Wider specifications, More characterization
 - ▶ Data is based on a lot of historical knowledge and animal data
- **Phase 1-3**
 - ▶ Characterization (both clinical and laboratory) leads to better understanding of safety profile
 - ▶ Review physical chemical attributes
 - ▶ Better knowledge around Stability and compatibility
- **Filing**
 - ▶ More batches & history of impurity profiles
 - ▶ Efficient analytical methods
 - ▶ More robust Methods
 - ▶ Increase precision, accuracy
 - ▶ Effective controls
 - ▶ Formal Stability Studies

More stringent and science based specifications
as a function of products lifecycle



Specification for API

- **Identity (2)**
 - Want to ensure you have the right compound!
 - 2 methods like 2 engines on an airplane ... yes you only “need” one
- **Assay (HPLC/NIR/UV-VIS)**
 - Measures the purity of the API – typically >98%
- **HPLC Impurities**
 - <1% unspecified, 1-3% specified, <3% generally unacceptable
 - Again, these will change as a function of development time
- **Specific rotation**
- **Chiral Purity (HPLC or CE)**
- **Water content (Karl Fischer or loss on drying (LOD))**
- **Residual solvents**
- **Heavy Metals**
- **Residue on Ignition (ROI)**

Specification for Tablet

- ▶ Identity (2)
 - ▶ HPLC, TLC, UV, IR, optical rotation
- ▶ Assay (HPLC, NIR, UV/VIS)
- ▶ HPLC impurities
- ▶ Chiral HPLC (or CE)
- ▶ Dissolution or Drug Release
- ▶ Water Content
- ▶ Hardness, Friability, Disintegration
- ▶ Content uniformity
 - ▶ Consistency of a dosage form (90-110%)

ICH Quality Guidelines

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Q12	Lifecycle Management
Q13	Continuous Manufacturing of Drug Substances and Drug Products
Q14	Analytical Procedure Development

ICH Q7

-
- “Guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality”
 - Quality management
 - Personnel
 - Buildings and facilities
 - Process equipment
 - Documentation and records
 - Materials management
 - Production and in-process controls
 - Packaging and identification labelling of APIs and intermediates
 - Storage and distribution
 - Laboratory controls
 - Validation
 - Change control
 - Rejection and re-use of materials
 - Complaints and recalls
 - Agents, brokers, traders, distributors, repackers, and relabellers
 - Specific guidance for APIs manufactured by cell culture/fermentation
 - Contract manufacturers (including laboratories)

ICH Quality Guidelines

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Q13	Continuous Manufacturing of Drug Substances and Drug Products
Q14	Analytical Procedure Development

**QUALITY BY
DESIGN (QBD)**

ICH Q8-Q12: QbD

- ▶ A harmonized pharmaceutical quality **system** applicable across the **life cycle** of the product emphasizing an **integrated** approach to **quality risk management and science**
 - ▶ New ICH guidelines (High level guidelines, more visionary, less prescriptive, flexible regulatory approaches)
 - ▶ Pharmaceutical Development (Q8)
 - ▶ Quality Risk Management (Q9)
 - ▶ Pharmaceutical Quality Systems (Q10)
 - ▶ Continuous validation (Q11)
 - ▶ Development and Manufacture of Drug Substance (Q12)
- ▶ Focused on defining **design space** and proposed **control strategy** to ensure product is maintained in the intended multivariate specifications

Design Space Determination

- ▶ First-principles approach
 - ▶ combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to ***model and predict performance***
 - ▶ *Desirable but not required or expected in every case*
- ▶ Statistically designed experiments (DOEs)
 - ▶ efficient method for determining ***impact of multiple parameters and their interactions***
- ▶ Scale-up correlations
 - ▶ a semi-empirical approach to translate operating conditions between different scales or pieces of equipment
- ▶ Any combination of the above

Why QbD?

- ▶ Higher level of assurance of product quality
- ▶ Cost saving and efficiency for industry and regulators
 - ▶ Facilitate innovation to address unmet medical needs
 - ▶ Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
 - ▶ Minimize/eliminate potential compliance actions, costly penalties and recalls
 - ▶ Enhance opportunities for first cycle approval
 - ▶ Streamline post approval manufacturing changes and regulatory processes
 - ▶ More focused PAI and post approval cGMP inspections
 - ▶ Opportunities for continual improvement

Summary Quality

- ▶ **Leverage guidance's to help guide development processes**
 - ▶ Provides minimum requirements on what you must file. Keep your eye on the ball when developing a pharmaceutical product.
 - ▶ Ensure you are systematic in your approach throughout development. Helps define design space as you move through development
 - ▶ Remember: Guidance's are larger than any single organization, so engage your partners, but understand how their requirements link into these requirements
- ▶ **Goal is to drive quality control methods into the process plant**
 - ▶ PAT technologies that are used in other industries, apply to pharmaceutics
 - ▶ E.g., Moisture, NIR, Particle Size Analysis

Developing a Control Strategy

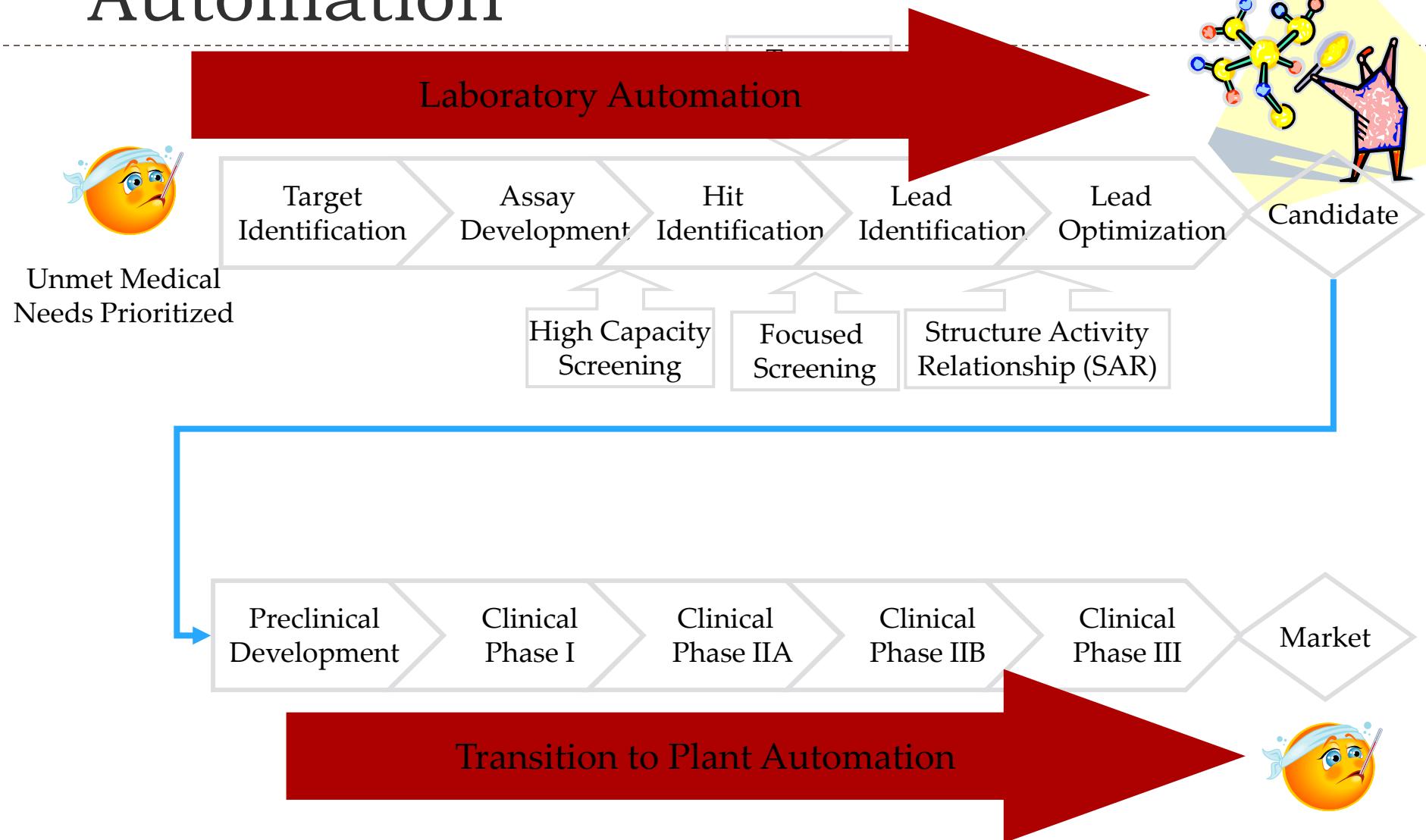


Informatics and Automation

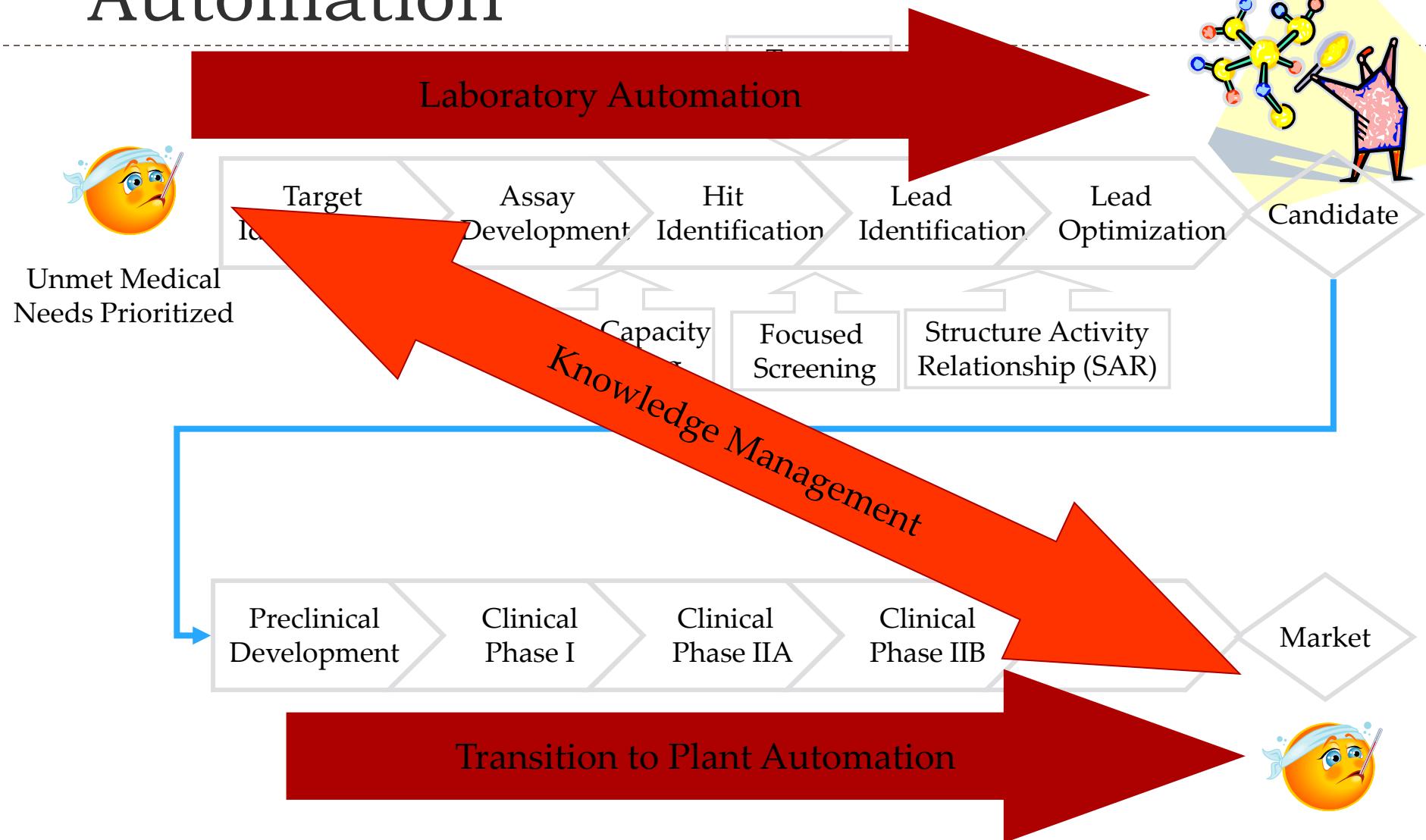
- ▶ Playing a role and changing the manner in which research is conducted
- ▶ Three basic levels in automation
 - ▶ Hardware components
 - ▶ Software components
 - ▶ Knowledge Management Requirements
- ▶ If successful...you'll gain an understanding on how scientists are embracing technology to transform R&D and hopefully give insight to career opportunities



