Leveraging Compound Management Capabilities in Support of Drug Discovery: From Sample Archive to Sample Distribution - Driving Efficiency and Improving Productivity

Laboratory Robotics Interest Group
Somerset, NJ
January 13, 2005

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Bristol-Myers Squibb Company

Overview

- Vision and Responsibilities
- Support for Drug Discovery
  - Sample Archive
  - High Throughput Screening
  - Compound Ordering
  - Lead Optimization sample handling
- QC, Performance Measurement and Impact

Compounds as Key Strategic Assets

"Access to chemically diverse…compound collections has been a very important competitive advantage to pharmaceutical drug companies and thus…have been considered to be one of the pharmaceutical companies carefully guarded assets" Strategic Mgmt J. 2002

For the future success of the business, it is critical that these compound assets be effectively managed and leveraged to support all drug discovery needs from lead generation through lead optimization.

BMS Technology Investments
1998 - 2002

Compound Management

High Throughput Screening

Impact ?

Global Vision for Compound Management at BMS

- Improve hit identification by enhancing the quality of the content and integrity of compound collection
- Accelerate Global Drug Discovery
  - Improve cycle time for all services
  - Improve overall organizational efficiency
  - Improve quality of processes
  - Build synergies across the entire drug discovery continuum

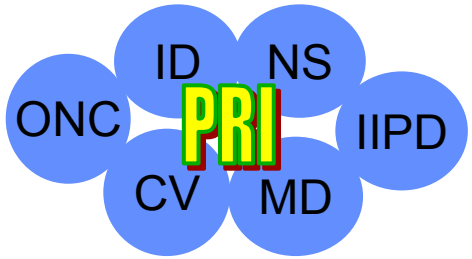
"The impact of screening and the integrity of screening data are only as good as the compound inputs"

BMS

Compound Management Responsibilities

- Sample registration
- Archive for all discovery substances
- Sample handling needs at all stages of drug discovery
  - HTS
  - TA *in vitro* and *in vivo*
  - Liability Profiling
- Build and manage the screening deck and other compound sets to enable hit identification efforts

