



Halteres Associates Case Study Strategic Options – Clinical Diagnostics



***Iconix Biosciences, Inc.
November 2004***



Halteres from Ancient Greece
National Archaeological Museum in Athens

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Summary and Conclusions (1)

- **A significant opportunity exists for molecular diagnostics to predict drug induced toxicity in a number of disease states**
- **There is a strong medical and business rationale for this**
- **Iconix is uniquely positioned to identify and create products to capture this opportunity**
- **We have identified a few opportunities that have the potential to:**
 - Significantly improve patient care
 - Demand high reimbursable pricing (> \$500 per test)
 - Offer significant market potential (i.e., product sales of \$50 M annually)
 - Fit with Iconix's existing expertise
 - In certain cases improve sales of specific drugs (e.g., EPO)

Summary and Conclusions (2)

➤ Blood toxicities are of particular interest

- A small number of toxicities involving blood constitute more than half of the frequent and severe adverse drug events (ADEs) associated with the 400 top selling drugs worldwide

➤ Liver and kidney toxicities are also attractive targets for molecular diagnostics

➤ A relatively modest investment is required to take this to the next logical step

- Access clinical samples
- Confirm and validate technologies
- Build reference lab capabilities
- Create an IP-protected proof of concept for pursuit of financing and collaboration partners

Introduction

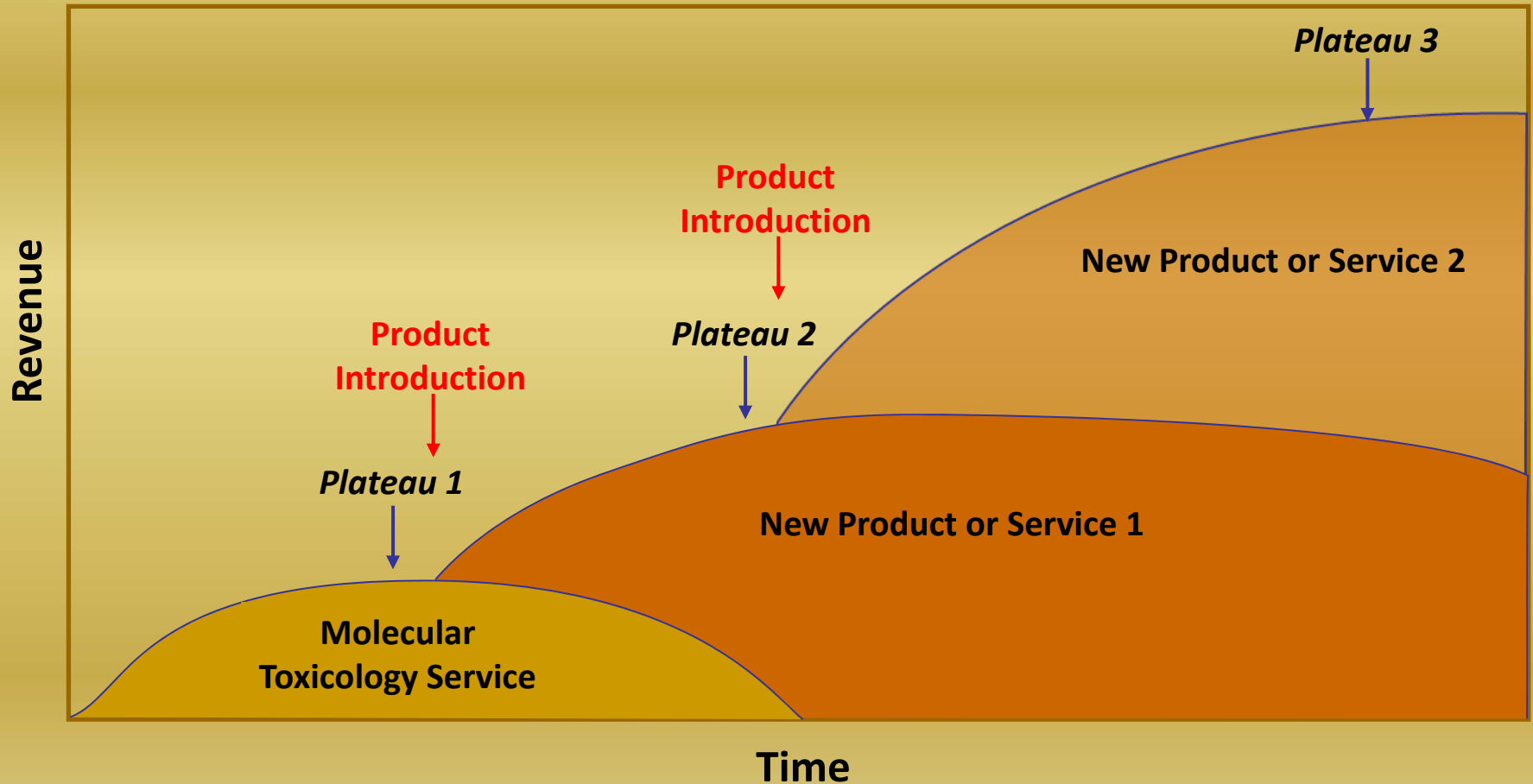
➤ What did Iconix need from Halteres?

- Understanding and direction on where to focus their technology
- Assessment of the value of their core competence

➤ What was the Halteres solution?

- Structured, analytical approach to identify:
 - ❖ The top indications that are impacted by ADEs
 - ❖ The top drugs on the market with high ADEs
 - ❖ Focus on the most relevant ADEs
- Identification of the focus opportunities
 - ❖ Pantox
 - ❖ Drug advantage
 - ❖ Most important diseases

What is Next for Iconix?