Laboratory to Plant Automation



Laboratory to Plant Automation



Laboratory to Plant Automation: Hardware and Software

▶ Hardware

- ▶ Integrated Robotics to perform traditional laboratory tasks
- ▶ Sophisticated large scale equipment to perform standard unit operations



▶ Software

- ▶ User interface that enables the control of the robotics to large scale equipment but also...
- ▶ Chemometrics
- ▶ Mathematical models that can simulate processes to help design and/or analyze the data



Knowledge Management



Laboratory Automation

- ▶ a system in which a workplace or process has been converted to one that replaces or minimizes human labor with mechanical or electronic equipment*



Automated Solution
Preparation



Sample Prep Robots



Stress Station



LC/MDW

*<http://encarta.msn.com>

Plant Automation

- ▶ Transforming raw materials to finished product

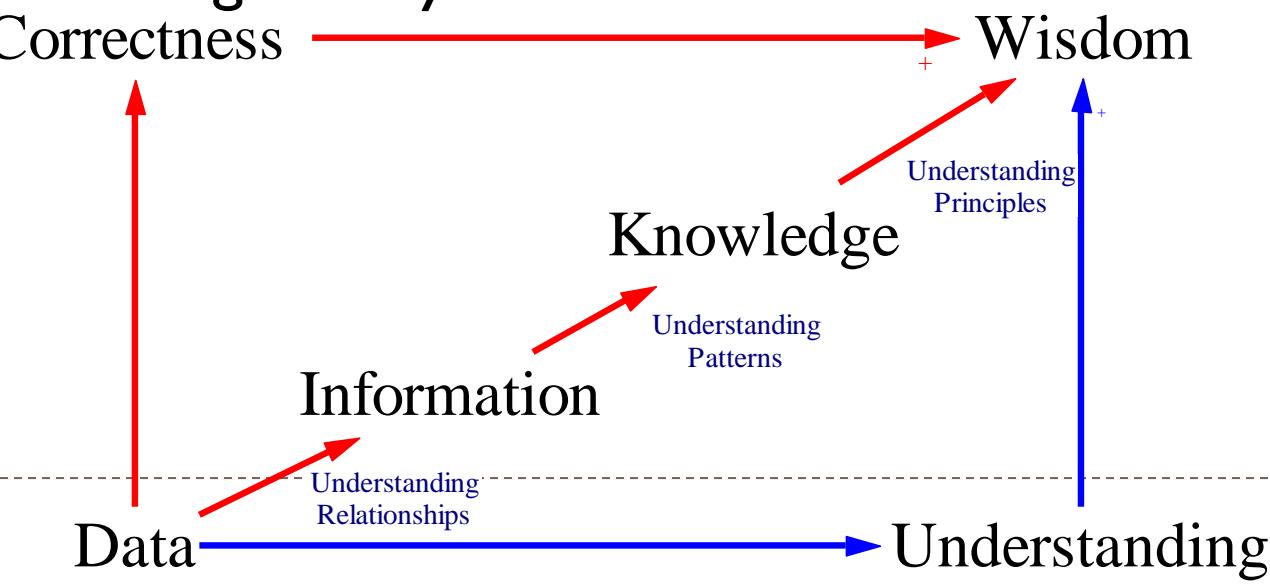


- ▶ Speed, Quality and Safety focused



Knowledge Management

- ▶ As a scientist you need to focus on publishing the right data at the right time
- ▶ Leveraging automation you can generate a lot of information quickly
- ▶ Organizing the information in a manner that can help you transform your data into information and subsequent long term knowledge is key





Knowledge Management

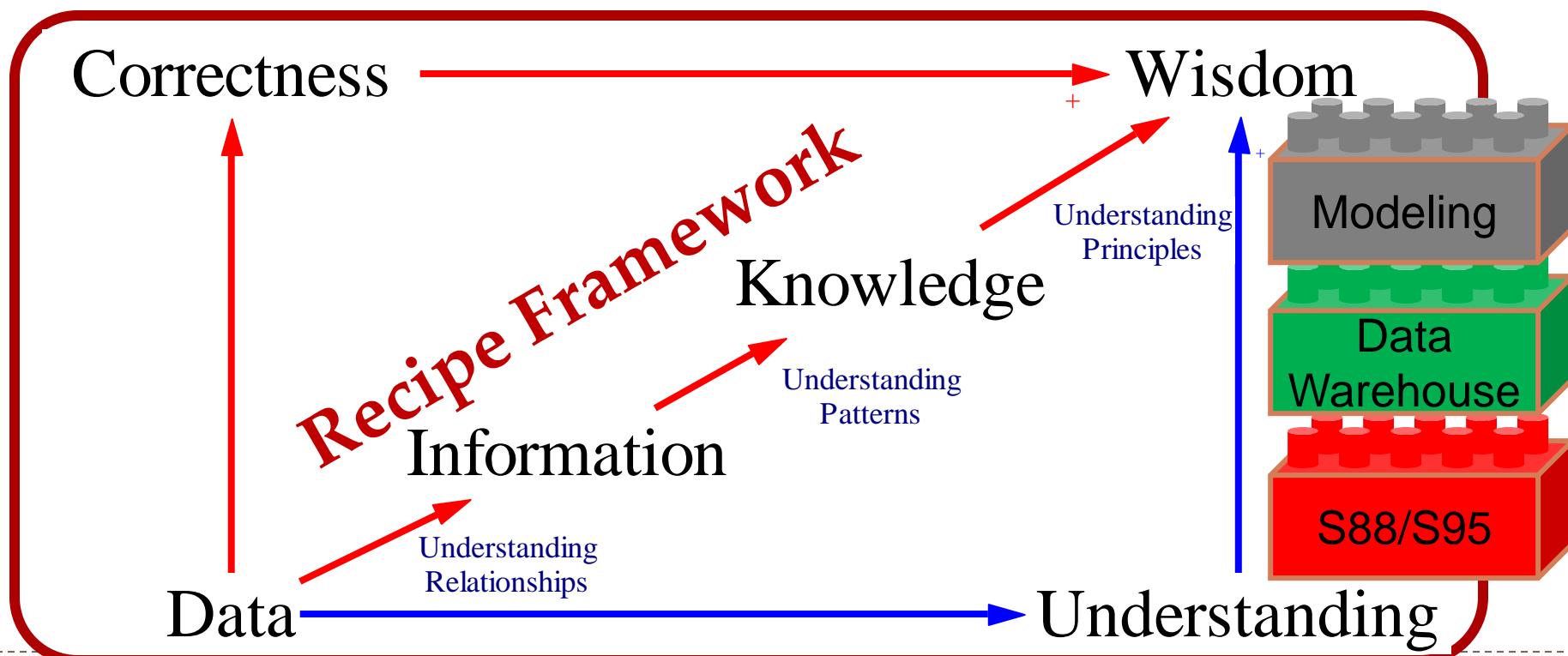


Easy to say...but how?



What's Knowledge?

- ▶ Transformation of data into knowledge and eventually wisdom
 - ▶ Knowledge = Understanding what happened in the past and why
 - ▶ Wisdom = What will happen in the future and why



What is a Database?

- Database is an organized collection of tabulated data
- The term database first arose in the 1960's.
- The relational database model was first proposed by E. Codd of IBM in 1970. The concept did not take off until the release of Oracle and DB2 in 1980s.
- In the 1990s, attention shifted to object-oriented databases. These database can handle more “complicated” datasets (non text, images, ect.). Codd coins the concept of OLAP.
- Currently the XML database is popular. The strategy seeks to dissolve the line between a database and reports.

In general – databases are a self describing collection of integrated data

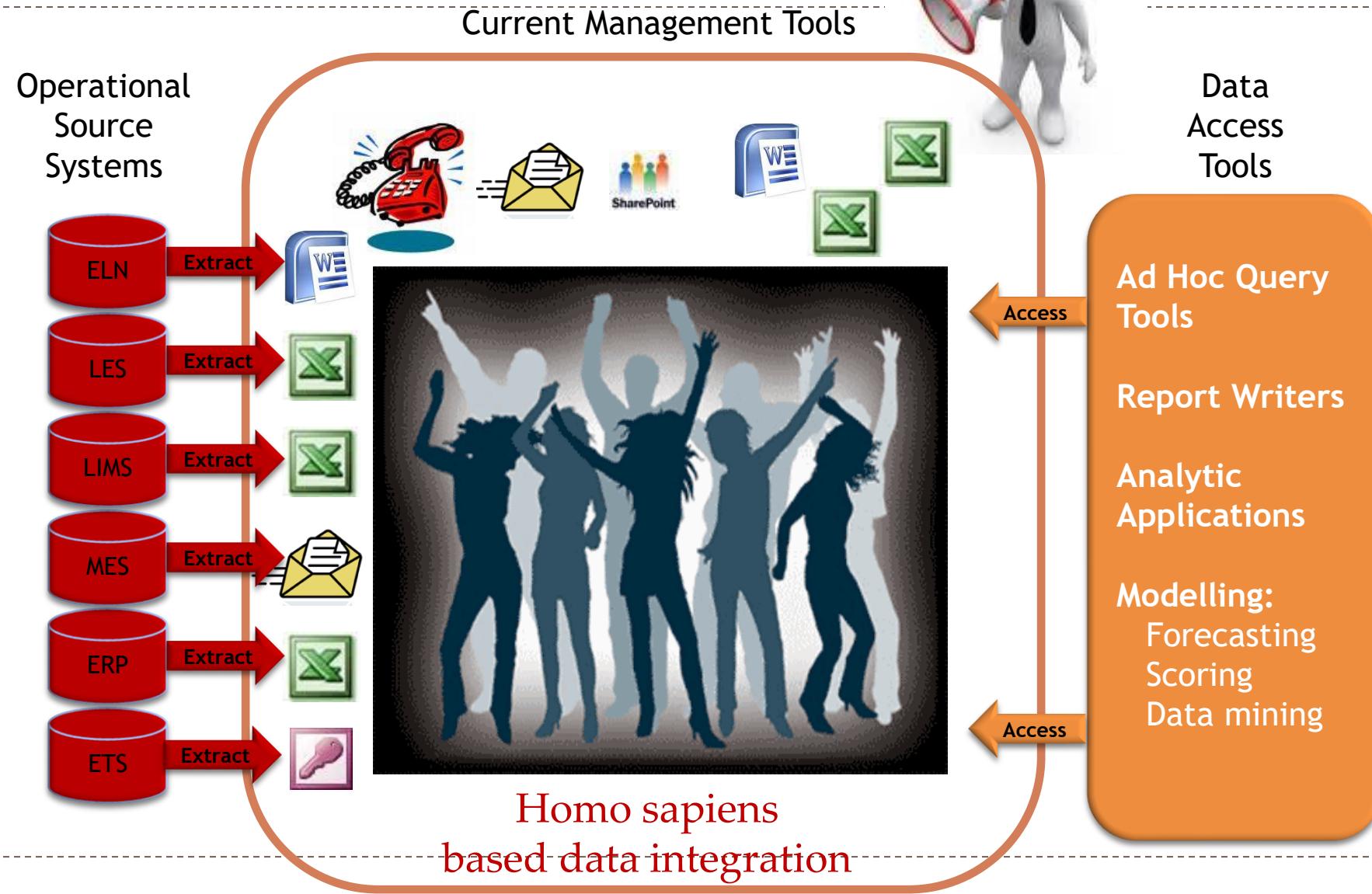


Data warehouses/databases and Scientists

- ▶ “Self describing collection of integrated data”
- ▶ Sounds like a notebook?
 - ▶ A notebook contains all pertinent information that would enable another scientist with similar training to repeat the experiments
 - ▶ Can not delete information
 - ▶ Must be secure
- ▶ Therefore a database can be viewed as an electronic notebook😊