Enabling Drug Discovery



Therapeutic Area Biology

Single Cmpds, 96 & 384 Well Custom Sets, Focused decks, Special HTS Decks

Lead Optimization Screening Core

- Primary Screening
- Secondary Screening
- In vitro Selectivity Screening

HTS

384, 1536,
Focused Decks
Hit Picking,
Retest, CRC's

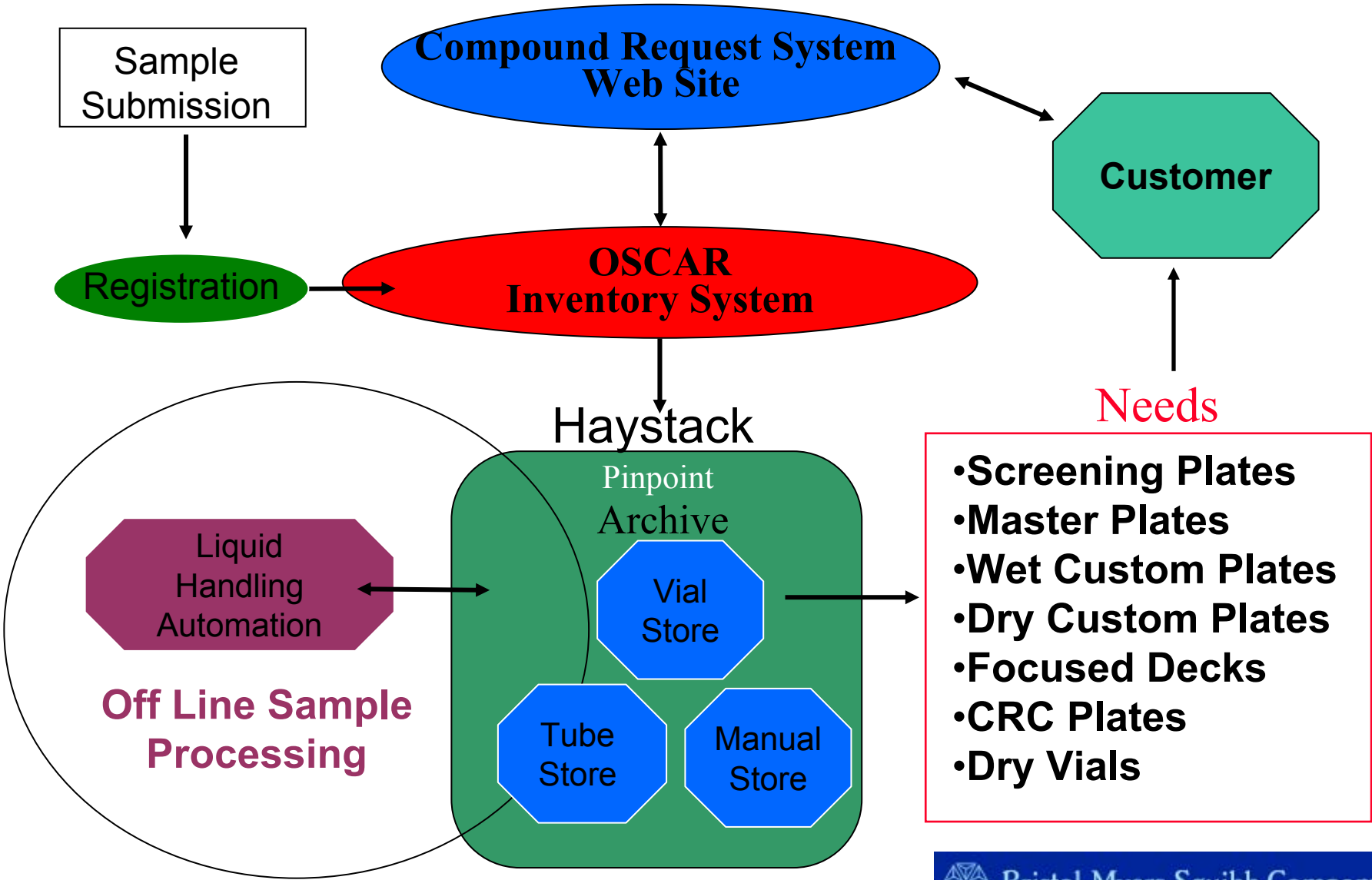
Compound Management

Chemistry

Cmpd Liability Profiling

Single Cmpds, 384 well sets

Compound Management Environment



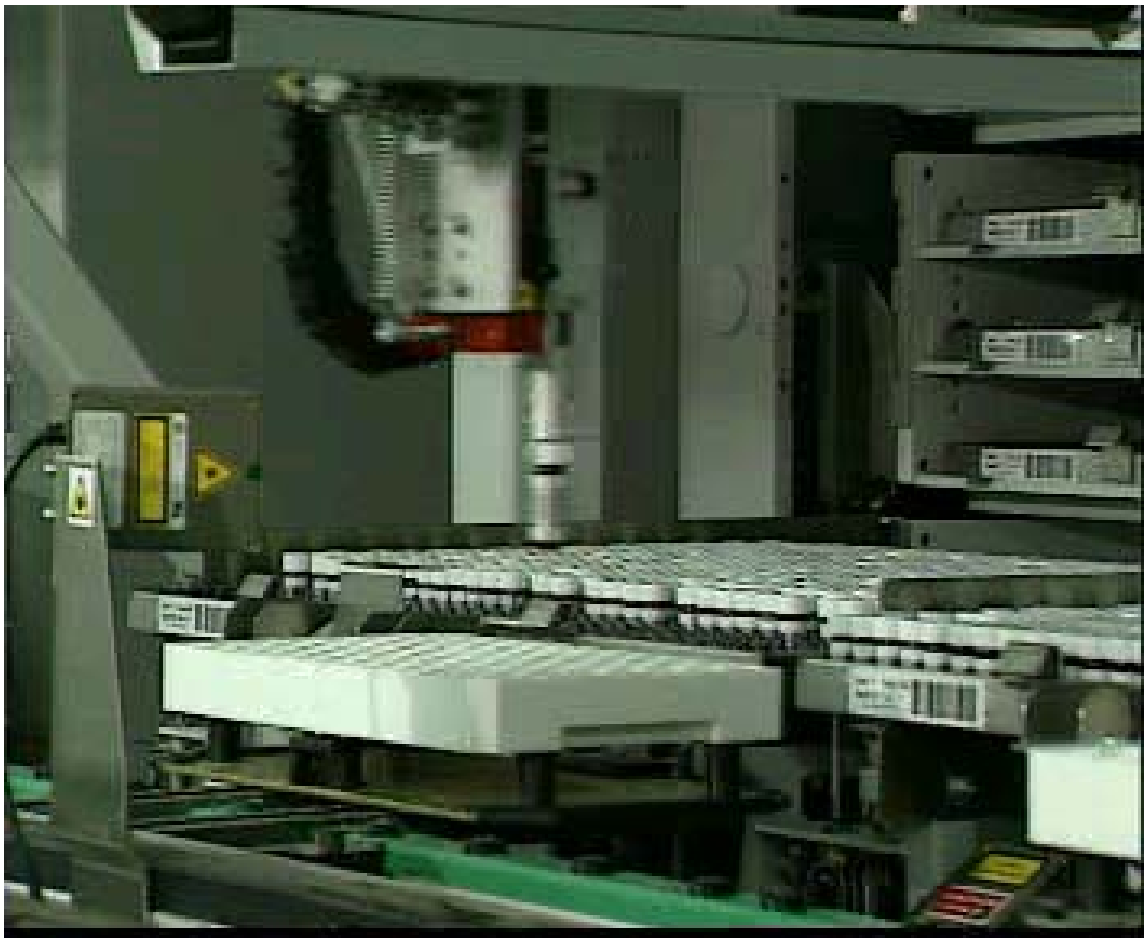
BMS Haystack Archive

Vial Store and Tube Store Units

System Metrics

- > 5000 scientist orders processed
- > 500,000 samples requested
- > 900,000 samples processed
- Averaged >12,000 picks & places per day (tube store)

Archive - Haystack Vial Store



- Capacity: 762K Vials
- >75% Full
- Barcoded Glass Vials
- 4°C
- Controlled humidity
- Dry powders, oils and dry films

Archive - Haystack Tube Store

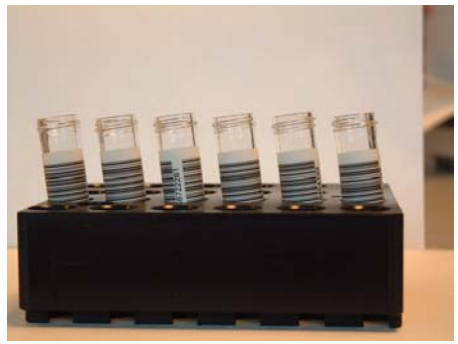
- Capacity: 5.2MM Tubes
- >85% Full
- Non Barcoded PP tube
- Dry tube
- Dry HTS Deck tube
- Wet Tubes (3 mM DMSO)
- 4^{o}C
- Controlled humidity

Volatile Solvent Transfer Process

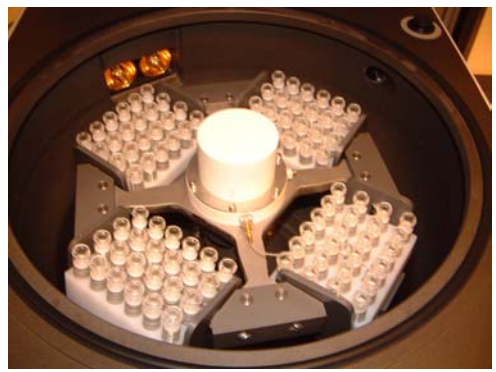
Total Process Integration across

Liquid Handlers, weigh stations

Haystack and Concentrators



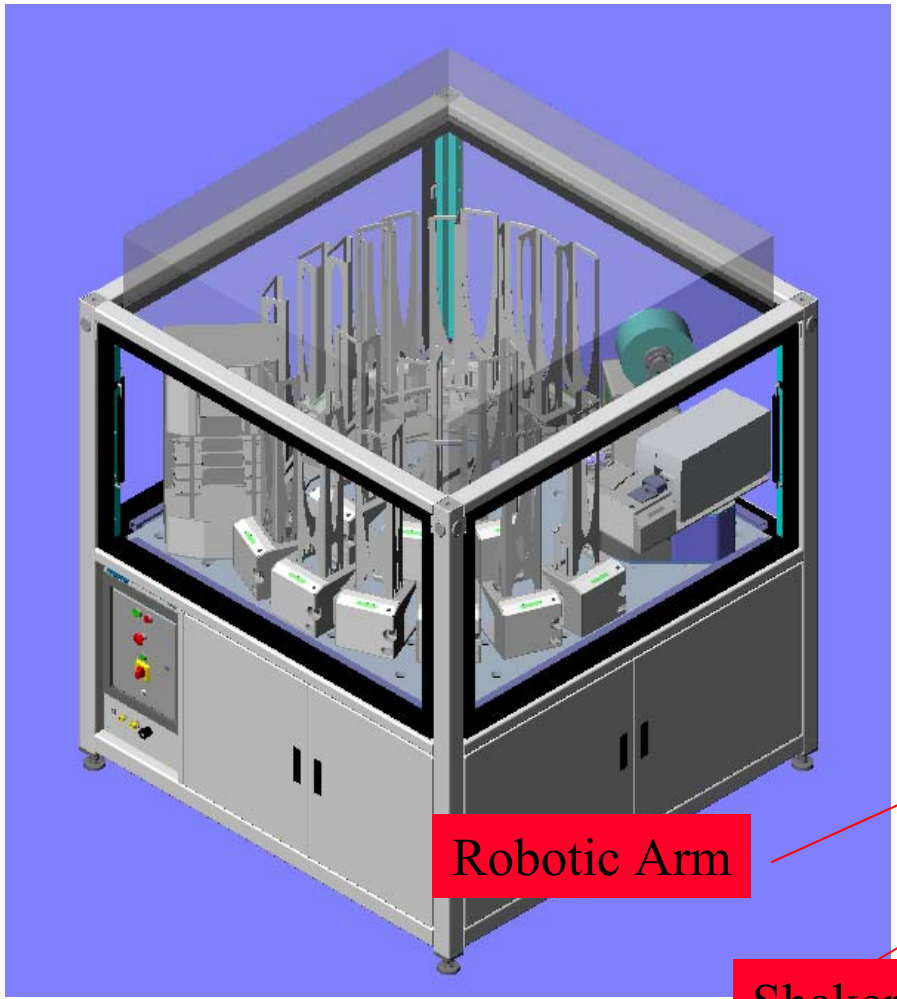
- **Common Solvents – DCE/MeOH, AcCN, DMF, DMSO**
- **Genesis of all Deck Sets**
- **60% of all orders managed through VST**
  - **Reduce manual processing**
  - **Distribute smaller amounts of material (150 nmoles)**
  - **Conservation of compound**