Assess the Opportunities from Different Directions

➤ All ADEs

- ADEs frequency were derived from both the literature and the PDR
- Developed a ranking methodology to distinguish the importance of a specific ADE (frequency of the ADE times the severity of the ADE)

➤ All Drugs

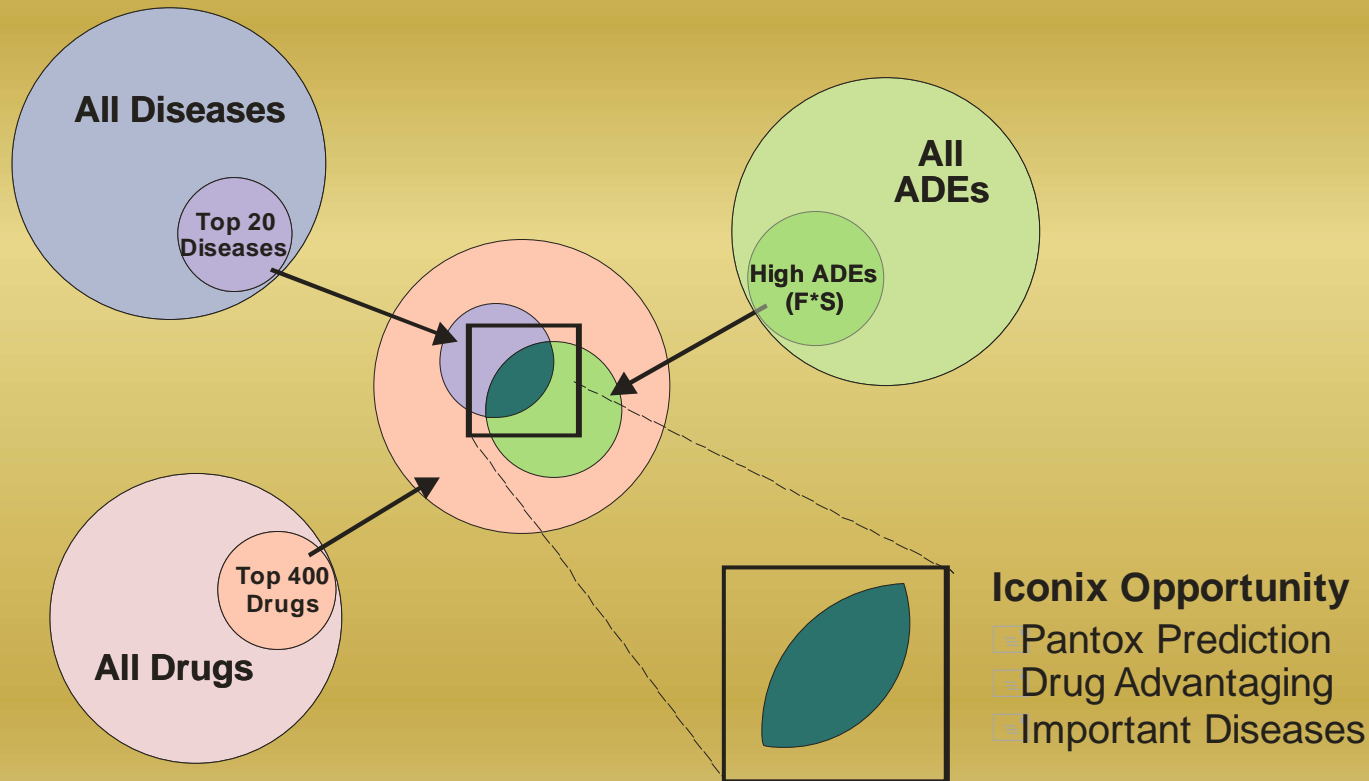
- Top 400 drugs were derived from a database of the top revenue generating drugs in the US

➤ All Diseases

- Halteres maintains a database of diseases
- Criteria were created to assess which were the most interesting diseases to pursue as they pertained to ADEs

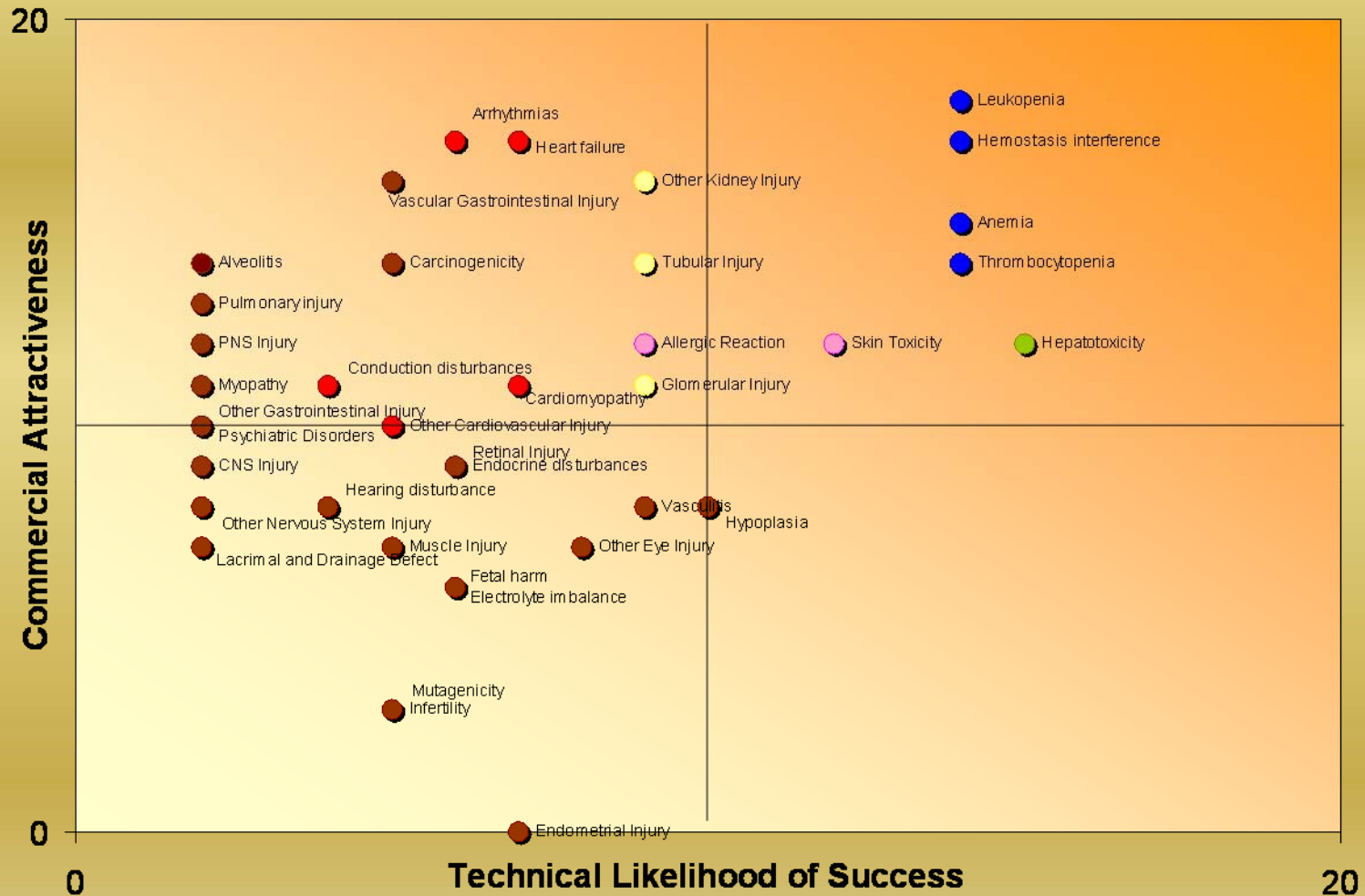
Opportunity Assessment

We used a variety of approaches to determine which opportunities were the most valuable and had a reasonable technical likelihood of success . . .