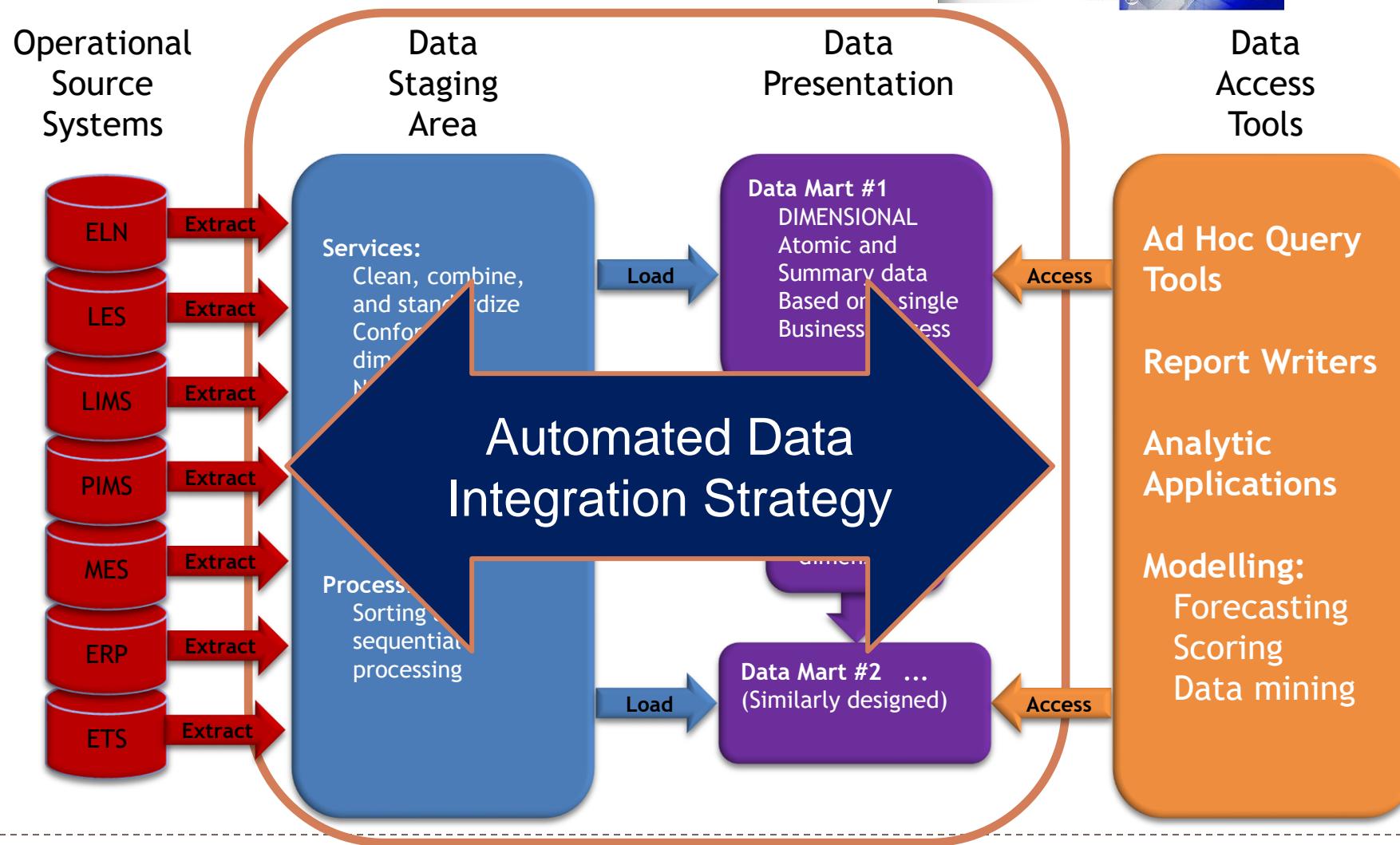
Current Reality





Data Warehouse

S88/S95 Model



Semantic Web



Tim Berners-Lee – 1999 “I have a dream for the web (in which computers) become capable of analyzing all the data on the Web – the content, links and transactions between people and computers. A “Semantic Web” which should make this possible, has yet to emerge, but when it does the day to day mechanisms of trade, bureaucracy and our daily lives will be handled by machines talking to machines. The “intelligent agents” people have touted for ages will finally materialize.”

Informal versus Formal Models

- ▶ Models are intended to be created, amended and interpreted in a mechanism that can ultimately refine knowledge around a particular area of interest for a community.
 - ▶ These models can be used to explain past phenomena (knowledge) and predict future (wisdom). Informal models rely on the context of its reader for interpretation of information to transform into their own knowledge and wisdom and are therefore subjective (i.e., same model can lead to different interpretations). Formal models on the other hand are typically based on first principles, also known as an axiom or postulate(ref), as a starting point of reasoning and objective communication is provided to the reader that lacks controversy for interpretation.
 - ▶ Legislation is a great example of informal models
 - ▶ Loop holes easily created – hard to test
 - ▶ Great science is based on formal models
 - ▶ Easy to test mathematical models

Overview

- ▶ Integrating multiple data sources into a generic and common platform is the foundation of building a data warehouse
- ▶ The data warehouse can be subsequently used to retrieve diverse data to ultimately analyze and build mathematical models that can lead to a broader knowledge of your product
- ▶ Automation is the engine to:
 - ▶ Generate the data
 - ▶ Organize the data
 - ▶ Analyze/Report the data
- ▶ Goal is to move from informal to formal models to demonstrate scientific understanding



Laboratory and Plant Automation Strategies

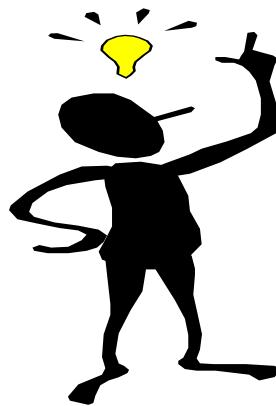
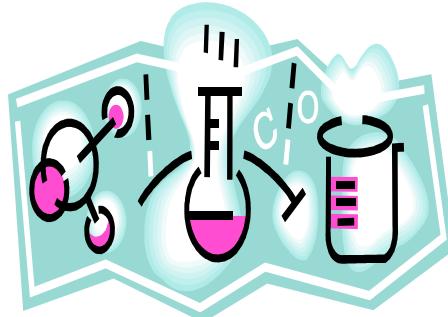
Defining strategies that can help facilitate automated workflows



Conforming the Manual to the Automated Process

► Manual Process

- Extremely Flexible
- Faster initial setup
- However... Tasks become redundant and collecting data limiting step



► Automated Process

- Must standardize
- Longer setup times
- Repetition is a strength



Automating workflows

- ▶ Sample submission to reporting
 - ▶ Various proven approaches
 - ▶ Shipping industry probably the best example
 - ▶ Customer has various, but limited, sample submission possibilities (on-line forms, manual handwritten forms)
 - ▶ Package is tracked via a unique identifier regardless of sample submission process
 - ▶ Theoretical route of package is determined
 - ▶ Actual route is recorded
 - ▶ Follow the scientist
 - ▶ Sample submission = email, phone call, hallway discussion
 - ▶ Package = Sample
 - ▶ Theoretical Route = sample processes required to answer the questions = “Template Based Workflow”
 - ▶ Actual route = what it took to answer the question
 - ▶ Process should enable the workflow – not create a detour
-



Leveraging Currently Owned Technology

- ▶ **Don't fall into the “New Technology” Trap**
 - ▶ Leverage the historical investments of your corporation
 - ▶ Fighting city hall for funding of your project can be difficult, time consuming and have little rewards
- ▶ **Try to minimize diversity in software and hardware**
 - ▶ Common hardware and software enables your staff to become more versatile to move between groups
 - ▶ Leverage knowledge across groups to help trouble shoot and realize unforeseen opportunities
 - ▶ Easy to re-organize teams ☺
- ▶ **Leveraging Currently owned Technology is the most cost effective model**
 - ▶ Current technology may already have the tools you are looking for!



Template Based Workflows

- ▶ Template based workflows are experimental procedures that are standardized for a given process - For example:
 - ▶ Stability assessment – Conditions and Temperatures
 - ▶ LC methods development – columns and modifiers
 - ▶ Dissolution Screening – what preferred media
- ▶ Analytical is largely a service based organization
 - ▶ Customers are requesting similar tasks independent of project
- ▶ Template based workflows enable optimizations to occur as a function of time and support data mining/trending
- ▶ Automation Friendly! *Like Recipes for a Cook!*



Matrix Managing Workflows

► Template Based Workflows

► Design once – execute many times

Workflow	Powder Handling	Liquid Handling	Vision	Raman	L C	I R	TGA	XRD
Crystallizations	X	X	X	X	X	X	X	X
Excipient Compatibility	X	X	X	X	X	X		
Dissolution Testing	X	X	X		X			
Solubility	X	X	X		X			
LC Methods Development	X	X	X		X			
Chemical Reaction Screening	X	X	X	X	X	X		

Instruments are the ingredients for a Cook to design their recipes!!





Case Studies: Template Based Workflows Utilizing “Databases”

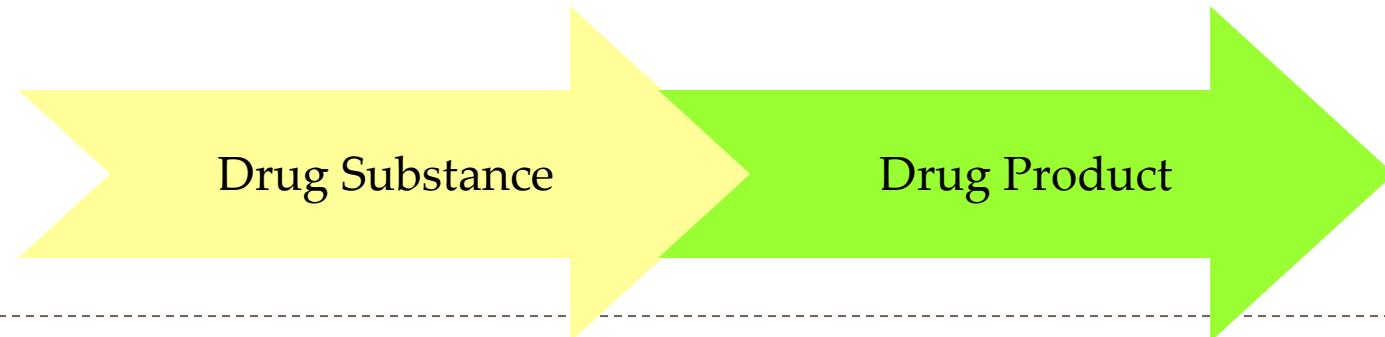


Developing Stability Indicating LC Methods



Automated Stability Assessment Process

- ▶ ASAP is a term used to describe the following research activities (i.e., non-GxP):
 - ▶ Drug Substance Stress Studies
 - ▶ Excipient Compatibility Studies
- ▶ These studies are used to help develop a better understanding of the stability of our compounds from a chemical standpoint. Solution, suspensions and dry blends are tested through the process.



Importance of Formulation

A bad formulation can make a good compound look bad!

But...

A good formulation can not make a bad compound look good!

Drug discovery has gone through a lot of work to bring the compound forward thus assuring a good formulation to give the compound its best chance of success is mandatory

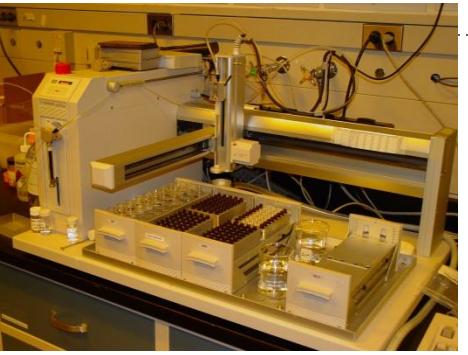
A specific and robust analytical method is a key component to decipher good formulations from bad formulation



Tools for ASAP



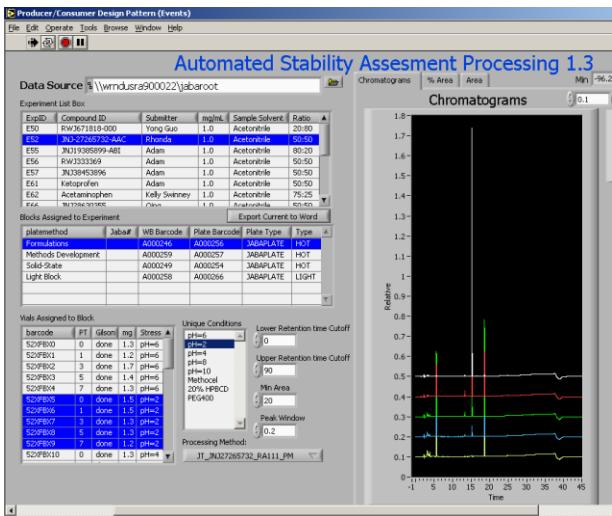
Solids Weighing



Liquid Handling



Stress Station



Report Findings



Automated Solution Preparation



LC/MDW



Automated Mobile Phase Generator



Help Automate Solution Preparation while forcing electronic data collection



Automated Mobile Phase Preparations

- ▶ The Automated Mobile Phase Generator is a system designed for the preparation of routine mobile phases.
- ▶ GMP Compliant
- ▶ Accuracy meets or exceeds Class A Graduated Cylinders
- ▶ Automatic Labeling that complies with our SOPs
- ▶ Labels include Expiration dates, lot #'s, CAS# and warnings.