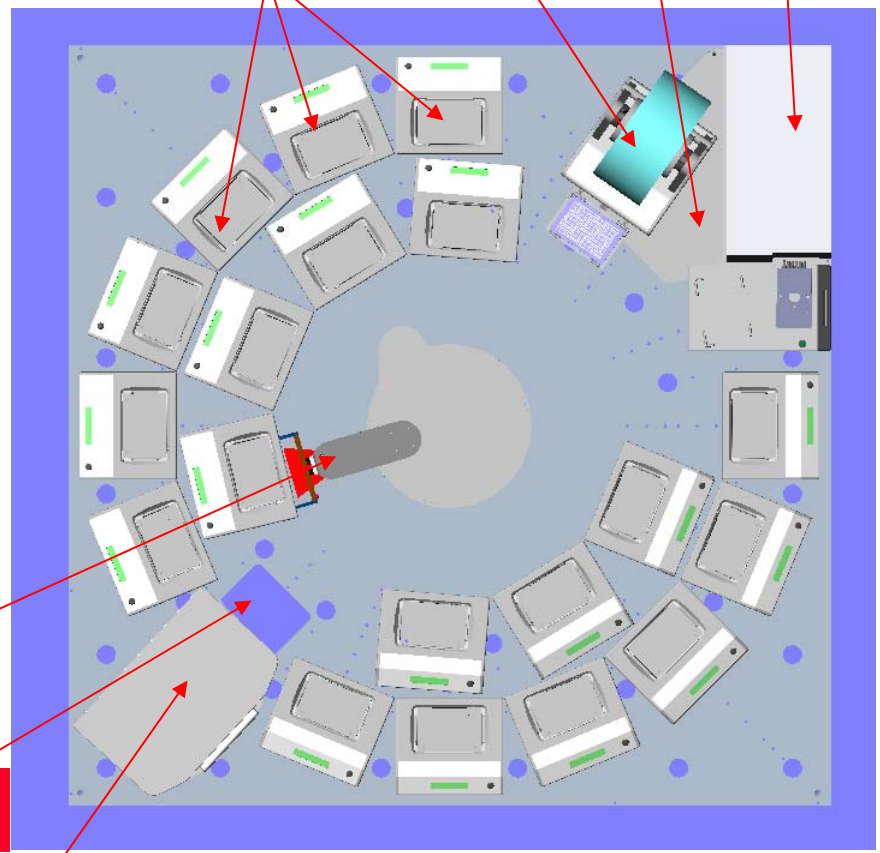


Screening Support

- Plate Replication
  - Master plate creation
    - Dry plates
    - VST processing
  - Assay ready plates
- Cherry Picking for Retests
  - From primary archive sample
- Concentration Response Plates
  - From primary archive sample
- Data Transfer
  - Fully integrated

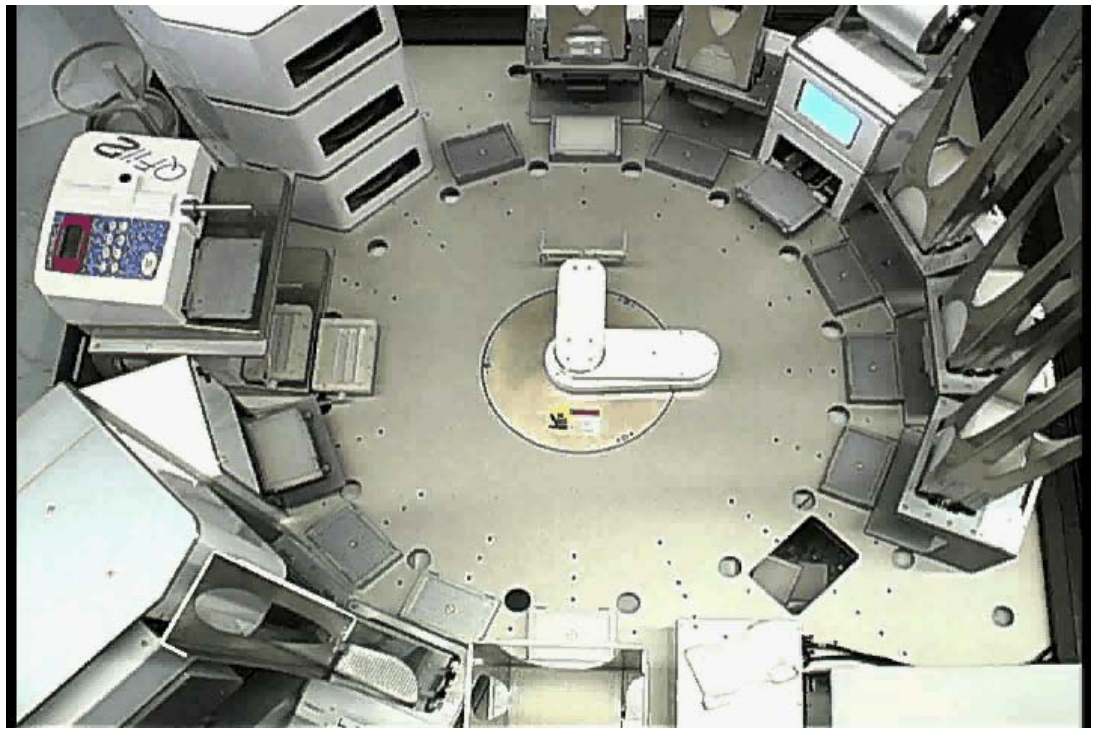
HTS - Compound Processing





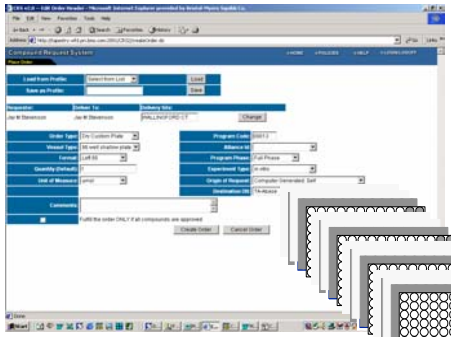
Velocity11 BioCel

HTS - BioCel in Action



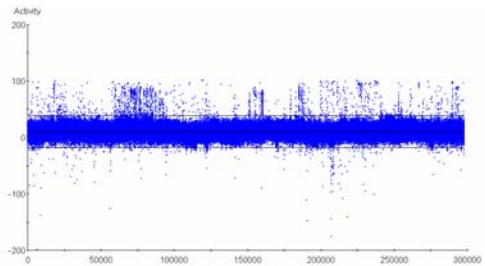
	Capacity per run				Throughput per day	
Process Type	# Tube Racks or Plates	# Compounds	# Copies	Wells Replicated	# of runs	Wells Replicated
Tube to Plate						
Master Plate Creation	80	7,040	9	63,360	2	126,720
Custom Plate Creation	220	19,360	1	19,360	2	38,720
Plate to Plate						
HTS Screening Plates	50	17,600	8	140,800	3	422,400
Assay ready Plates	400	140,800	1	140,800	2	281,600

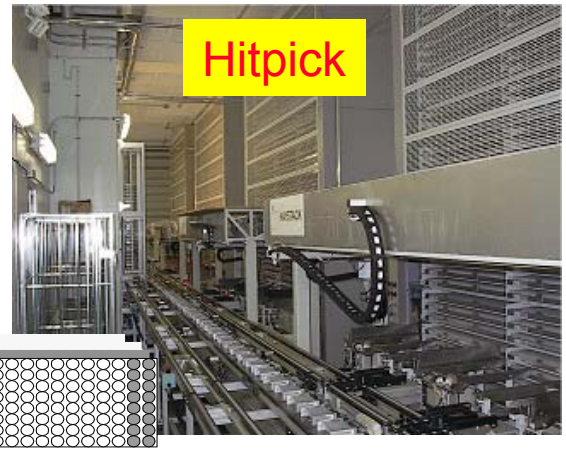
Integrating CM and Screening

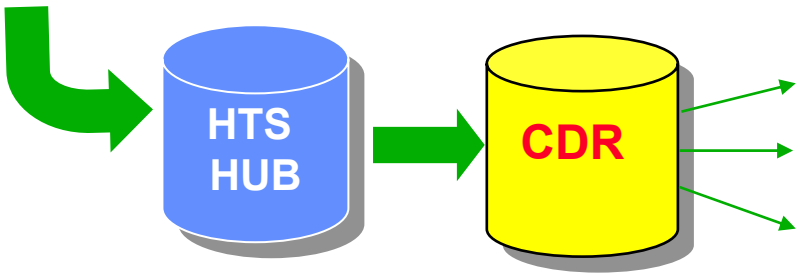


Subdecks

1.....