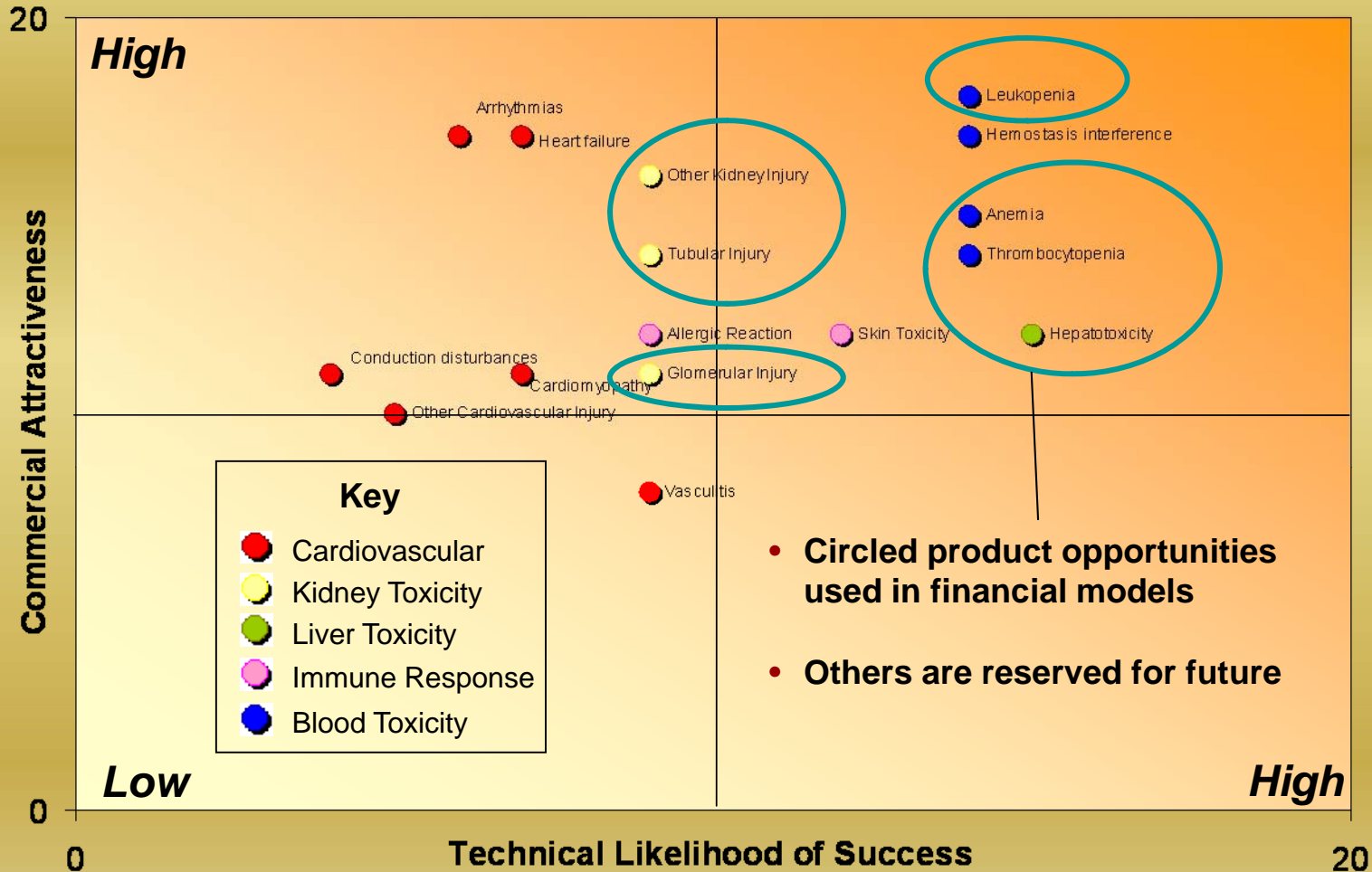


ADE = Adverse Drug Event

Opportunities Cluster into Different Classes



Opportunities Used in Financial Projections



A Good Example of an Attractive Opportunity: Thrombocytopenia

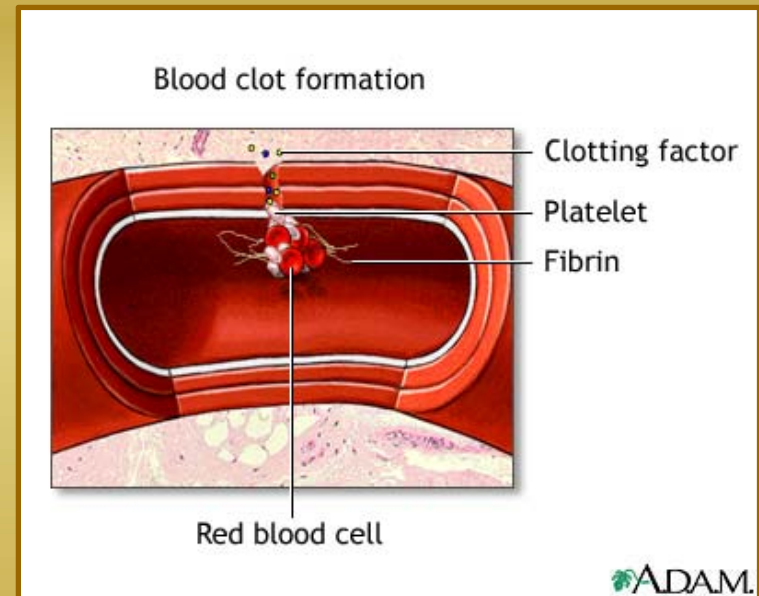
- 460 drugs listed in the PDR with thrombocytopenia as ADE, of which 63 (16%) have >3% incidence