AMPG Printed Label

- ▶ Three labels printed on 1 sheet
 - ▶ One for the notebook documenting the mobile phase preparation + One for the bottle
 - ▶ Always reports the actual volume of each mobile on the label

Mobile Phase Name
50%-Water, 50% Acetonitrile

01/30/2007

Results									
Component	Density (gm/mL)	Actual % (%)	Target Vol (mL)	Actual Vol (mL)	Actual Mass (gm)	Manufacturer	Lot Number	CAS Number	Expiration
Water	0.9971	50.00	1000.00	1000.09	997.19	Burdick&Jackson	CP281	7732-18-5	11/16/2006
Acetonitrile	0.7860	50.00	1000.00	999.91	785.93	Burdick&Jackson	CP536	75-05-8	11/16/2006
Totals		100.00	2000.00	2000.00	1783.12				
Total 100.00 %	Prepared By jtroisi	Preparation date 08/01/2006	Preparation ID 02-21-2006_10-32-02	Max Error 0.009 %					
Preparation Notes	Hazards/Notes								



Case Studies: Template Based Workflows



Developing Stability Indicating LC Methods



Manual Operations

- ▶ Prepare Solutions
 - ▶ Weigh Compound
 - ▶ Add Stress solutions
- ▶ Place in ovens for stressing
- ▶ Pull samples over time
- ▶ Prepare samples for LC analysis
- ▶ Run LC on samples
- ▶ Analyze data
- ▶ Report findings

Automated

← Powder Dispensing Robot

← Liquid Handler

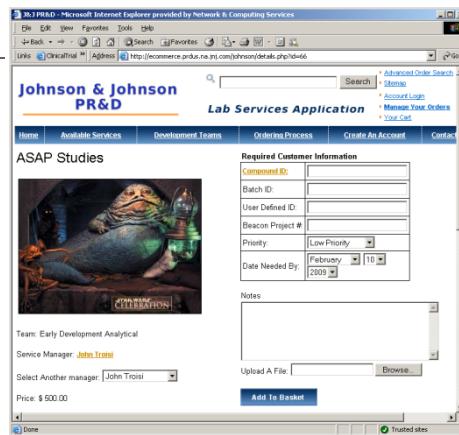
} ← Custom System

← Liquid Handler

} ← Standard LCs and Software



Sample Process Overview



A screenshot of a Microsoft Internet Explorer browser window. The title bar says "Microsoft Internet Explorer provided by Network & Computing Services". The address bar shows "http://ecommerce.prds.jnj.com/johnson/details.php?d=6". The main content area is titled "Johnson & Johnson PR&D" and "Lab Services Application". It has tabs for "Home", "Available Services", "Development Teams", "Ordering Process", "Create An Account", and "Contact". A sub-section titled "ASAP Studies" features a cartoon character of Jabba the Hutt. Below it, there's a form for "Required Customer Information" with fields for "Compound ID", "Batch ID", "User Defined ID", "Beacon Project #", "Priority" (set to "Low Priority"), and "Date Needed By" (set to "February 2009"). There's also a "Notes" text area and "Upload A File" and "Browse" buttons. At the bottom, there's an "Add To Basket" button.

Sample Submission



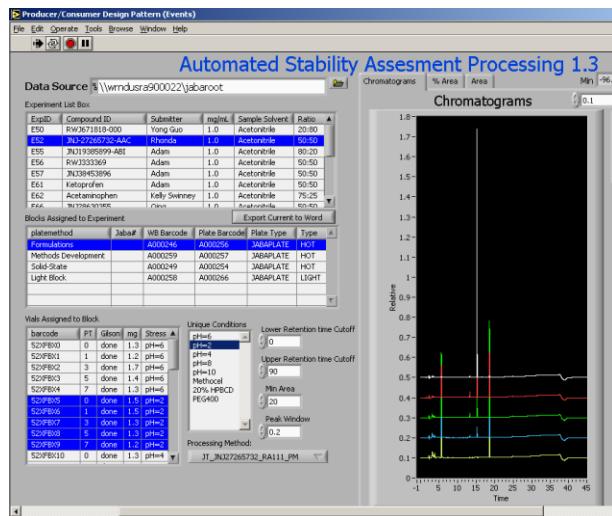
Dispense into Vials
and Label Accordingly



Add Stress Solvents



Stress and Sample



Report Findings



Assay by LC



Add Sample Diluent

Dispense Drug into Vials

- ▶ Autodose adds ~1 mg into ~160 vials
 - ▶ Takes ~ 2 hours to complete
 - ▶ Brown Vials for all but light box studies



Gilson Reconstitutes Samples

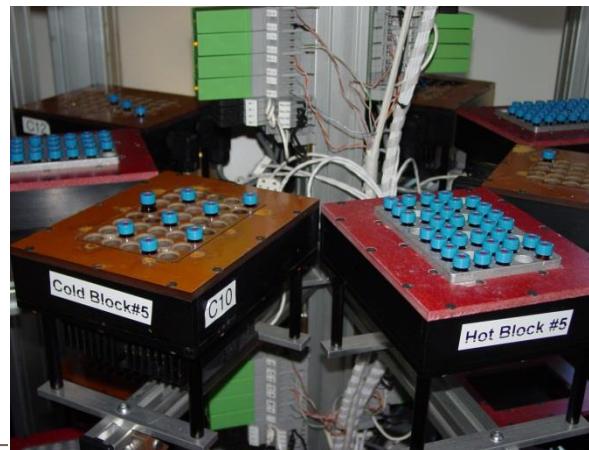
- ▶ Samples are prepared for study by diluting to a set concentration.
- ▶ Concentration depends on the solubility of the compound and final desired sample solvent



The Degradation Robot



- ▶ Conditions
 - ▶ Solid State
 - ▶ Heat
 - ▶ Heat + 75% RH
 - ▶ Indoor Fluorescent Light
 - ▶ Solution/Suspension
 - ▶ Acid/Base
 - ▶ pH 2, 4, 6, 8 and 10
 - ▶ HOOH
 - ▶ Indoor Fluorescent Light
- ▶ Provides temperature control



The Degradation Robot (Movie)



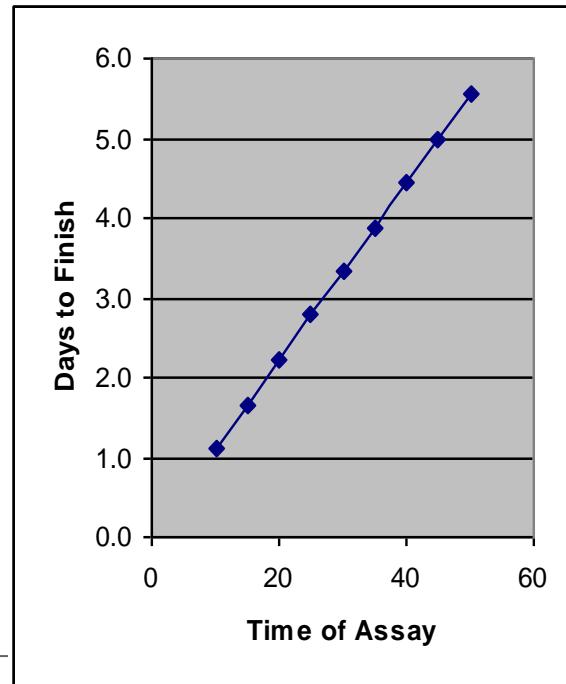
LC Sample Preparation of Stressed Samples

- ▶ Samples are diluted to a final sample concentration for LC analysis
 - ▶ Need to know sample solvent composition
 - ▶ Solid state samples prepared in sample solvent
 - ▶ Aqueous samples cut with pure organic