- Accelerate the process
- Improve data quality
- Improve decision making

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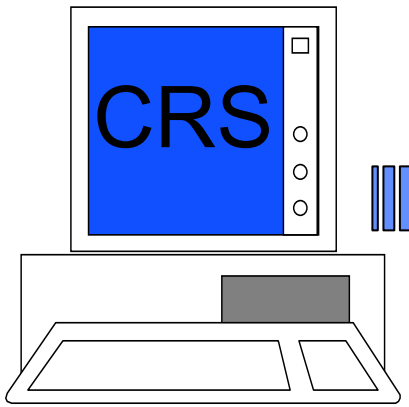
Ordering Compounds



Scientist selects compounds and order type

ARCHIVE

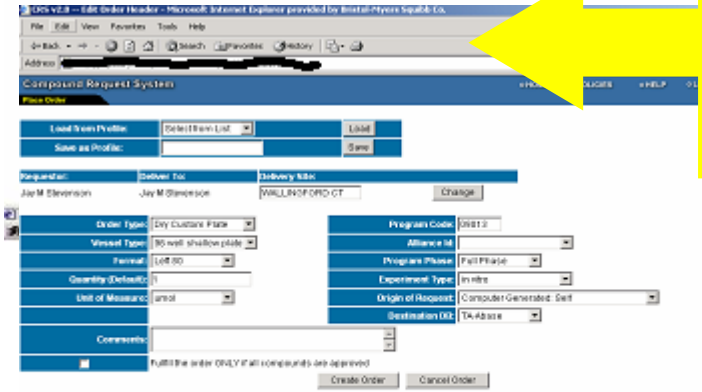
Based on nature of CRS input, embedded logic picks sample

Sample Reprocessing

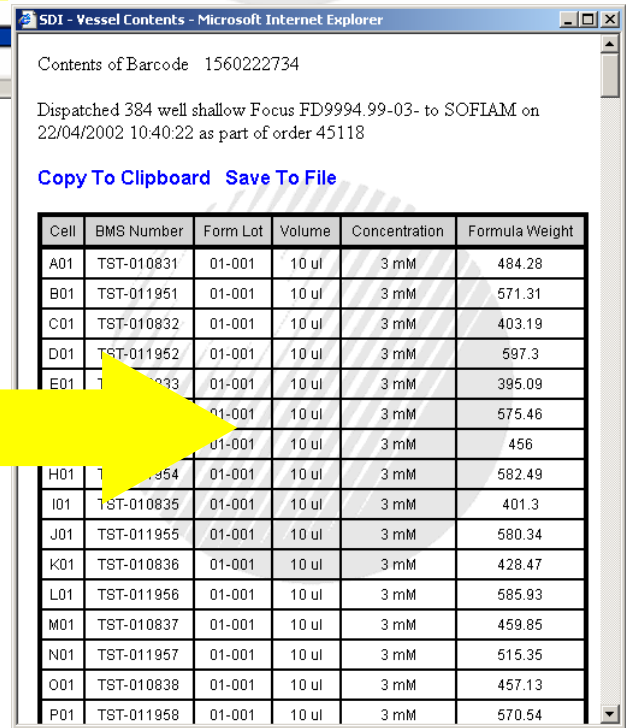
- Dry Resupply (powder, oil)
- Wet (DMSO) custom plate
- Dry film (VST)

Turnaround times determined by established SLAs

All the Compound Information You Need

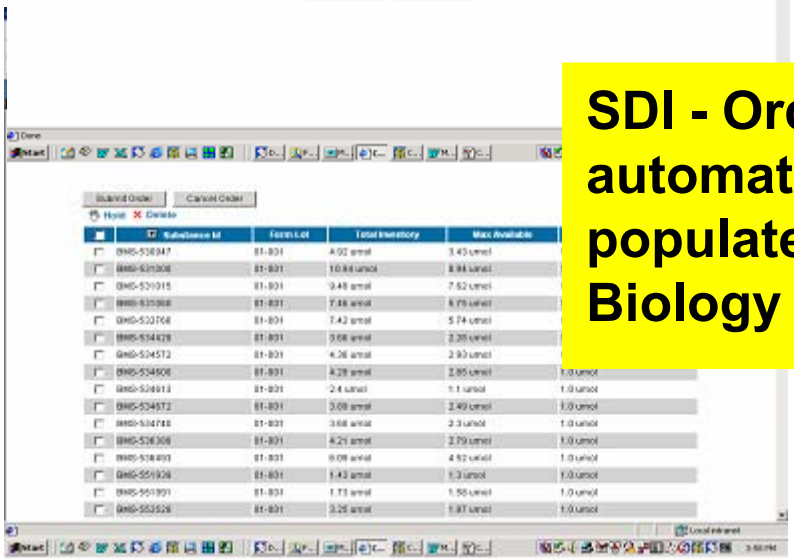


CRS Compound Request System



Cell	BMS Number	Form Lot	Volume	Concentration	Formula Weight
A01	TST-010831	01-001	10 ul	3 mM	484.28
B01	TST-011951	01-001	10 ul	3 mM	571.31
C01	TST-010832	01-001	10 ul	3 mM	403.19
D01	TST-011952	01-001	10 ul	3 mM	597.3
E01	T[illegible]33	01-001	10 ul	3 mM	395.09
F01	T[illegible]	01-001	10 ul	3 mM	575.46
G01	T[illegible]	01-001	10 ul	3 mM	456
H01	T[illegible]954	01-001	10 ul	3 mM	582.49
I01	TST-010835	01-001	10 ul	3 mM	401.3
J01	TST-011955	01-001	10 ul	3 mM	580.34
K01	TST-010836	01-001	10 ul	3 mM	428.47
L01	TST-011956	01-001	10 ul	3 mM	585.93
M01	TST-010837	01-001	10 ul	3 mM	459.85
N01	TST-011957	01-001	10 ul	3 mM	515.35
O01	TST-010838	01-001	10 ul	3 mM	457.13
P01	TST-011958	01-001	10 ul	3 mM	570.54

SDI - Order info automatically populated to Biology Databases



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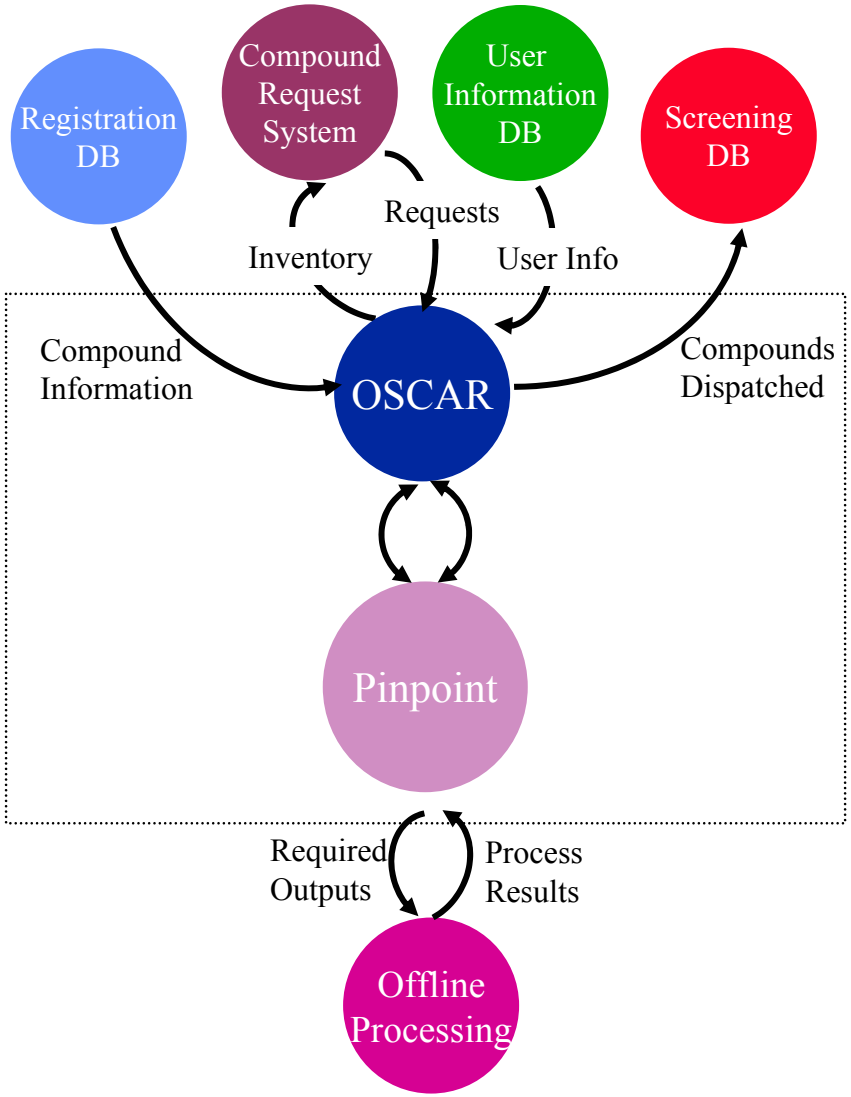
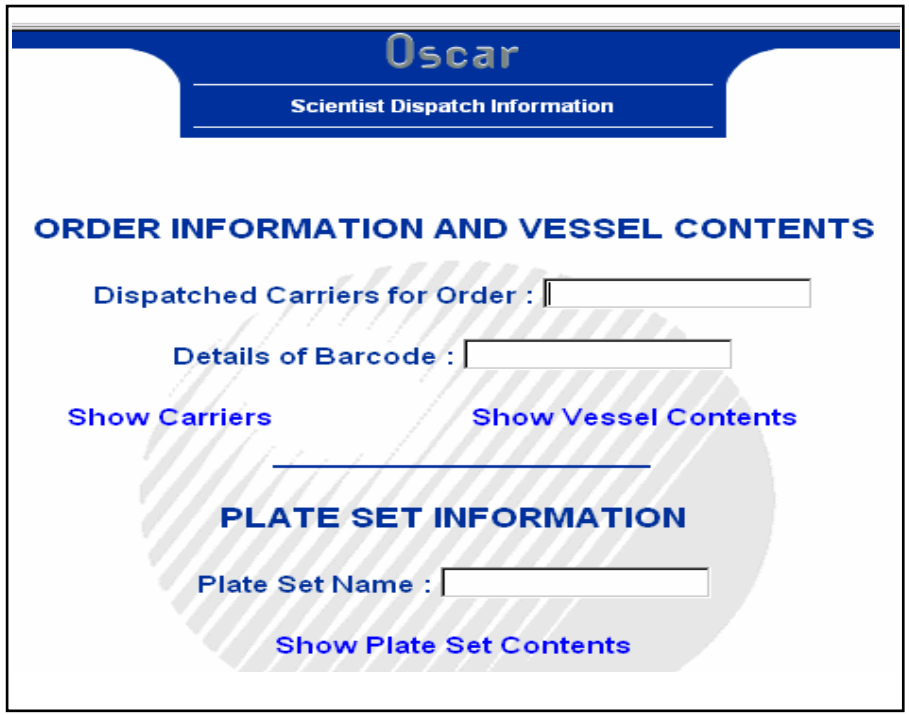
Seamless Data Flow