- **Potential clinical consequence**

- Pulmonary embolism
- Myocardial infarction, stroke
- Limb ischemia and amputation

- **Bleeding (mucocutaneous)**

- From minor haemorrhage to life threatening GI or intracranial haemorrhage



Heparin Induced Thrombocytopenia (HIT)

➤ Type I:

- Usually mild
- Typical onset after 4 days
- Mortality <1%

➤ Type II:

- Potential emergency with life-threatening thromboembolic complications
- Typical onset of 4 – 14 days
- Potential for development is greater with unfractionated heparin than with low molecular weight heparin (LMWH)

	Heparin		LMWH	
	HIT-I	HIT-II	HIT-I	HIT-II
Patients with antibodies (day 21)		21%		4%
Incidence	10-20%	2-6%	1.20%	0.5-1%
Onset after treatment	4 days	4-14 days	4 days	4-14 days
Mortality	<1%	20%	<1%	20%
Mean cost per patient	\$2,500	\$43,000	\$2,500	\$43,000

Heparin Induced Thrombocytopenia (HIT)

➤ Heparin use (unfractionated heparin and LMWH):

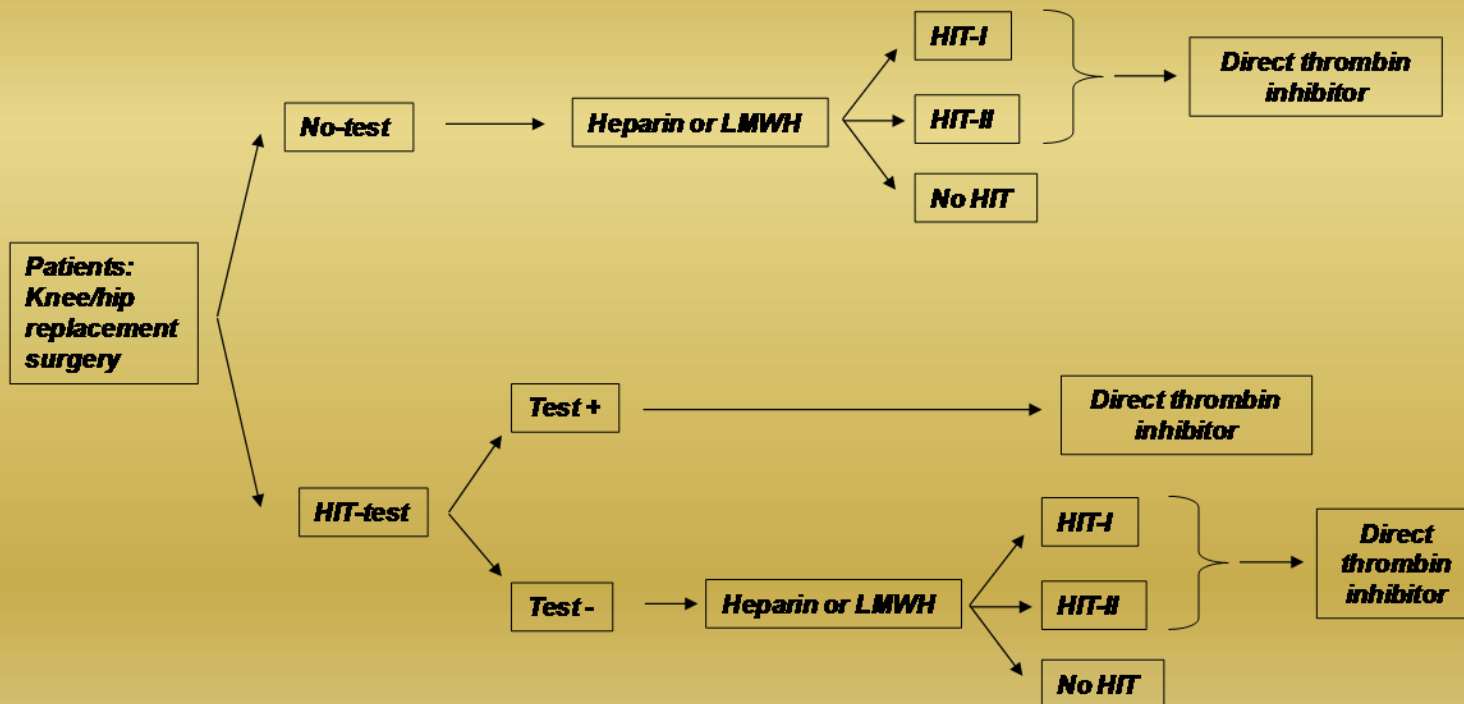
- Deep venous thrombosis and prophylaxis during surgery (e.g., hip and knee replacement...about 700,000 patients annually in the US)
- Stroke
- Atrial fibrillation
- Acute myocardial infarction and unstable angina
- Pulmonary embolism
- Renal dialysis (about 140,000 patients in the USA)

➤ Number of patients treated annually in the US: About 6 million

Heparin Induced Thrombocytopenia: Economic Model

Two health economic models to test hypothesis:

- Unfractionated Heparin: High incidence of ADEs results in potentially higher reimbursement level for a predictive PanTox test
- LMWH: Lower incidence ADEs results in relatively lower level of reimbursement



Heparin Induced Thrombocytopenia: Economic Model Results

Heparin:

	No Test	HIT Test	Benefit of HIT Test	
			Total (\$MM)	Per Test (\$)
Rx cost of heparin (\$MM)	\$32	\$20	\$12	\$93
Rx cost of Argatroban (\$MM)	\$190	\$190	\$0.8	-\$7
HIT I cost (\$MM)	\$66	\$5	\$61	\$494
HIT II cost (\$MM)	\$302	\$23	\$279	\$2,271
Total cost (\$MM)	\$590	\$238	\$353	\$2,851
Deaths	1,663	129	1,534	0.013

Potential HIT pricing scenarios:

- On a “Costs Avoided” basis: up to \$500
- On a “Lives Saved”¹ basis: up to \$6,000²

¹ Lives saved calculation uses a value of \$30,000 per year-of-life gained
² price of \$750 used in financial modeling

Heparin Induced Thrombocytopenia: Economic Model Results

LMWH:

	No Test	HIT Test	Benefit of HIT Test	
			Total (\$MM)	Per Test (\$)
Rx cost of LMWH (\$MM)	\$59	\$38	\$21	\$165
Rx cost of Argatroban (\$MM)	\$27	\$66	-\$39	-\$318
HIT I cost (\$MM)	\$9	\$1	\$8	\$63
HIT II cost (\$MM)	\$57	\$3	\$54	\$434
Total cost (\$MM)	\$152	\$108	\$44	\$344
Deaths	298	20	278	0.002

Potential HIT pricing scenarios:

- On a “Costs Avoided” basis: up to \$60
- On a “Lives Saved” basis: up to \$1,100

Heparin Induced Thrombocytopenia: Conclusions

- HIT is an increasingly recognized clinical issue, awareness driven by new direct thrombin inhibitors like Argatroban
- HIT is a relatively frequent problem, more so with unfractionated heparin than with LMWH
- Mortality for HIT type II is about 20%
- Predictive HIT tests could have significant impact on clinical and economic outcomes
- Drug with higher incidence of HIT (unfractionated heparin) has higher test reimbursement potential than drug with lower incidence of ADEs (LMWH)
- Potential upper limit for reimbursement for a predictive HIT test could be (based on \$30,000 per life year gained):
 - \$6,000 for heparin
 - \$1,100 for LMWH

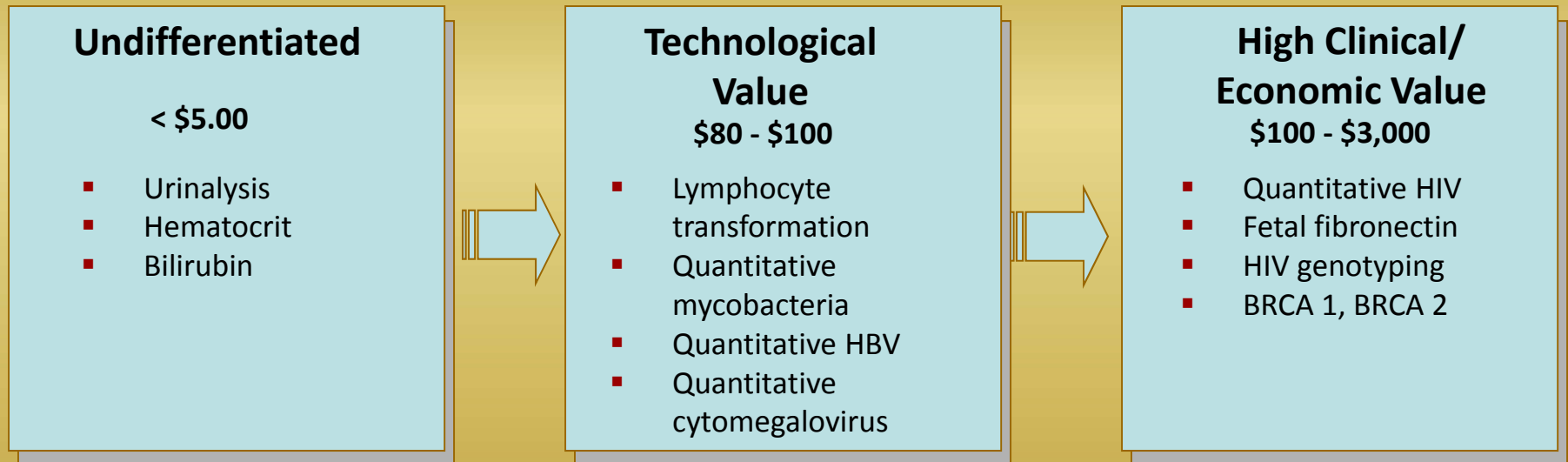
Evaluation of PanTox Opportunities: Summary and Conclusions

The following products are worth investigating in order of priority:

Opportunity (tox)	Offending drugs analyzed	Patients/disease relevant for testing	ADE clinical consequence	Potential testable population USA	Reimbursement in financial model	Savings per test	Reimbursement at \$30,000 per life year gained	Benefits healthcare	Benefits pharma
Heparin induced thrombocytopenia (HIT)	Heparin / LMWH	Hip & knee replacement + other	Thrombosis and bleeding, high mortality	Hip + knee USA: 700,000. Other indications	\$750	\$350 - \$2,900	\$1,00 - \$6,000	Potentially high cost savings, lives saved and improvement in quality of life	Potential benefits / positioning new anticoagulants
Chemotherapy induced anemia	Chemotherapy	Patients receiving chemotherapy	Increased mortality and reduction in quality of life	1.2 mill	\$1,200	-\$48	\$1,650	Substantial reductions in number transfusions, reduced mortality, improved quality of life	Increased sales (+\$1 bill) and more rational prescription of epotin drugs
Chemotherapy induced neutropenia	Chemotherapy	Patients receiving chemotherapy	Bone marrow suppression, reduced neutrophils, severe infections	1.2 mill	\$750	\$555	\$7,500	Potentially substantial cost savings, reduced mortality, improved quality of life	Increased sales (+\$950 mill) and more rational prescription of colony stimulating factors
Liver tox	Interferons for HCV	Hepatitis	Mostly reversible liver injury, rarely complete failure	About 200,000	\$250	\$240	\$260	Some savings and lives saved	Interferons may benefit
Renal tox	Antivirals + other drugs	HIV infected patients	Mild to severe kidney failure	About 700,000	\$1,700	\$1,700	>\$10,000	Potential substantial savings and reduction of mortality	Possibly for selected drugs and patient groups
Drug induced allergy	High allergy potential drugs	Broad range	Mild skin rash to potentially lethal shock	Estimated 8-10% of all ADEs	NA	\$13	\$285	Limited savings and life savings potential	Possibly for high risk patient groups
Drug induced vasculitis	Colony stimulating factors	Cancer	Mostly relatively mild skin manifestations to organ failure, 10% mortality	About 900,000	NA	\$1.47	\$8.75	Limited savings and life savings potential	Possibly for selected patient groups
Cardiac tox	Vioxx (COX-inhibitor)	Rheumatoid arthritis, osteo arthritis	Rheumatoid arthritis: 2.5 mill, osteoarthritis: 20 mill	World-wide: 7.5 mill	NA	\$120	\$850	Potentially good savings and potential reduction of mortality	Possibly for selected drugs, too late for Vioxx though
Drug induced aplastic anemia	Felbamate	Epilepsy	Red and white cells + platelets affected	Prevalence US: 2.3 mill, incidence US: 180,000	NA	NA	NA	Very low incidence but potential for reduced mortality	Potentially great benefit, too late for Felbamate