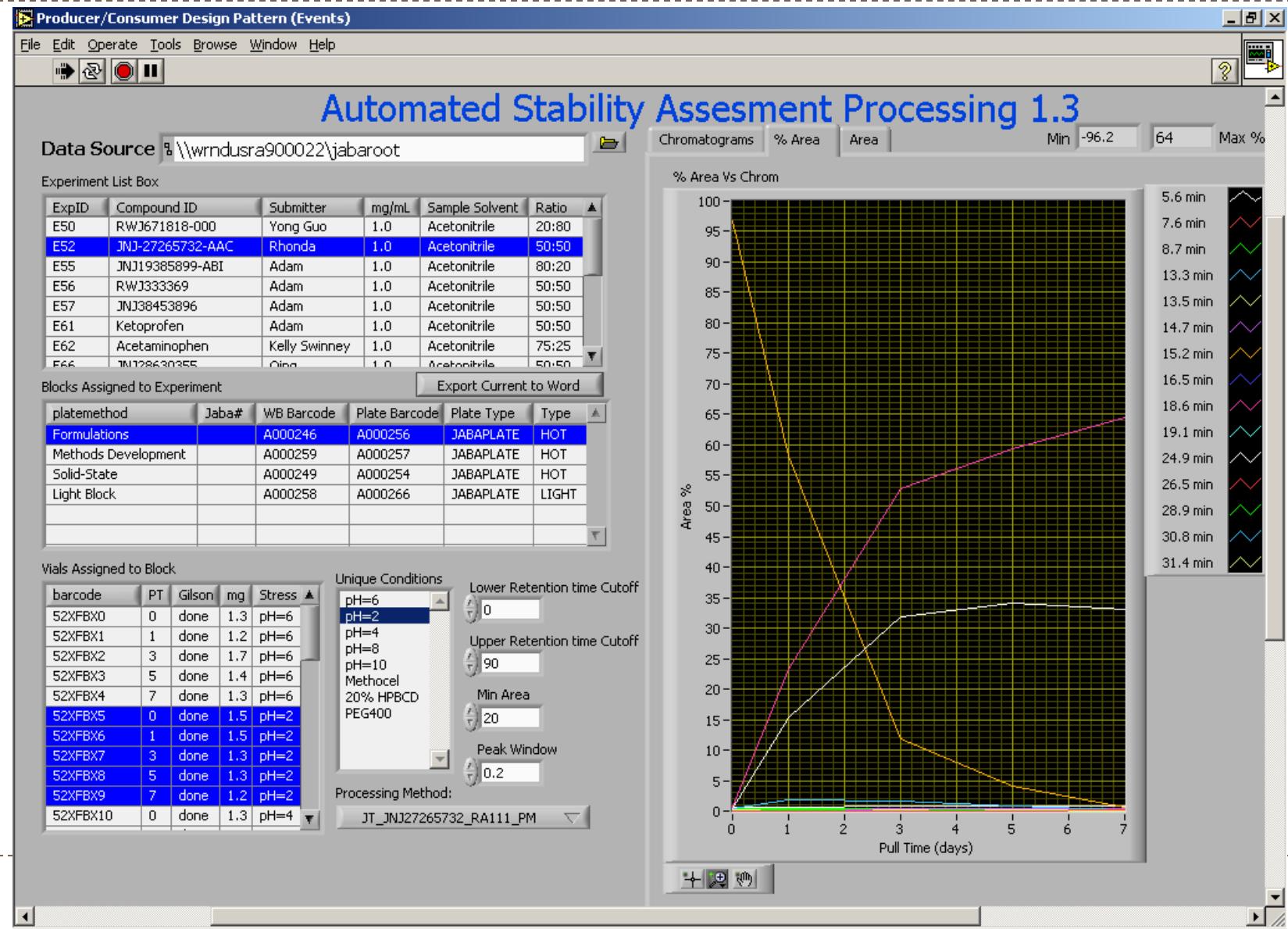


LC Analysis of Stressed Samples

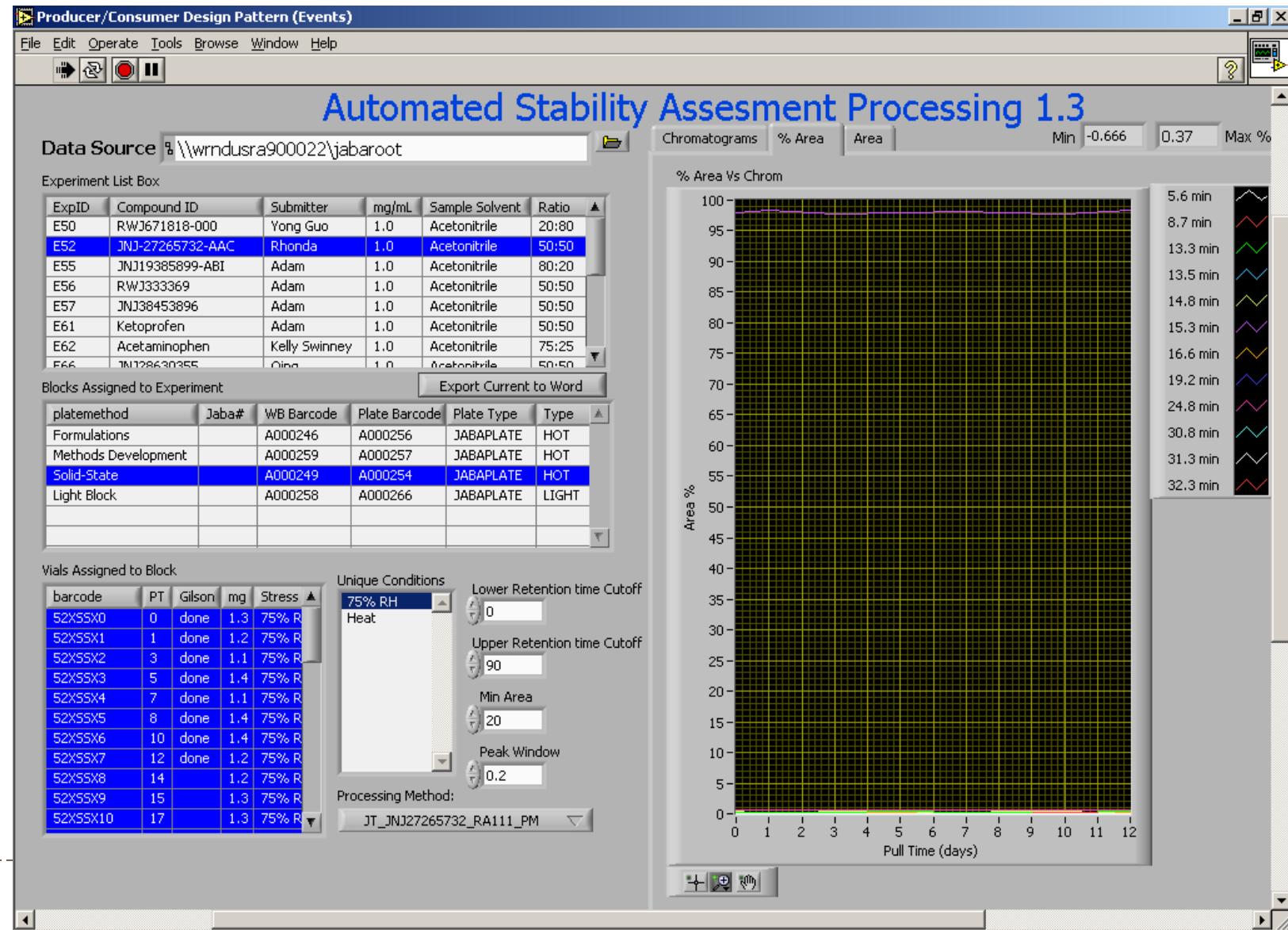
- ▶ Samples are then analyzed by LC
 - ▶ Generic method or method supplied – depends on phase of development



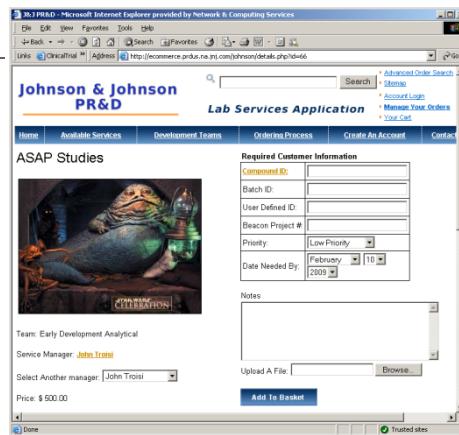
ASAP Portal



ASAP Portal – UI to tap into “database”



Sample Process Overview



A screenshot of a Microsoft Internet Explorer browser window displaying the "Johnson & Johnson PR&D" website. The page is titled "Lab Services Application" and shows a form for "ASAP Studies". The form includes fields for "Compound ID", "Batch ID", "User Defined ID", "Beacon Project #", "Priority" (set to "Low Priority"), and "Date Needed By" (set to "February 2009"). There is also a "Notes" text area and a "Upload A File" section with a "Browse" button. At the bottom, there is an "Add To Basket" button.

Sample Submission



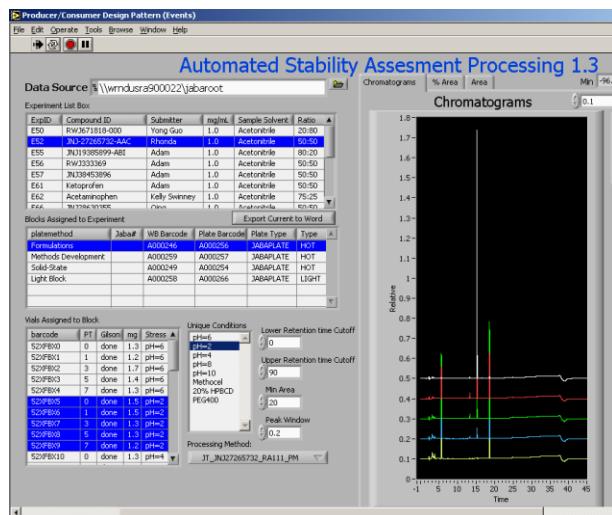
Dispense into Vials
and Label Accordingly



Add Stress Solvents



Stress and Sample



Report Findings



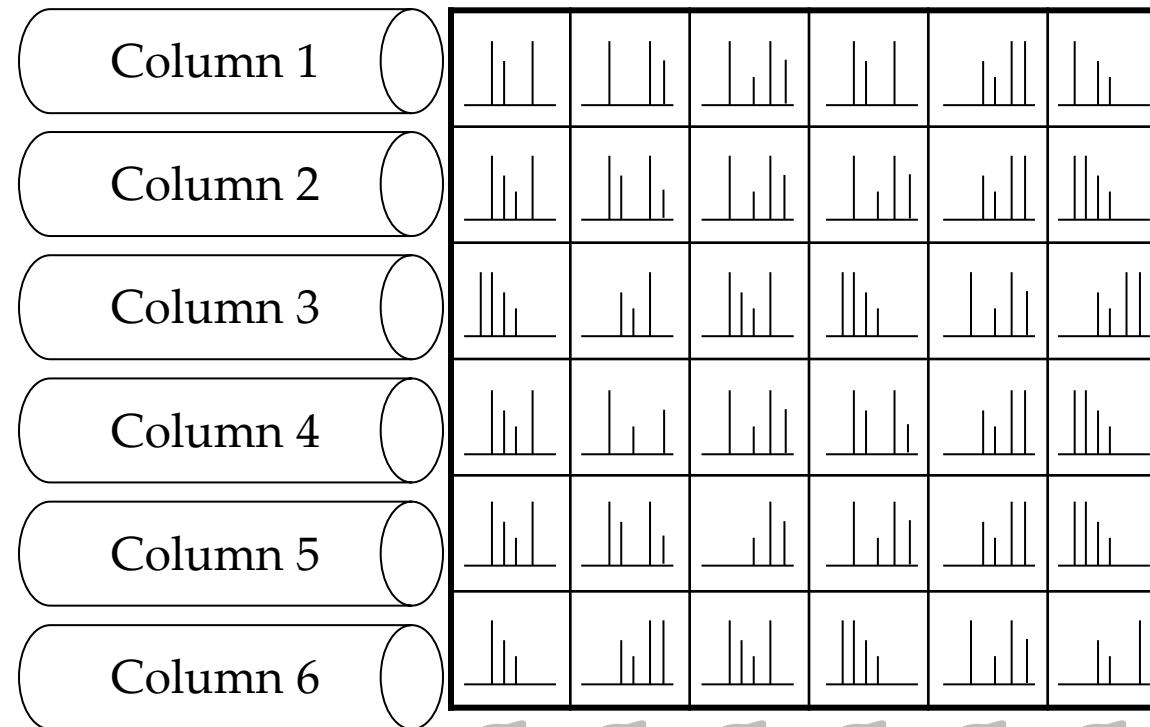
Assay by LC



Add Sample Diluent

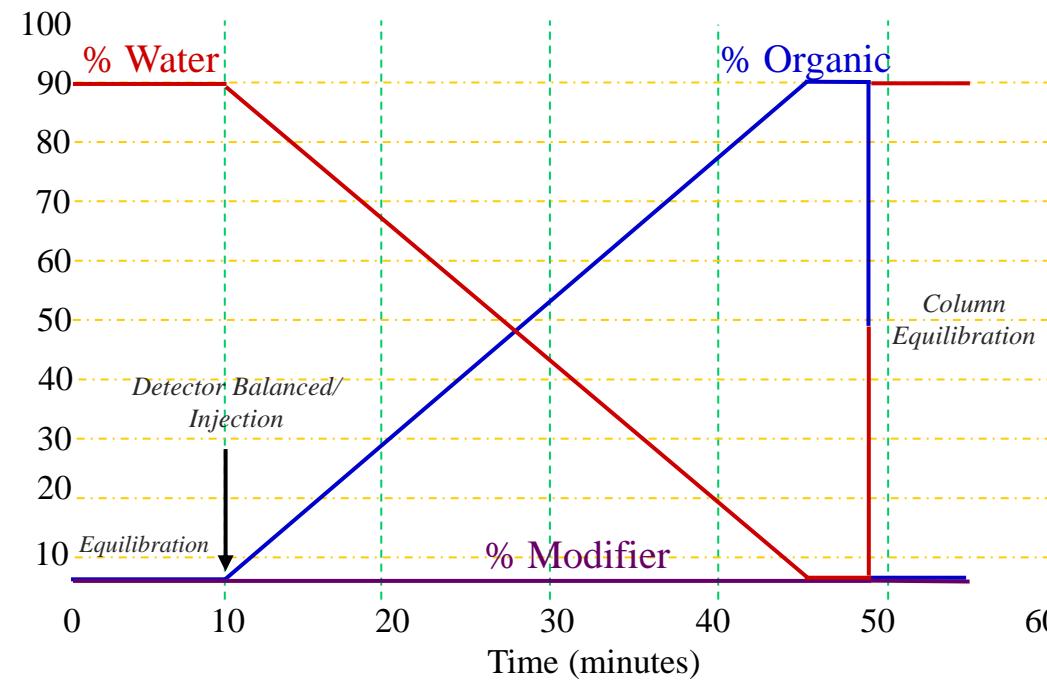
Automated Orthogonal Screening

Method Development Workstation: an Agilent 1100 HPLC that is configured with a column switcher and customized to handle multiple mobile phases.



Instrument Setup

- ▶ Stock Modifiers are prepared at 20 times desired concentration
- ▶ Hook up columns, purge and you're off!