- **Paperless tracking**
- **"Cradle to Grave" tracking of Compounds**

Leveraging CM to Improve Processes in Lead Optimization

Goal

Build on our successes and experience in the lead discovery arena to reinvent how we do lead optimization

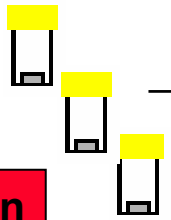
- Improve in vitro evaluation process
- Improve data and information management
- Improve sample handling

Lead Optimization and Profiling Sample Processing

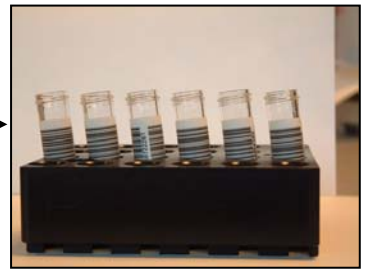
TA Biology

Lead Profiling

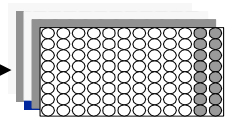
Lead Optimization

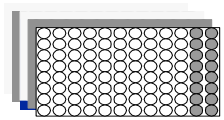


Solubilize



Serial Dil

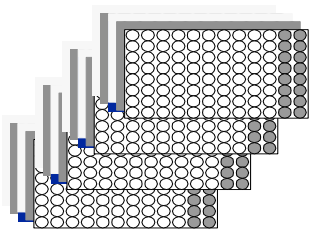




≤24 h

Master plates
-Bioassay Suites
-Profiling Suites

Replicate



Medicinal Chemistry Samples

Initial Distributions

"Just in time" sample preparation based on screening schedules

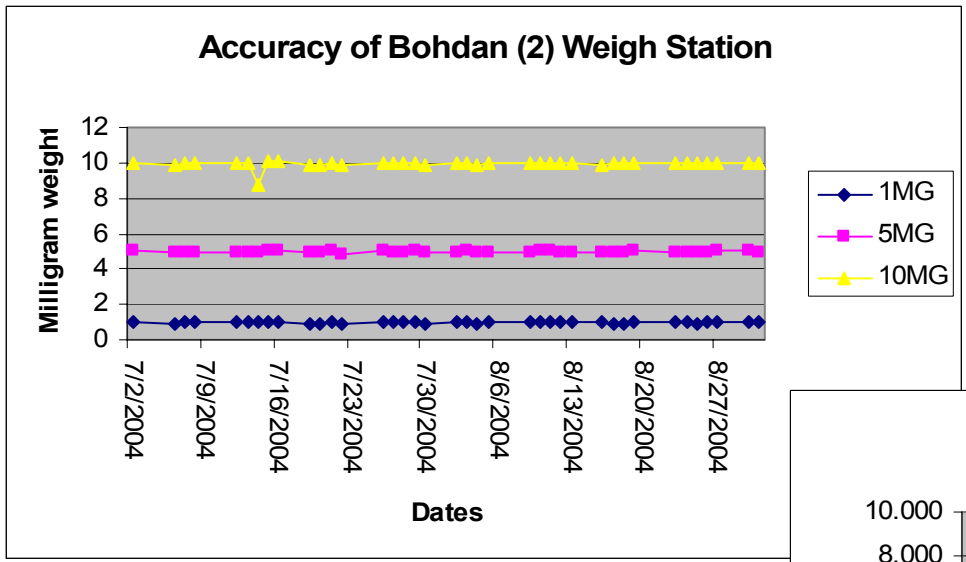
- Primary Screening
- Secondary Screening
- In vitro Liability Profiling

Quality Control
and
Performance Measurement

What Do We Measure and Why?

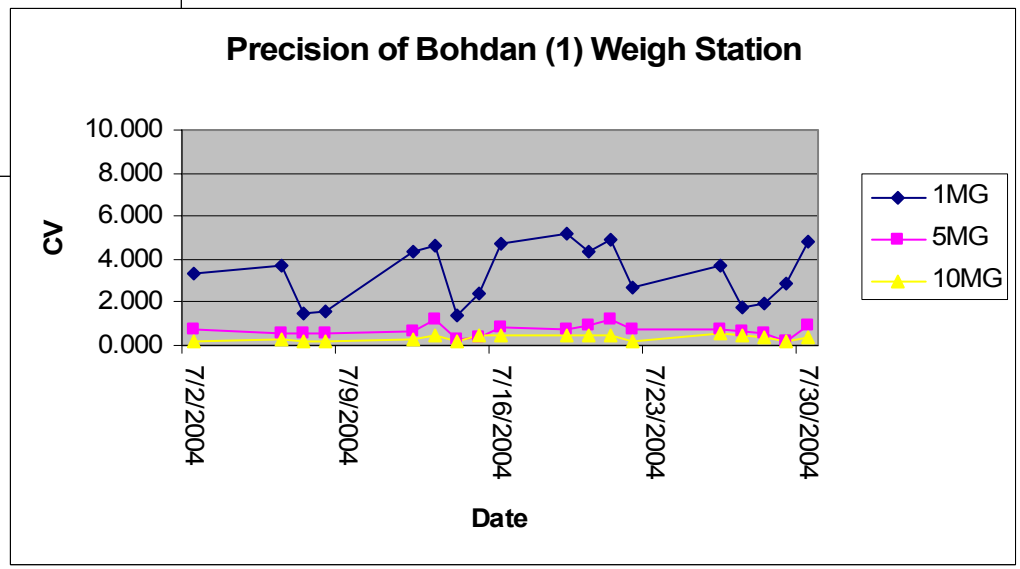
- **Instrument performance**
  - Ensure quality of downstream discovery efforts
    - Quality of data
- **Organizational performance and efficiency**
  - Guarantee high quality service
  - Improve overall discovery productivity and efficiency
  - Drive down operating costs