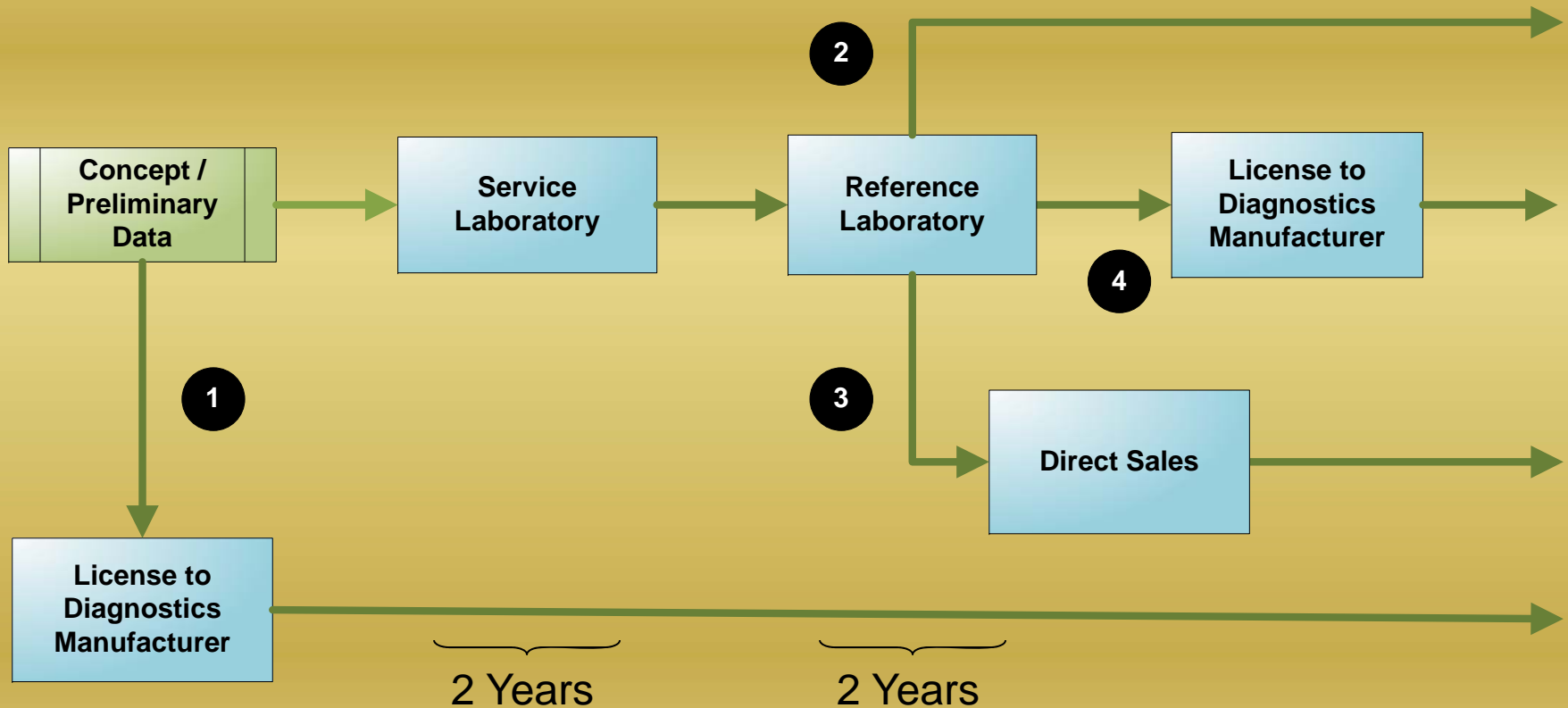
Diagnostics Tests Can Command High Reimbursement

Increased value of diagnostic testing results from the clinical value, economic value, technology investment, and product differentiation . . .



Business Model Flow

Multiple options. . .



Four Business Models

Diagnostics License Only

- No internal discovery
- Show clinical utility
- Out-license as a prototype to a diagnostics manufacturer
- No internal service laboratory
- No internal kit manufacturing

1

Reference Lab Model

- Do internal discovery
- Show clinical utility
- Set up internal reference lab to:
 - Create awareness
 - Establish pricing (ASP)
 - Obtain reimbursement
- Transfer to a major commercial reference laboratory
- Stop internal lab service

2

Direct Sales to End-Users

- Do internal discovery
- Show clinical utility
- Set up internal reference lab to:
 - Create awareness
 - Establish pricing (ASP)
 - Obtain reimbursement
- Transfer to a major commercial reference laboratory
- Stop internal lab service
- Become a Dx kit manufacturer and sell product directly

3

Simultaneous Model

- Do internal discovery
- Show clinical utility
- Set up internal reference lab to:
 - Create awareness
 - Establish pricing (ASP)
 - Obtain reimbursement
- Transfer to a major commercial reference laboratory
- Stop internal lab service
- At the same time, transfer to a Dx manufacturing partner

4

Comparison of Business Models

Time and Cost to Cash Flow Positive

	<u>Years to Break Even</u>	<u>Total Losses to Positive</u>	<u>Total Expenses to Positive</u>
DxLicenseeOnly	9	(\$35,376,882)	\$29,101,931
Reference Lab	4	(\$20,809,410)	\$20,781,957
Simultaneous	4	(\$22,230,031)	\$22,295,225
Direct Sales	5	(\$33,595,806)	\$46,471,471

Net Present Value (NPV)

Base Case	
Dx Licensee Only	(\$23,252,946)
Reference Lab	\$345,986,489
Simultaneous	\$190,428,055
Direct Sales	\$160,405,040

Sensitivities

Depending on the business model these are the key drivers of value:

Reimbursement
Market Share
Time to Market
Pricing
Penetration/Adoption

Example Companies with Similar Business Models

We have looked at a number of related companies and considered their pros and cons, and believe that the Reference lab model is the best value for the investment