Template Sample Set/Sequence

- ▶ Standard template enables efficient setup of screen
 - ▶ Two custom fields (Column_Description & Modifier) store the conditions for the particular run

Methods_Dev_Screen_2006 on WATP as afermier/Chemist - Project

File Edit View Tools Database Application Help

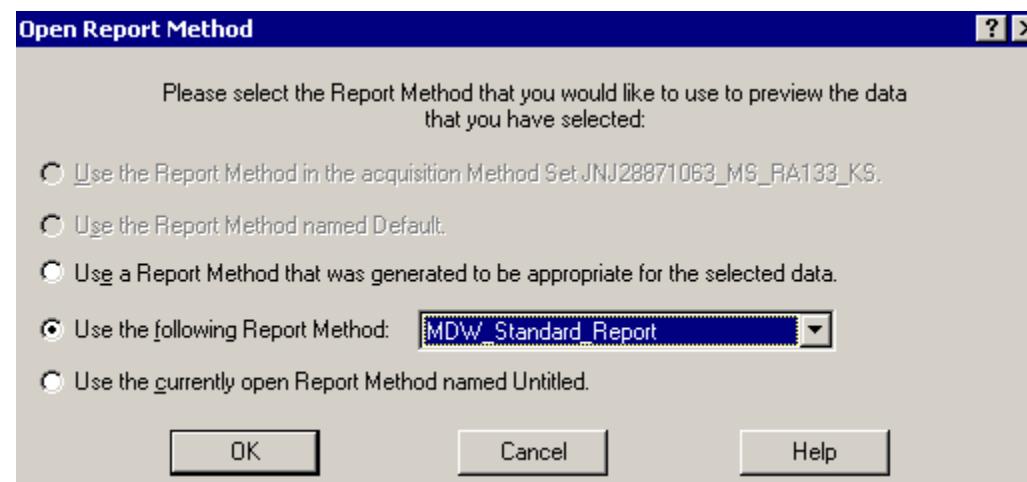
Filter By: IMDW_Real_Injections Edit View Update

Sample Sets Injections Channels Methods Result Sets Results Peaks Sign Offs Curves View Filters Custom Fields Audit Trails

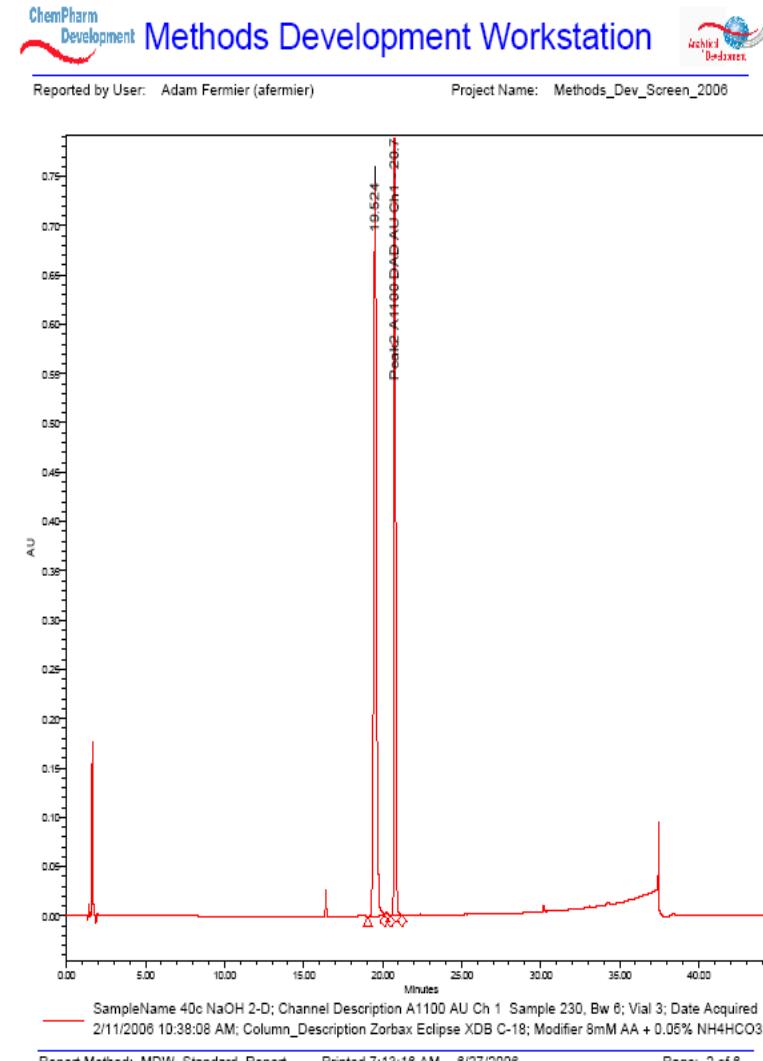
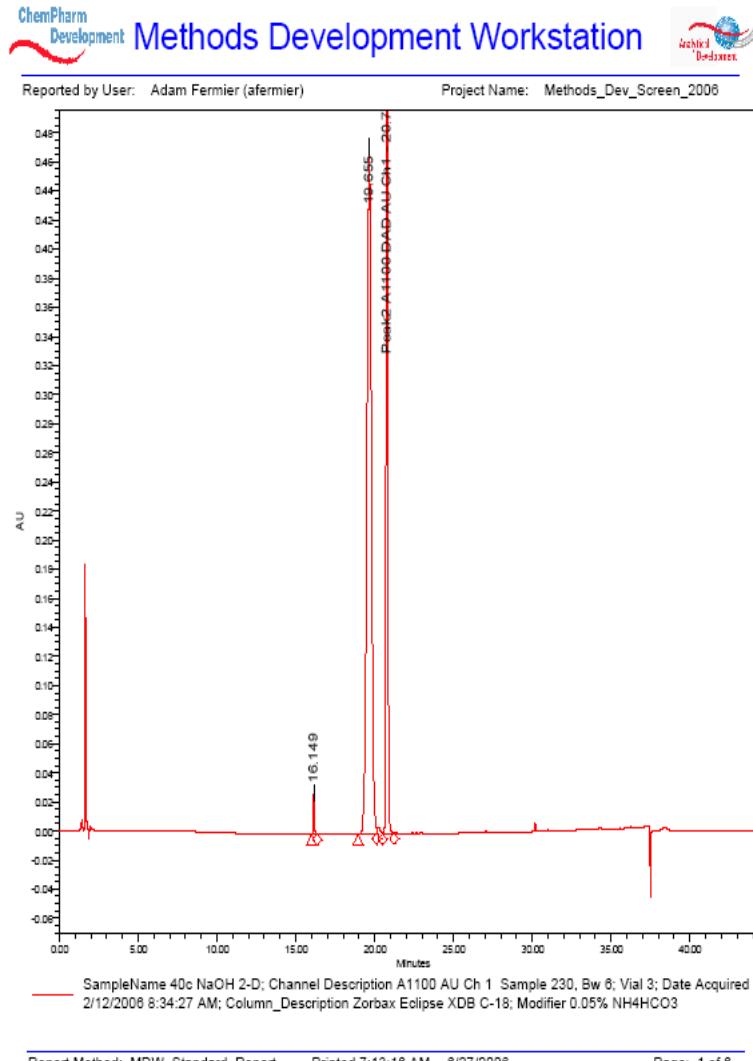
	Injection Volume (uL)	SampleName	Vial	Injection	Date Acquired	Sample Set Name	Column_Description	Modifier
1	10.00	Blank H2O/ACN 20/80	2	1	6/9/2006 8:54:22 PM	060906_28871063_KS_RA133	Synergi Polar-RP 4u	0.1% Formic Acid
2	10.00	28871063	3	1	6/9/2006 9:40:51 PM	060906_28871063_KS_RA133	Synergi Polar-RP 4u	0.1% Formic Acid
3	10.00	Blank H2O/ACN 20/80	2	1	6/9/2006 10:57:50 PM	060906_28871063_KS_RA133	Atlantis dC18 5u	0.1% Formic Acid
4	10.00	28871063	3	1	6/9/2006 11:44:45 PM	060906_28871063_KS_RA133	Atlantis dC18 5u	0.1% Formic Acid
5	10.00	Blank H2O/ACN 20/80	2	1	6/10/2006 1:01:47 AM	060906_28871063_KS_RA133	Luna C18 (2) 5um	0.1% Formic Acid
6	10.00	28871063	3	1	6/10/2006 1:48:14 AM	060906_28871063_KS_RA133	Luna C18 (2) 5um	0.1% Formic Acid
7	10.00	Blank H2O/ACN 20/80	2	1	6/10/2006 3:05:18 AM	060906_28871063_KS_RA133	Eclipse XDB 3.5um	0.1% Formic Acid
8	10.00	28871063	3	1	6/10/2006 3:51:45 AM	060906_28871063_KS_RA133	Eclipse XDB 3.5um	0.1% Formic Acid
9	10.00	Blank H2O/ACN 20/80	2	1	6/10/2006 5:12:18 AM	060906_28871063_KS_RA133	Gemini C18 5um	0.1% Formic Acid
10	10.00	28871063	3	1	6/10/2006 5:58:45 AM	060906_28871063_KS_RA133	Gemini C18 5um	0.1% Formic Acid
11	10.00	Blank H2O/ACN 20/80	2	1	6/10/2006 7:15:46 AM	060906_28871063_KS_RA133	Xterra RP 18 3.5um	0.1% Formic Acid
12	10.00	28871063	3	1	6/10/2006 8:02:12 AM	060906_28871063_KS_RA133	Xterra RP 18 3.5um	0.1% Formic Acid
13	10.00	Blank H2O/ACN 20/80	2	1	6/10/2006 9:25:24 AM	060906_28871063_KS_RA133	Synergi Polar-RP 4u	8mM AA + 0.1% Acetic Acid
14	10.00	28871063	3	1	6/10/2006 10:11:49 AM	060906_28871063_KS_RA133	Synergi Polar-RP 4u	8mM AA + 0.1% Acetic Acid
15	10.00	Blank H2O/ACN 20/80	2	1	6/10/2006 11:28:48 AM	060906_28871063_KS_RA133	Atlantis dC18 5um	8mM AA + 0.1% Acetic Acid
16	10.00	28871063	3	1	6/10/2006 12:15:13 PM	060906_28871063_KS_RA133	Atlantis dC18 5um	8mM AA + 0.1% Acetic Acid

Reporting

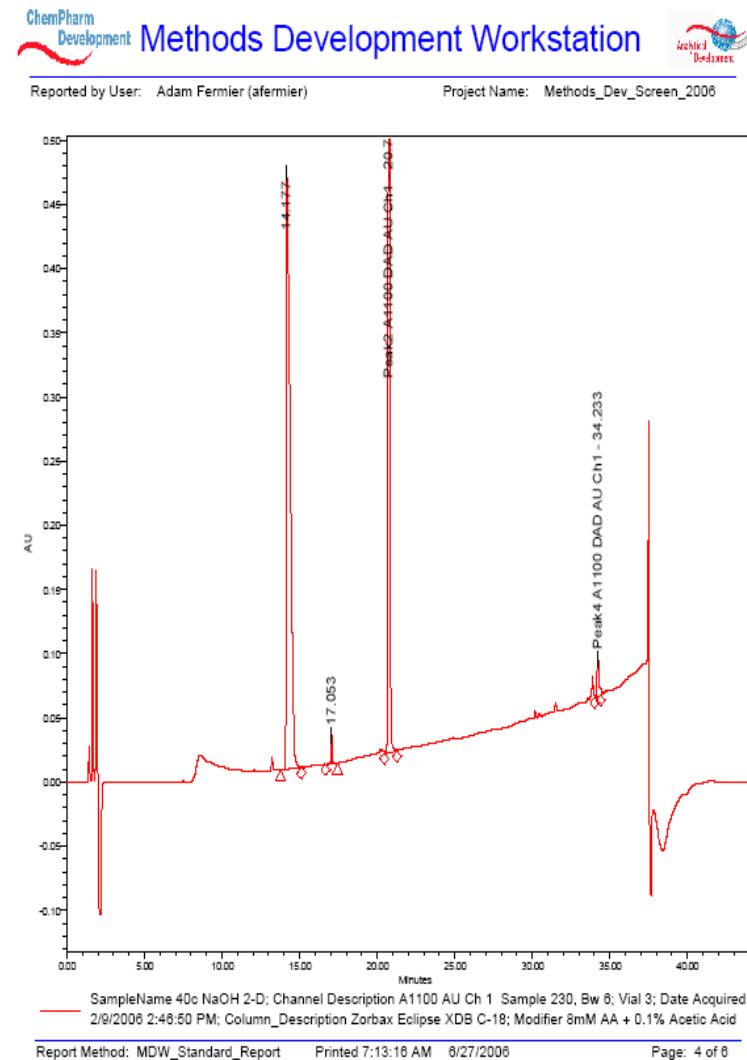
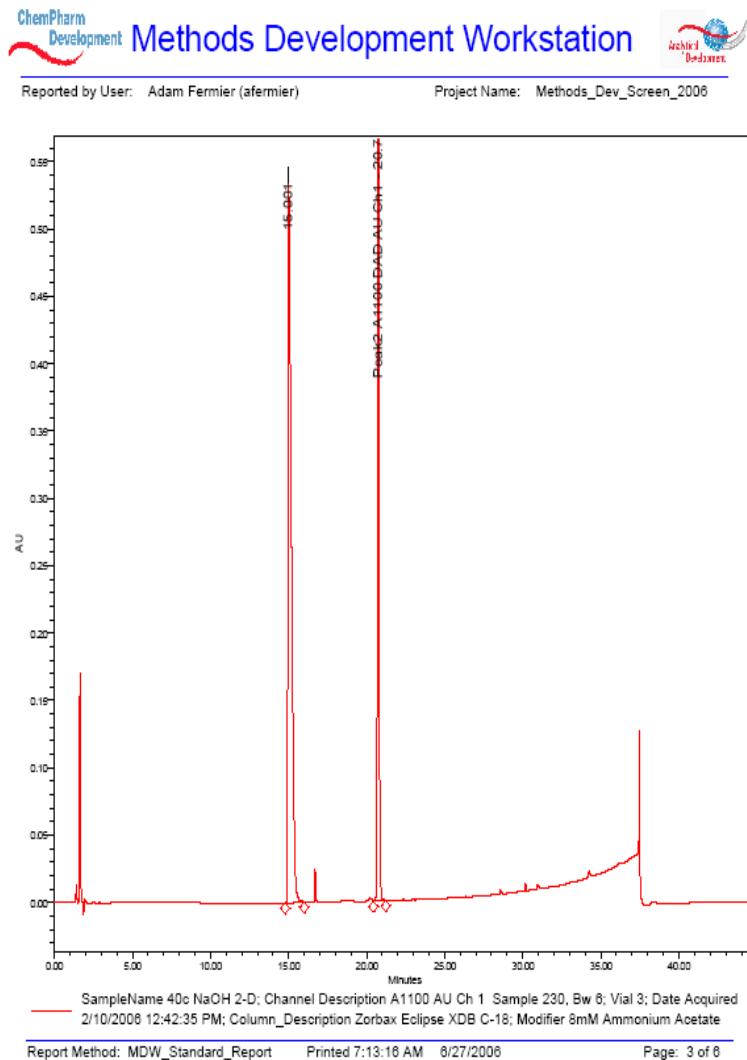
- ▶ Most CDS have quite extensive built in reporting – use them!
 - ▶ Here we created a template that organizes the chromatograms according to column and modifier
 - ▶ Therefore the user simply selects the chromatographic runs and runs the “MDW Standard Report”