QC - Haystack Vial Weighing



Ensure inventory weights are accurate

- Accurate inventory tracking
- Ensure downstream data quality

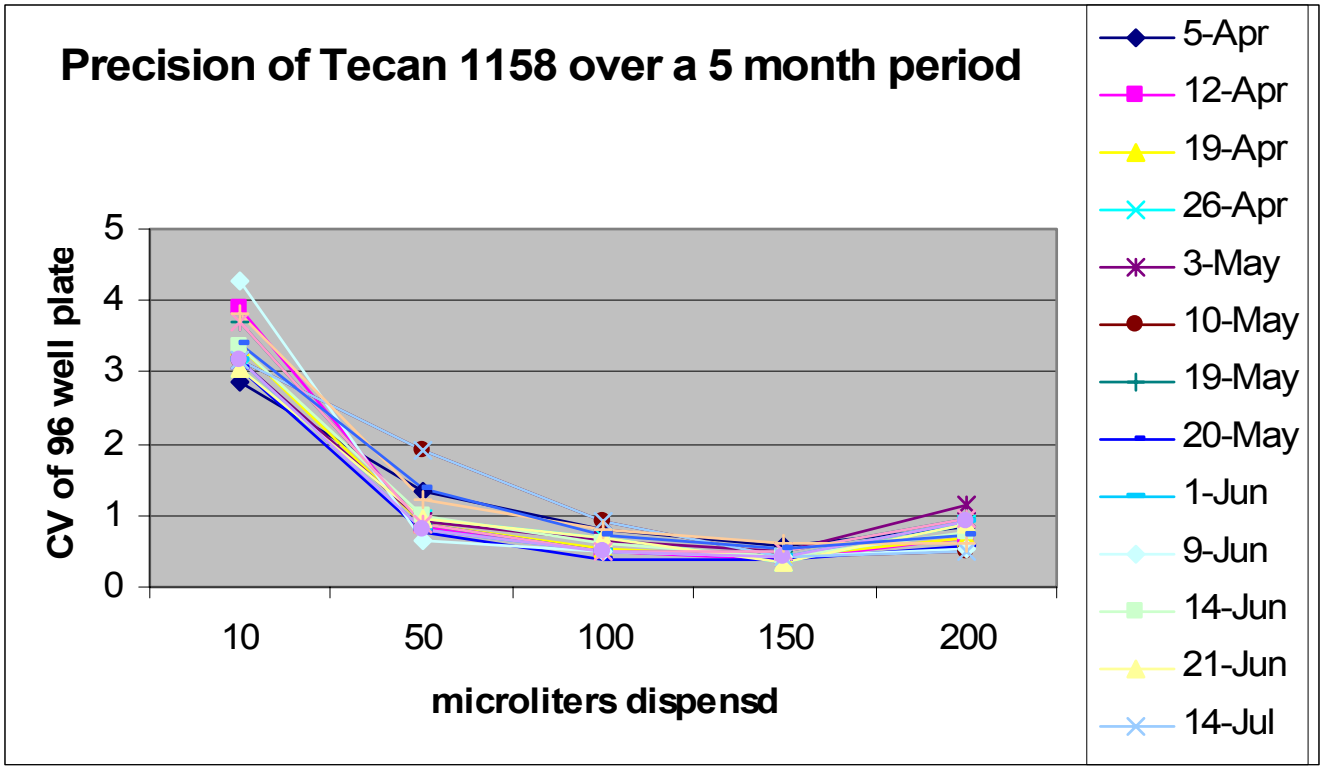


Daily Accuracy

&

Precision Validation

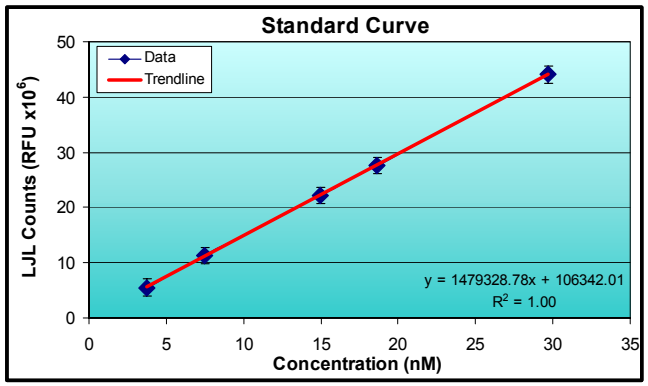
QC - TECAN Liquid Handling

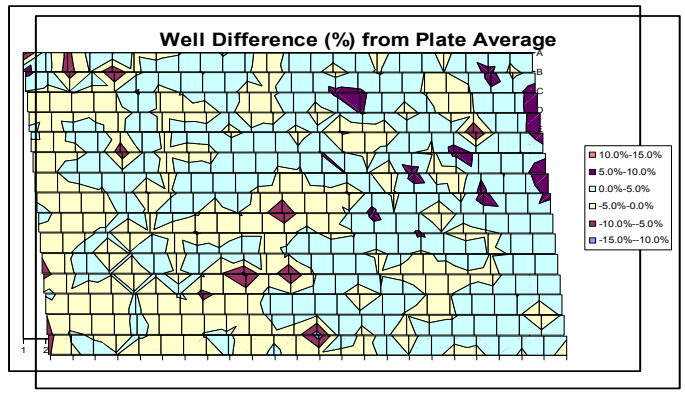


Weekly Accuracy and Precision Validation

Ensure accuracy of sample resupply processing

QC - VPrep Dispensing





Well Accuracy:
100 nL +/- 10 nL
1 µ L +/- 0.01 µL

Plate Precision:
100 nL CV range:
4.5 - 9.7%
1 µL CV range:
2.8 - 5%

Carry-over:
< 1 part in a 10,000,000

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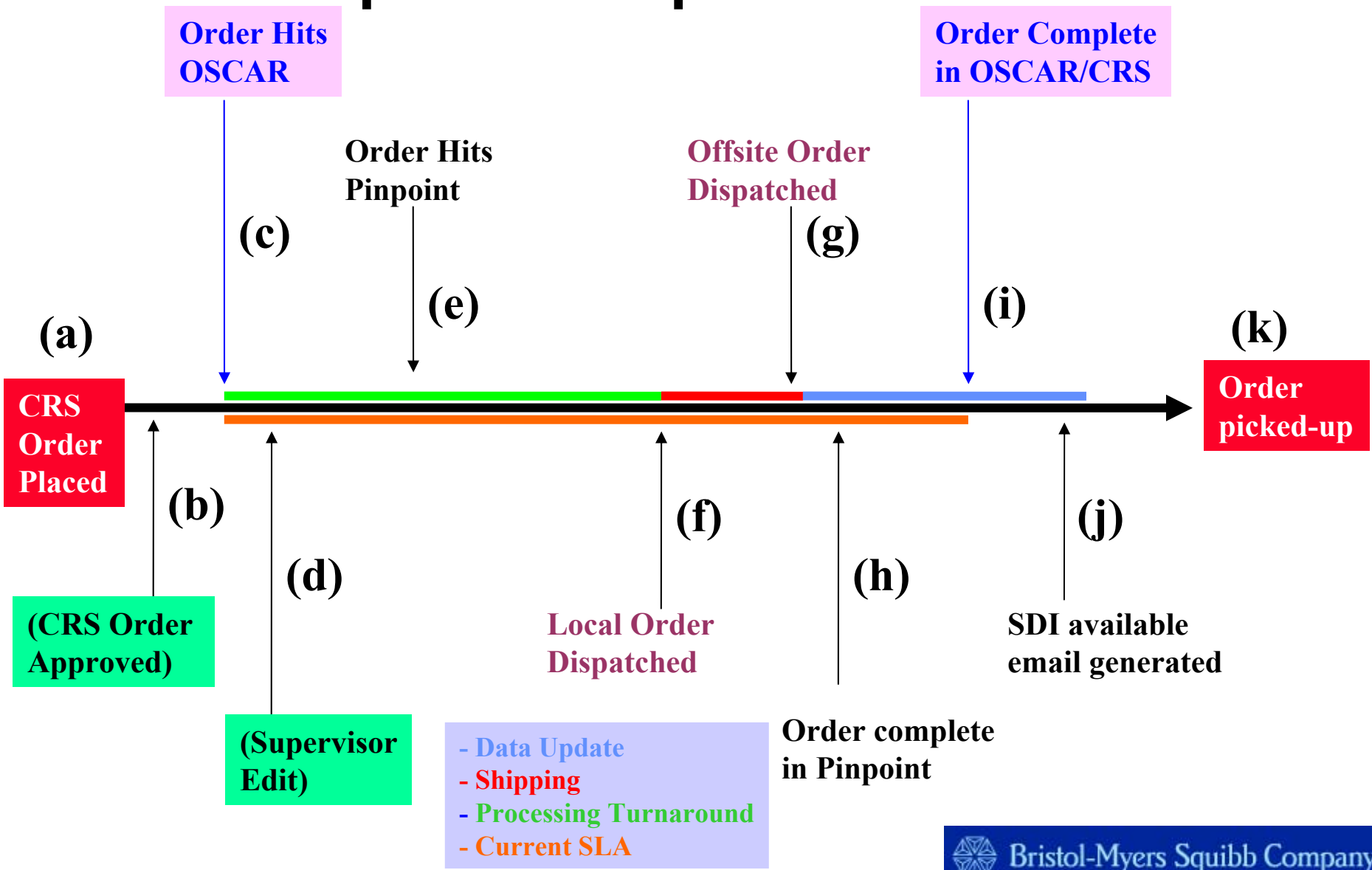
Performance Measurement - Compound Request Process