Company	Business Model	Comments
Exact Sciences	Dx License Only	Potential \$75M deal with LabCorp, but unlikely to see many milestones. LabCorp cannot promote well.
Surromed	Dx License Only	Discovery platform for metabolites is basis for partnership with the CRO PPD. Some good Pharma relationships (Pfizer). Will likely drift into drug development
Genaissance	Reference Lab (Simultaneous later)	Discovery platform of marginal value. Strong reference lab group, but the business is run poorly. All CYP testing to date for drug trials done by lab (17 trials). Great potential for LQT products, but not familiar with LQT. Drifting into drug development.
Expression Dx	Reference Lab	First product very well received, but niche. Concentrated heart transplant centers make it possible to market and serve directly. Very good reference lab set up. What's next?
Prometheus	Reference Lab (?)	Has acquired a few very good products (TPMT, IBD), but struggling with market penetration. Not quite there with IBD test performance. Strong IP. Drifting into drug development.
Genomic Health	Reference Lab (not planning to go beyond internal lab)	Expect to serve the market with their own reference lab. Lack of concentrated physician base for breast cancer makes this tough. Can buy into infrastructure of others for at least a while, but will be pressured to move test to big labs. No help from Pharma groups has meant high cost of market introduction.
Predicant	Direct Sales	Just getting to point of having discovery platform ready. Carefully planned focus. Beginning push toward internal reference lab. Intend to make and sell MS-based kits and instruments.
Ciphergen	Direct Sales	Many discovery centers and customers (by contract) will siphon discoverites to Ciphergen Dx. Although no plans for a reference lab have been revealed, Gail Page, former CTO of LabCorp, now CEO of Ciphergen Dx, is an expert. Intend to make and sell MS-based kits and instruments.
Metrigenix	Direct Sales	Poorly differentiated nucleic acid delivery system, but some interesting markers from Genelogic connection (liver tox, cancer). No reference lab plan.
Biosite	Direct Sales	Strongest player in Niche Dx in many years. BMP is standard of care due to their excellent marketing efforts. However, they stand to lose everything to big Dx manufacturers who will pull volume into the large reference labs for the foreseeable future.
Chiron Diagnostics	Direct Sales	Created first high value nucleic acid Dx. ASP higher than all previous by 10x. Road on coattails of Pharma. Tough competition from Roche (who flaunted IP). Too green on product development for too long. Would like to go back and use Reference Lab or Simultaneous business model.

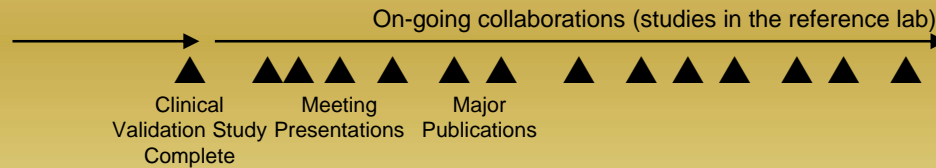
Focus on Reference Lab Business Model

- **The Reference Lab business model is recommended at this time**
 - Overall NPV is highest
 - Time to profitability shortest
 - Money to positive lowest
- **However, no final decision is necessary for at least 1 year**
- **The early stage activities required are the same across all models**
 - Signature determination
 - Clinical validation

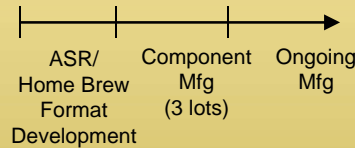
Diagnosics Timeline



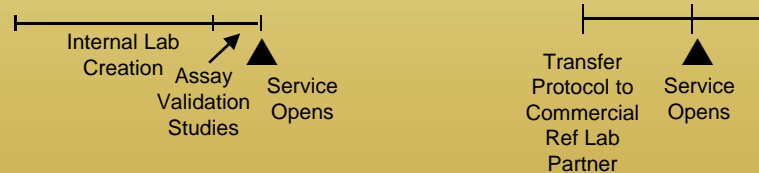
Research & Market Development



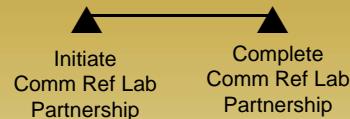
Internal Development & Manufacturing



Reference Lab (Internal & Outside)



Business Development



Risks

The following risks have been identified as the most significant for the business:

- Will there be predictive markers at all?
- Will the kinetics of the signature be favorable for timing the test?
- Will one sample per patient be possible?
- Would other marker types (proteins, metabolites, genotypes) make more sense?
- Can the value paradigm with high reimbursement be created and adopted in the time proposed?
- Can drug developers be coaxed to help?

Short Term Investment

The signature determination and clinical validation risks are the most critical in the near term:

- **It will take approximately \$2,000,000 and 12 months to conduct a set of studies on cancer patients to determine potential blood toxicity signatures for three PanTox options simultaneously**
 - Anemia
 - Neutropenia
 - Thrombocytopenia

- **Until this milestone is met, we do not propose making any further investment in the molecular diagnostics business**

Near Term Activities

The following steps are required in the near term:

- Plan the signature determination and clinical validation studies over the next 90 days
- Identify collaborators
- Determine the performance requirements in further depth for these three tests
- Construct a detailed timeline and budget for BOD review
- Upon approval, initiate study
- Construct the business development approach for Pharma partners

Potential Upsides

➤ Establish one or more relationships with drug development partners

- Favor drug positioning
- Increase revenue
- Increase market share
- Optimize pricing