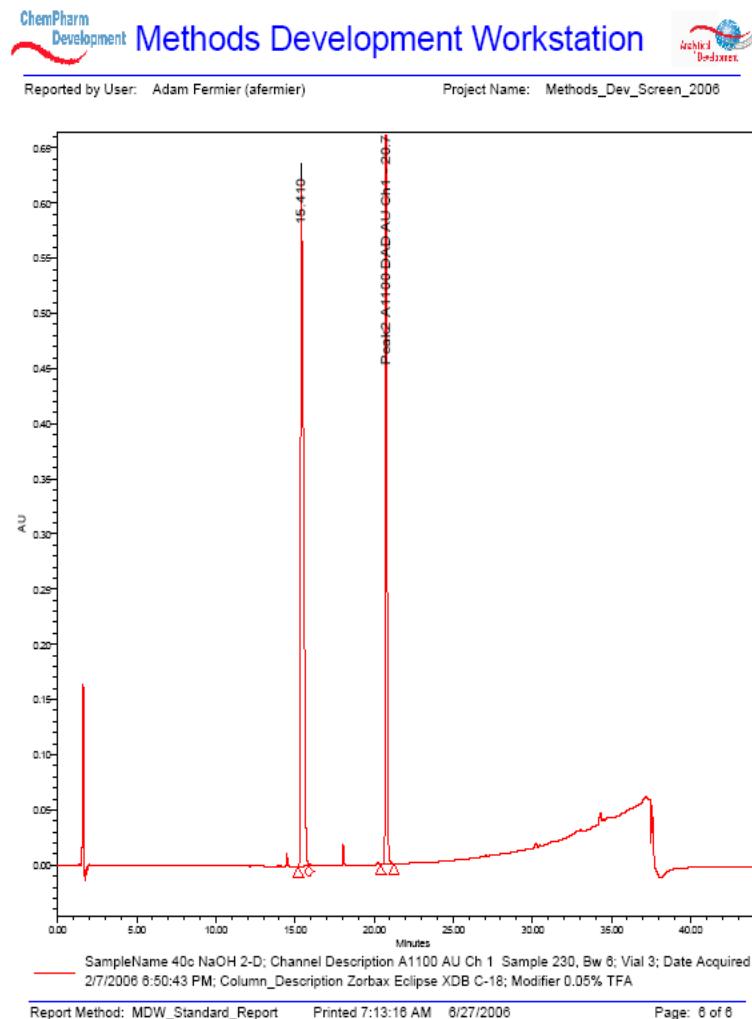
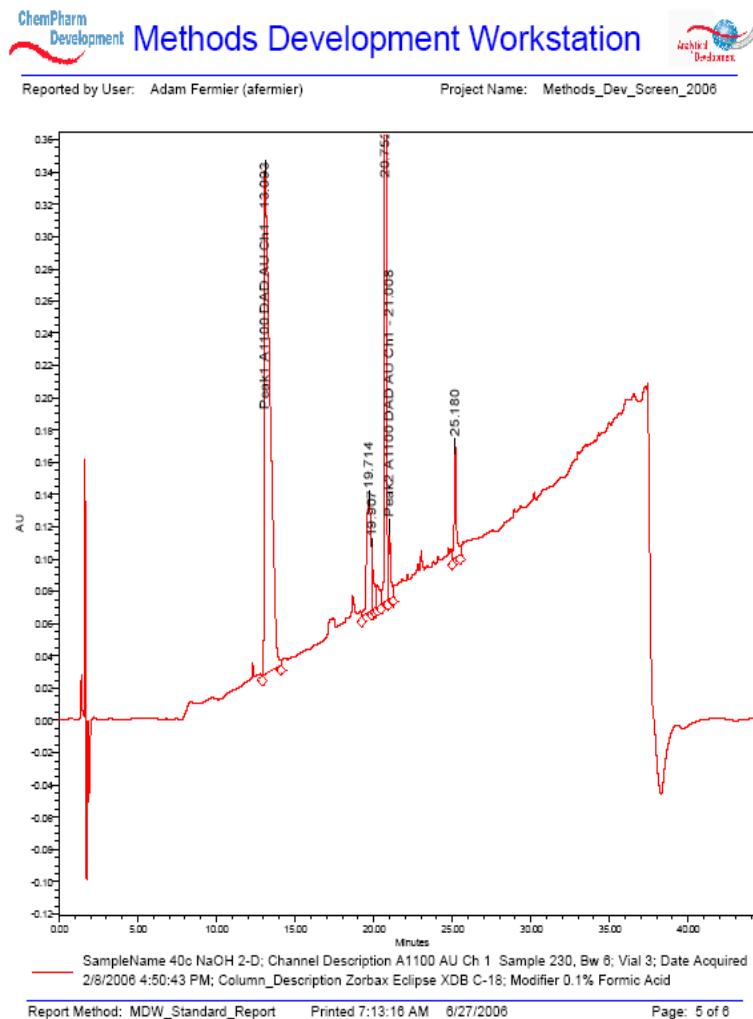
Final Report Generated using Empower



Final Report Generated using Empower



Final Report Generated using Empower



Methods Development Workstation Database

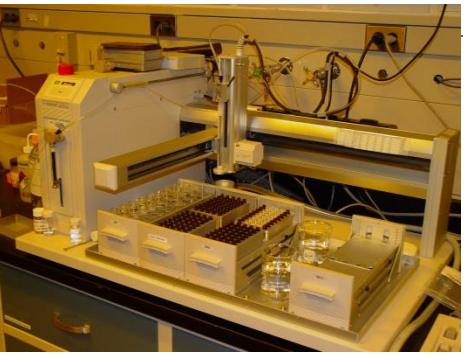
- ▶ **Leveraging Empower Database**
 - ▶ Utilize custom fields and store each study linked to a compound or experiment ID
 - ▶ Since most methods development chemists have access to this database – they can view the data without asking permission
 - ▶ Template based sample set provides for a “fast” approach to setup experiments
- ▶ **Hardware costs are minimal ~\$6,000**
 - ▶ Valves ~60% of costs, custom machining, PLC, ect provides the rest of the cost
- ▶ **Balancing software and hardware enabled an inexpensive solution to be delivered to the scientists**



Tools for ASAP



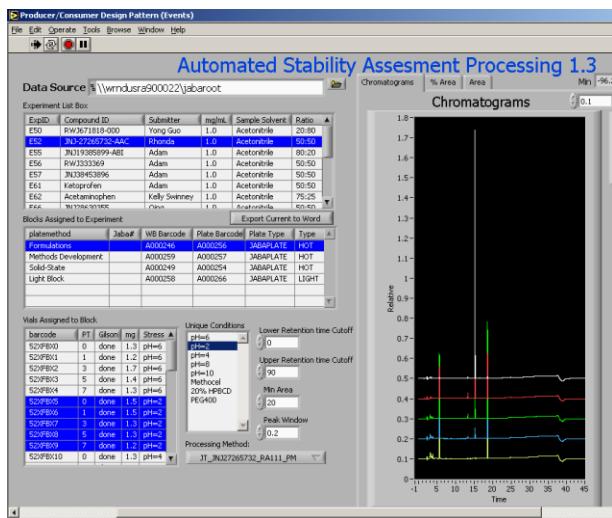
Solids Weighing



Liquid Handling



LC/MDW



Report Findings



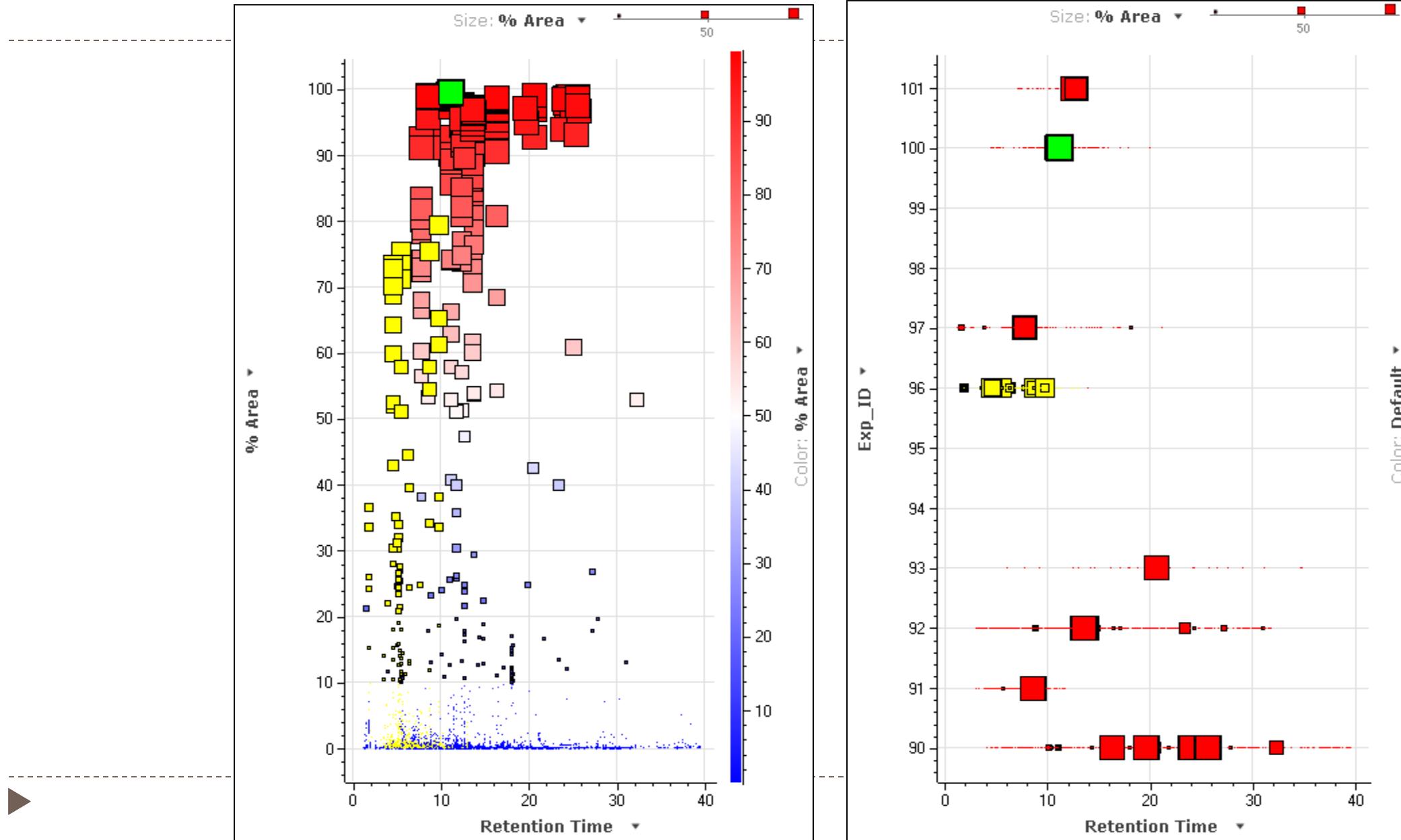
Automated Solution Preparation



Stress Station



Visualization of CPD Data ~10,000 points



Summary

- ▶ The Tier I process was automated using the Autodose, Gilson and JABA
- ▶ At the end of 7 days:
 - ▶ Methods development and formulations block finished, light box ~80% finished, solid state takes 1 month
- ▶ Provides samples ready for LC analysis
- ▶ Applied to 25 compounds in the past year
- ▶ Capacity of 100 compounds per year
- ▶ High degree of group acceptance
- ▶ Allows easy ranking of the relative stability of a series of compounds
- ▶ Allows stability approximations via the Arrhenius equation





Case Studies: Mathematical Modeling



Building a mathematical model that describes your process



Chemometrics: Mathematical Modeling

- ▶ A chemical discipline that uses mathematical and statistical methods to design or select optimal measurement procedures and experiments and to provide maximum chemical information by analyzing chemical data.
- ▶ Chemometrics is actually a collection of procedures, mathematics, and statistics that can help chemists perform well-designed experiments and proceed rapidly from data, to information, to knowledge of chemical systems and processes.