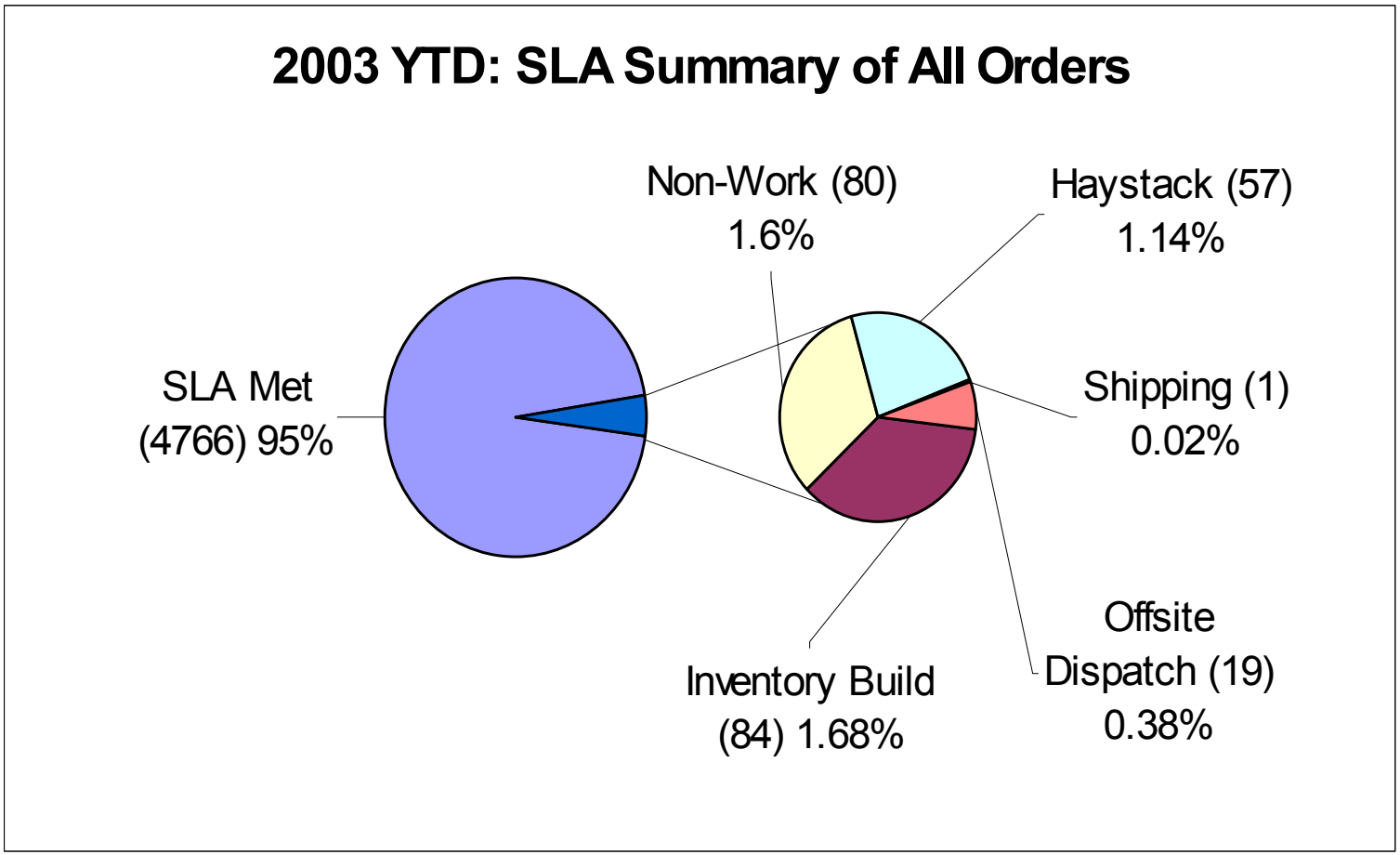


Service Level Agreements

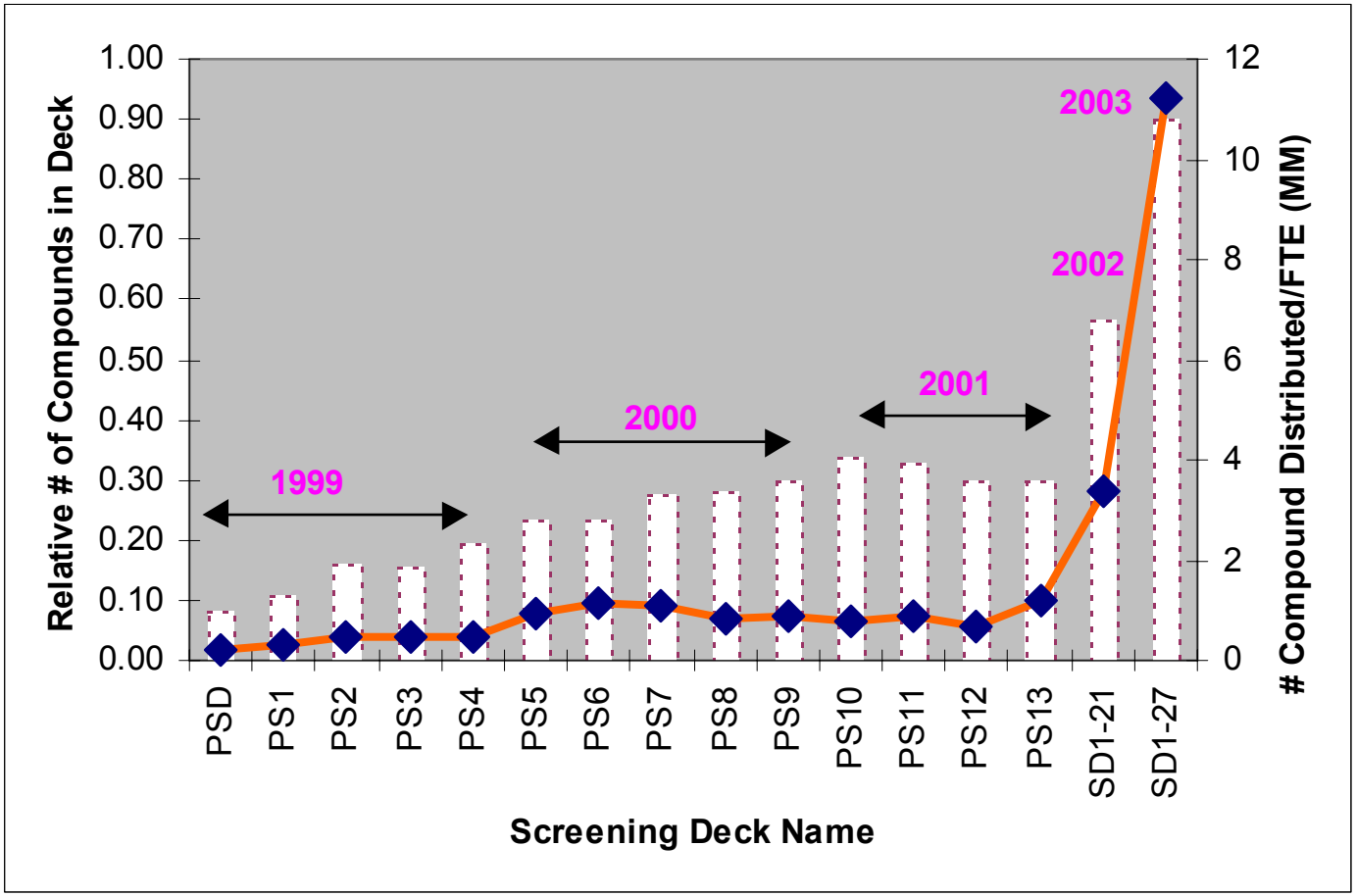
Service Level Agreements							
Order Type	# of cmpds						
	<100	<200	<500	<1000	<2000	<5000	<10000
Custom Plate/wet	2	2	2	2	3	4	5
Custom Plate/dry	2	2	3	4	4	5	6
Manual re-supply	2	3	4	NA	NA	NA	NA
Inbound TAD	1	1	1	3	4	5	10
Inbound Inventory	2	2	2	3	4	5	5-10
Med Chem dispensations	1	1	1	1	1	NA	NA
Med Chem Inventory	1	1	1	1	1	NA	NA