➤ Pharmaceutical company might pay for R&D investment

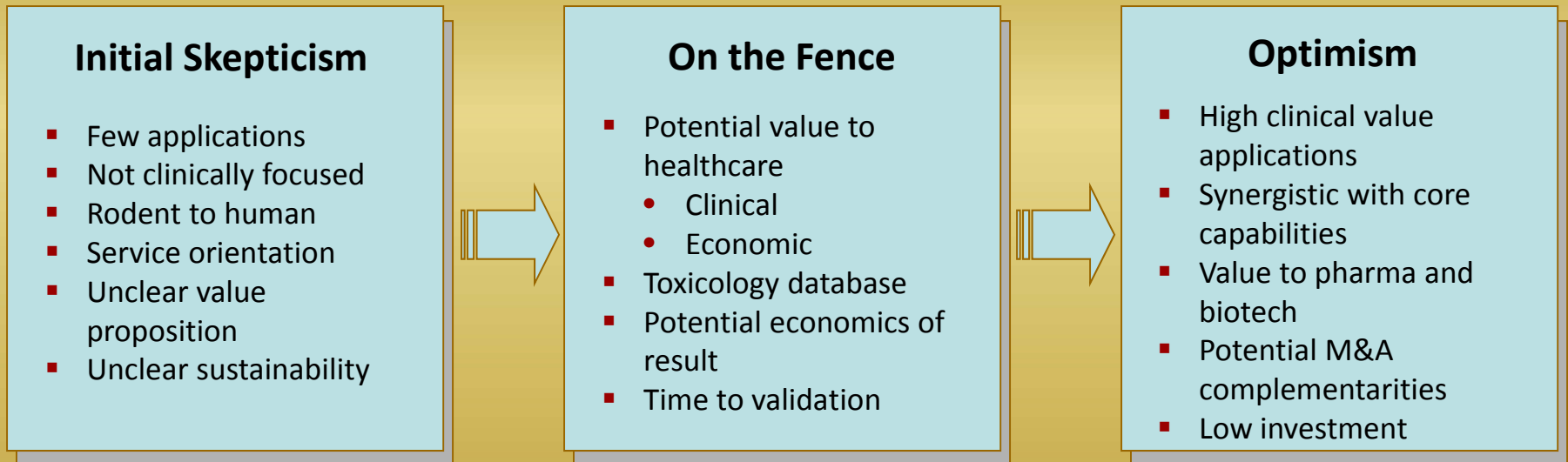
- Her2:Herceptin example

➤ Create value and credibility

- Identify signatures before talking to potential partners
- Establish IP position
- If drug developers are approached first, they will conduct the studies themselves
- Instead, walk in with the answer and the rights

Human Toxicity Testing

Although initially we thought this would lead to interesting options, we have been surprised to find that human toxicity testing could become one of the most valuable product lines in diagnostics history



The Iconix Advantage: Why Iconix?

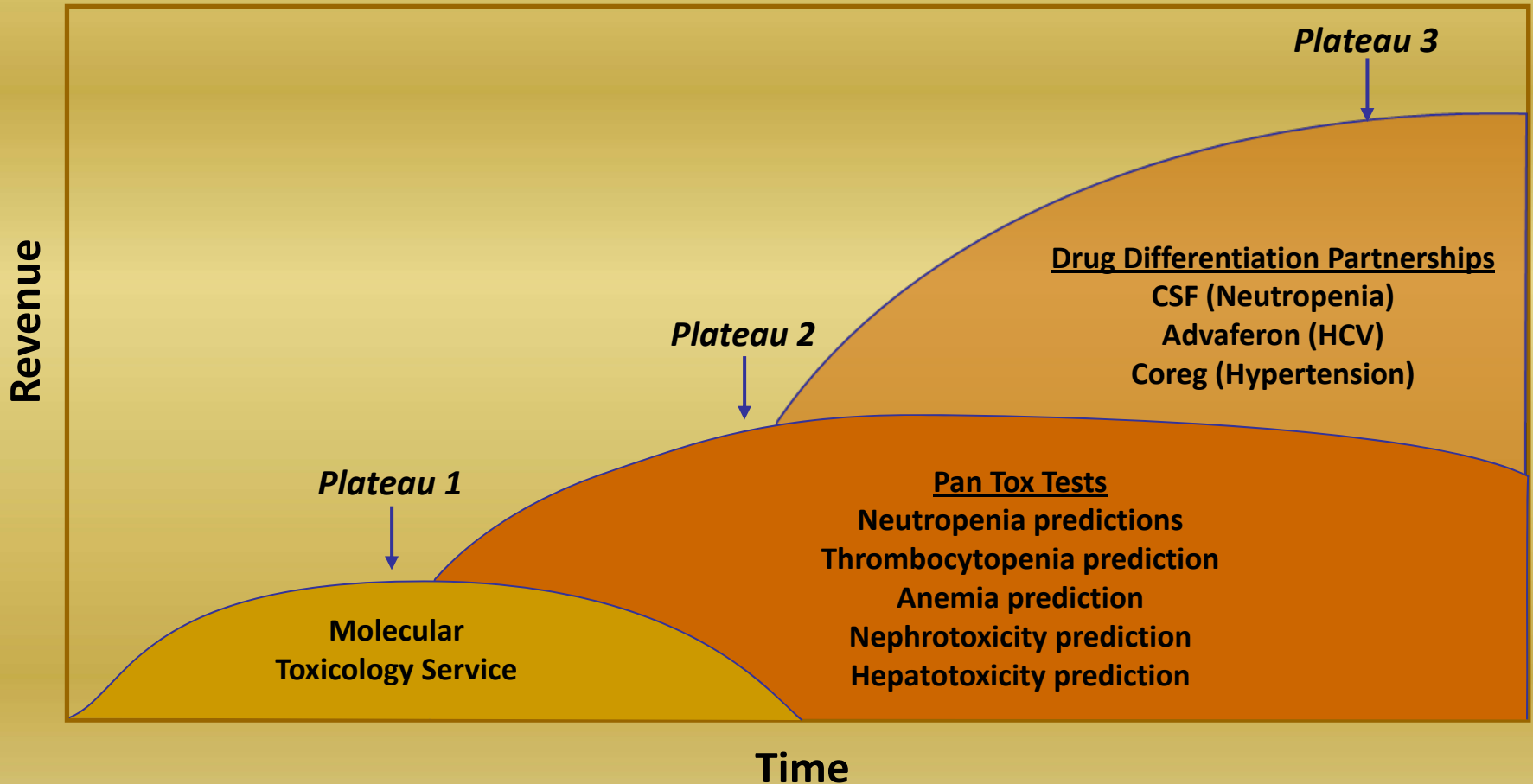
- **Most biomarker companies are focused on drug efficacy**
 - Iconix is focused on toxicity – the other half of the therapeutic index
- **Iconix's molecular toxicology competitors are not pursuing clinical toxicology testing**
- **The DrugMatrix database has given Iconix a unique perspective on adverse drug effects (ADEs) across diseases and drug usage**
- **PanTox will permit Iconix to use the same tests across many diseases and drugs thereby providing significantly larger market opportunities than is usual**
- **mRNA expression analysis is well suited to PanTox test development**
- **Iconix is focused on molecular toxicology**
- **Iconix is likely to be the “first mover” in a potentially very large market**

Partnering Potential

There are a number of potential complementary companies worth considering a relationship (M&A?) with . . .

- **Small Reference Laboratory**
- **Complementary technology(ies)**
 - Protein analysis
 - Metabolites
 - Genetics
- **Clinical focus**
- **Relevant IP**
- **Sources of samples**
- **Product delivery platforms**

What is Next for Iconix? The Future Is Becoming Clearer



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