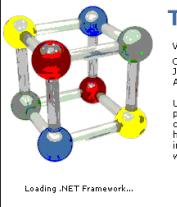


*<http://www.answers.com/topic/chemometrics>

Chemometric Modeling

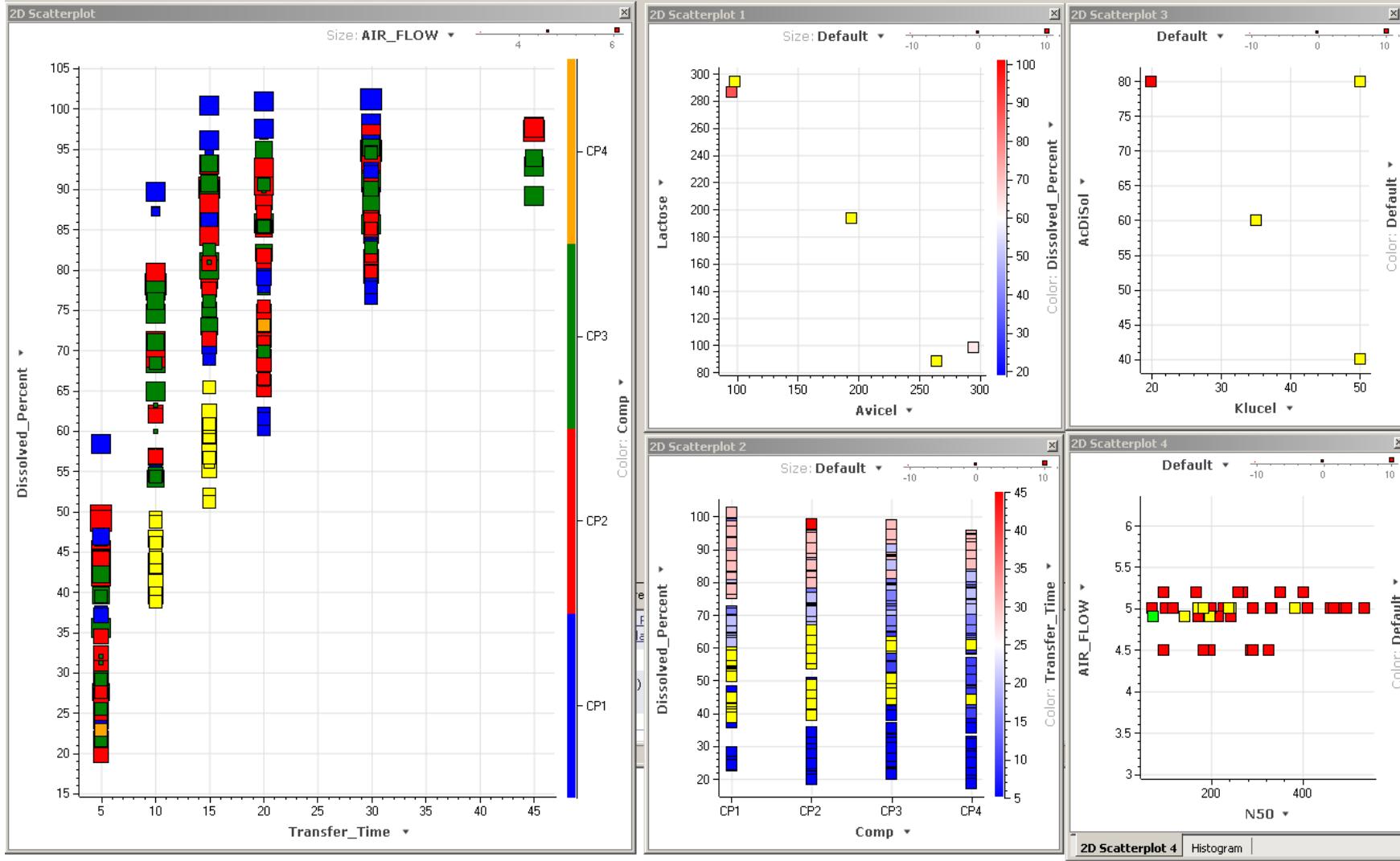
- ▶ Traditional Modeling
 - ▶ Linear Least Squares (1:1)
 - ▶ Calibration plots: Relates a signal to a known value
 - ▶ Partial Least Squares (1:many)
 - ▶ Used to transform spectra to a univariate measurement
 - ▶ Partial Least Squares 2 (many to many)
- ▶ Mining
 - ▶ Ability to visualize data sets quickly to gain an understanding on relationships without a prior knowledge and/or model
 - ▶ Neural Networks





Loading .NET Framework...

Data Visualization



Correlation to Dissolution

► PLS2 Model for Dissolution

Get value out of your data!

Version 9.7

Copyright © 1986 - 2007 CAMO Software AS

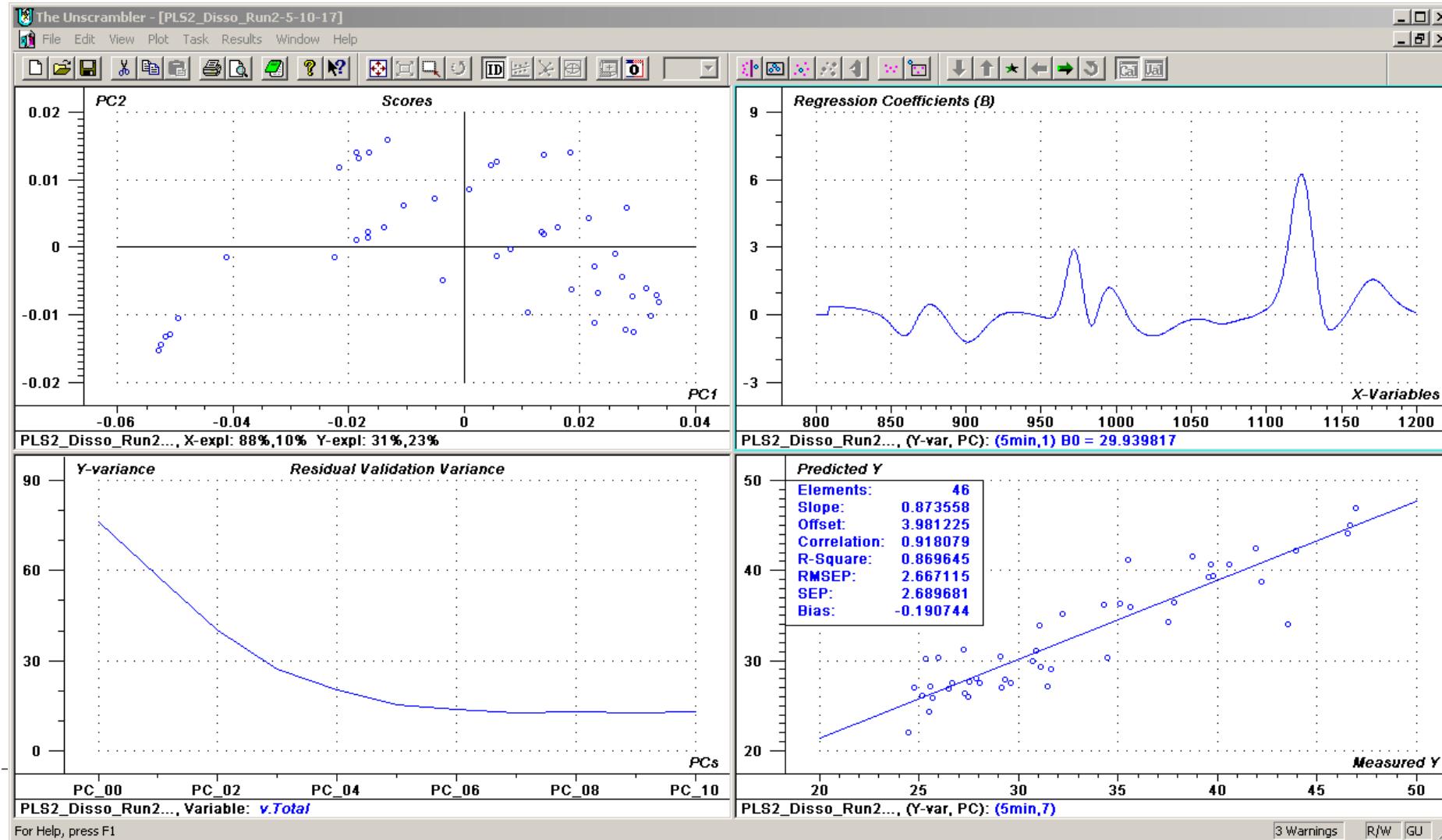
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agreement as enclosed with this software.
See the LICENSE.TXT file for details.



The Unscrambler®

Easy to use



Conclusions on Designing Automation Workflows

- ▶ Automation is going to continue playing a critical role in drug development and discovery
- ▶ Be creative – think of ways to “fake” robots into doing your work
- ▶ Think of the entire laboratory workflow
 - ▶ Sample submission/tracking
 - ▶ Sample preparation
 - ▶ Analysis
 - ▶ Reporting
- ▶ Remember long term goals
 - ▶ Storing data in a manner that will enable long term knowledge
 - ▶ Organize data for data mining
 - ▶ Template based workflows enable optimizations to occur as a function of time rather than study to study
 - ▶ Creating links between databases is a huge task requiring many diverse folks
- ▶ Begin to understand how to manage your own data



Future

- ▶ Leverage linked data – semantic type technologies...the future of knowledge management and data sharing is going to be awesome
 - ▶ Sharing of data and methods to help on future proofing
- ▶ A lot of problems exist ... leveraging
 - ▶ laboratory automation for horsepower
 - ▶ Hardware and software
 - ▶ Knowledge management for effective model building



Developing a Control Strategy



R&D Spending Related to NCE's?

PHARMA & HEALTHCARE

8/11/2013 @ 11:10AM | 143,565 views

The Cost Of Creating A New Drug Now \$5 Billion, Pushing Big Pharma To Change

One common mistake is allowing projects to linger on when the odds of success have become low, says Roger Perlmutter, who ran Amgen's R&D and is now doing the same thing at Merck. Another problem, he argues, is CEOs believing they can order up another drug like their last big hit, instead of following the science.

Who's to blame – Discovery or Development?



Where's all the money going?

- ▶ On average, drug companies spend about 37% of their overall R&D budgets on clinical affairs¹
 - ▶ Patient Recruitment - Patient recruitment costs more and consumes more time than any other aspect of clinical trials.
 - ▶ Budgeting and Performance Assessments - Timely results from patient recruitment campaigns should inform mid-trial decision-making and resource allocation.
 - ▶ Clinical Operations Structure and Workflow
- ▶ Thus Discovery and Development account for over 60% of the spending!
- ▶ We all must do our share to spend wisely😊

¹<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=109&STORY=/www/story/06-23-2004/0002198373>

²<http://www.cuttingedgeinfo.com/acceleratingclinicaltrials/>



The Challenges of Development

▶ Scientific Demands

- ▶ Development becomes a “material science” problem
 - ▶ Stability, solid state form and formulations
- ▶ Discovery has established a biological lead

▶ Business Realities

- ▶ Increased compound throughput
- ▶ Decreased timelines
- ▶ Static or decreased staffing resources

▶ Regulatory Compliance & Expectations

- ▶ Good laboratory and manufacturing processes (GxP)

Thus...Collect data in an organized and efficient manner!



Role of Automation

- ▶ Important to the entire process of drug discovery and development
 - ▶ Can help reduce costs while maintaining safety and quality
- ▶ Hardware components play a large role
 - ▶ Many components required to automate laboratory tasks can be purchased and “augmented” to fit your needs
- ▶ Future of Automation is going to be in software developments
 - ▶ Data visualization, integration, reporting, analysis
 - ▶ Helps pull data together for scientists from a variety of areas
 - ▶ Discovery – why they picked that molecule
 - ▶ Development – how they formulated the molecule
 - ▶ Clinical – how did the molecule and formulation effect the clinical outcome



Summary – Important Balance