- SLA's - expected delivery date for receipt of compound
  - Based on SLA matrix - size & type
- Goal
  - ***If Ordered by 11 am*** - 48 hr TT irrespective of site and size

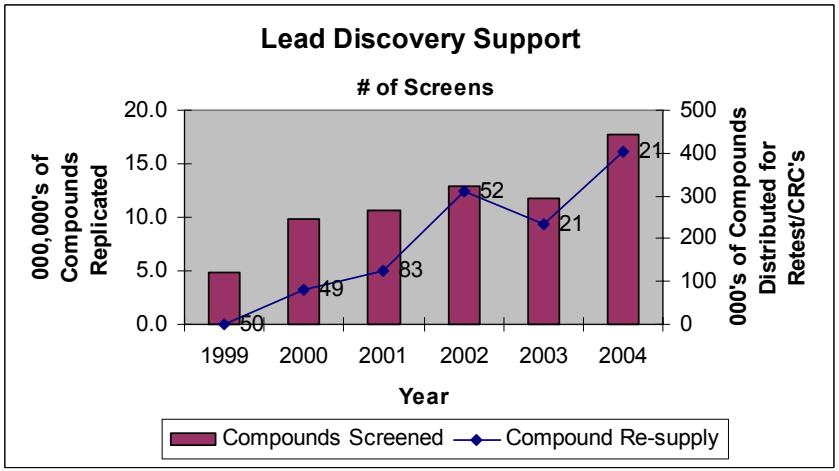
Productivity Gains in 5 Years

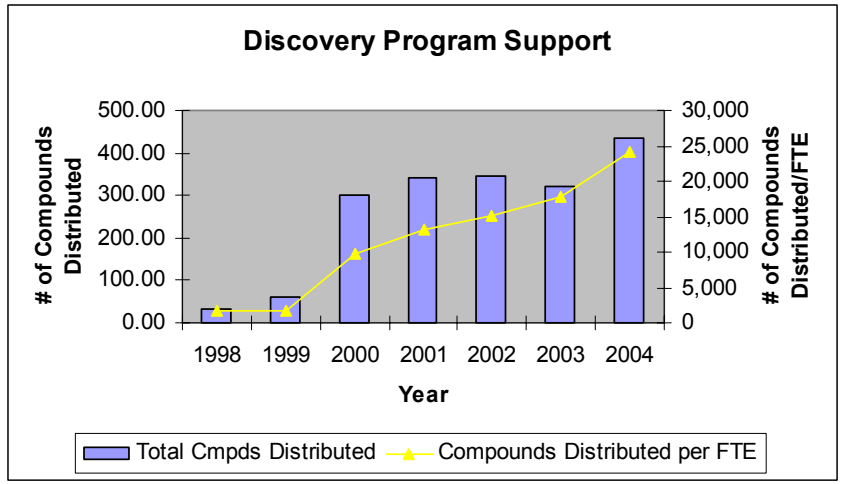


Productivity Gains in 5 Years



Technology and Process Driven Productivity and Efficiency Gains





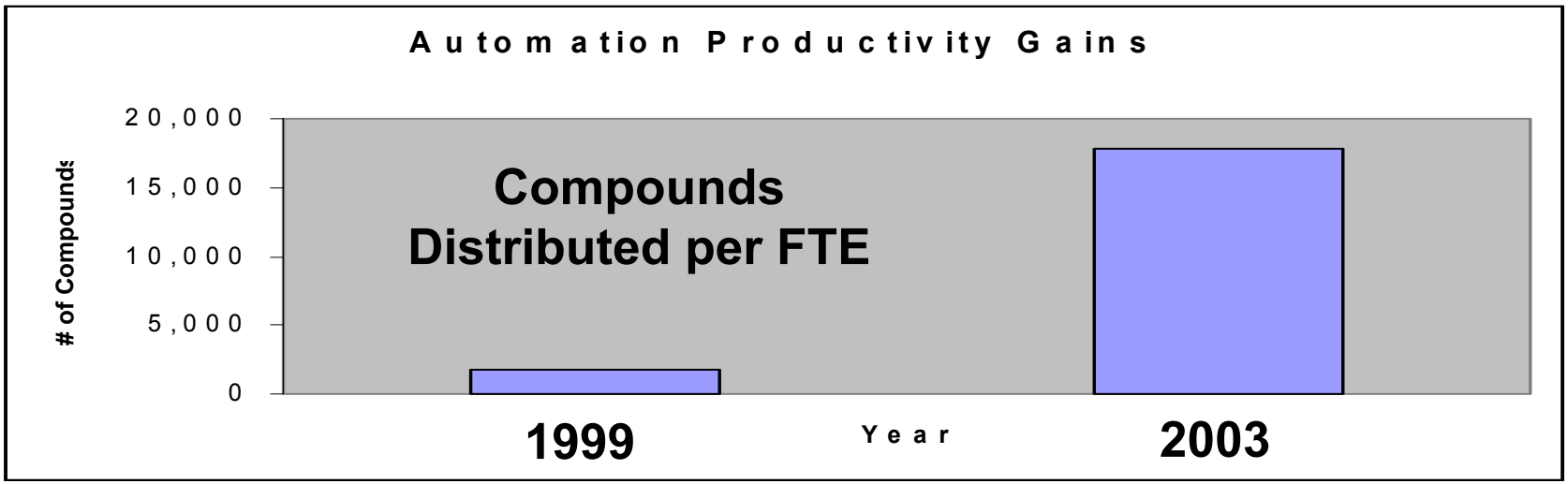
1999 – 143 k compounds/FTE

2004 – 990 k compounds/FTE

1998 – 1,630 compounds/FTE

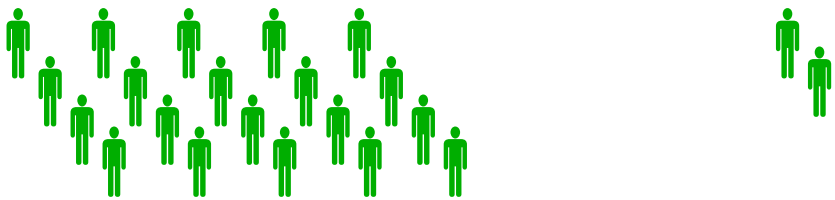
2004 – 24,000 compounds/FTE

Impact Through Automation



Automated Distribution

Manual Distribution



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Compound Management Impact

- **20 Fold increase in the number of compounds that have become accessible for testing since 1997**
- **Time improvements of 30-70% for compound re-supply for all order types and sizes**
- **Since 1998 increased productivity by 12X and efficiency by 12X**
- **Efficiency gains**
  - **50% less staff needed to support 12X more output**
- **Leveraged technology infrastructure and process analysis to improve retest rates, reduce timelines and increase hit quality**
- **Data and lead quality enhancements**
  - 25% improvement in lead generation impact
  - 70-80% of all screens generate validated progressable leads
  - Early liability assessment on leads enable progression of best compounds into lead optimization – improved FIH success rates

Acknowledgements

Many Thanks To:

- **Bristol-Myers Squibb**

  John Houston and Ed Petrillo,

  Compound Management Team

  Jay Stevenson, Moneesh Chatterjee, Jessica Hallock, Sandy Armento, Steve Head, Sandra Matson, Christopher Cooper and Rich Bischoff

  Discovery Tech Team

  Alastair Binnie, Jim Myslik, Andrew Bullen, Chris Bernard, Ben Carvalho, and Jeff Guss

- **The Automation Partnership Team**

- ***Velocity11* Team**

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