
Introducing and Growing Medical Technology Business in the USA

Pitfalls and Opportunities

Boston MedTech Advisors

www.bmtadvisors.com

November 2008

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Presenters Biographies

- **Zvi Ladin, PhD, Principal, Boston MedTech Advisors, Inc.**

Dr. Ladin has over 20 years of management experience in the medical industry, government and academia, focusing on clinical, regulatory affairs and reimbursement strategies. His experience includes establishing reimbursement and regulatory strategies for therapeutic and diagnostic medical device companies, submission of regulatory applications, representing companies in negotiations with the Food and Drug Administration (FDA), European and Asian regulatory agencies, serving as a scientific advisor to the FDA, and teaching biomedical engineering at MIT and Boston University.

- **David Barone, Principal, Boston MedTech Advisors, Inc.**

David's background consists of over 25 years' experience in the healthcare and medical industry in the U.S., including general, technical and operations management; strategic planning; marketing; and business development. David has held senior management positions in major medical device companies and has been the founder of several healthcare service companies, held various board-level positions, and consulted medtech companies ranging from start-ups to Fortune 500 on market development, opportunity analysis, regulatory and reimbursement strategies, business development, financing and more.

- **Michael Imhoff, MD, PhD, Managing Director, Boston MedTech Advisors Europe, GmbH**

Board certified in surgery and intensive care medicine, with 18 years of clinical experience and strategic consulting to leading companies in the global medical technology markets, as well as start-ups in the U.S. and Europe, Dr. Michael Imhoff focuses on technologies and clinical applications for the ICU, CCU, OR and ED. Research areas include trauma surgery, intensive-care medicine, patient monitoring, clinical data management, artificial intelligence in medicine and health economics, leading to over 300 publications and scientific presentations. Dr. Imhoff is a member of the editorial boards of the Journal of Critical Care and of Care of the Critically Ill.



Globalization of Clinical Trials

Promise and Reality

Zvi Ladin, Ph.D.

Boston MedTech Advisors

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November 2008

Outline

- Ethical principles
- Historical perspective
- Registration requirements
- FDA acceptance of foreign clinical data
- Global trends in conduct of clinical trials
- Global opportunities
- Global challenges



Ethics (or Example #1)



- New 'block buster' drug being developed
 - BIG profits?
- Need to quickly test it
- Some questions regarding side effects
 - Could be serious
 - Need large number of patients for testing
 - Too costly (and too risky?) to study in developed countries
- Solution
 - Go to Africa
 - Paint as 'humanitarian effort'
- Voilà – a 'blockbuster' movie

Historical Infamy (or Example #2)

- **Tuskegee Syphilis Study**

(1930s – 1972)

- 399 black men signed with the US PHS for free medical service
- Men were told they had ‘bad blood’
- Disease followed without treatment
- Penicillin – available since 1947
- Outcome:
 - 28 men had died of syphilis
 - 100 others were dead of related complications
 - At least 40 wives had been infected
 - 19 children had contracted the disease at birth
- Presidential apology (Clinton) – 1997



(Courtesy National Archives)



(CNN)

Protection and Improvement of Public Health

Information Supply

- Clear new drugs / technologies expeditiously
 - Quick studies
 - Limited populations
 - Limited duration
 - Limited Information
 - Adverse events (severity, incidence)

Information Demand

- Treat large populations
 - Adverse events
 - Low incidence
 - High severity
 - Lead to....
 - Complications
 - Public outcry



Developing a Legal Framework

- 1947 – Nuremberg Code
- 1964 – Declaration of Helsinki adopted – World Medical Assoc

USA

- 1966, NEJM – Henry Beecher, MD
- 1960's – Patient consent – FDC
- 1970's – IRB review of clinical protocols
 - 1972 – NIH established OPRR (Office for Protection from Research Risks)
 - Risks and benefits of research
- 1981 – FDA requires written patient consent

Europe

- Maurice Pappworth, MD
 - 1967 – Human Guinea Pigs
- 1960's – Patient consent
- 1970's – MDD
- Competent Authorities
- Notified Bodies



1998 Office of Inspector General (OIG) Report – Clinical Research's Shifting Environment

- Funding – from public to private
 - NIH → industry
- Nature – from single site to multi-center
 - Limited information to local IRB
- Size and numbers



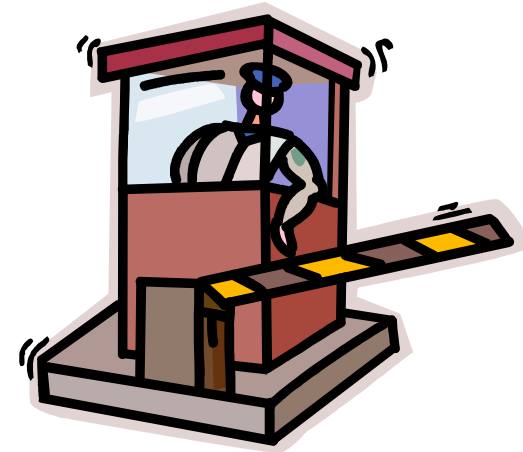
1998 OIG Report – Revamping the IRB

- Overwhelmed Local IRB
 - Time and expertise limiting review
 - New ethical issues (e.g. genetic screening)
- Evaluating IRB Effectiveness
- Conflict of Interest Inside the IRB
 - Part of the organization that gains from research
- Limited Training of IRB Members and Researchers



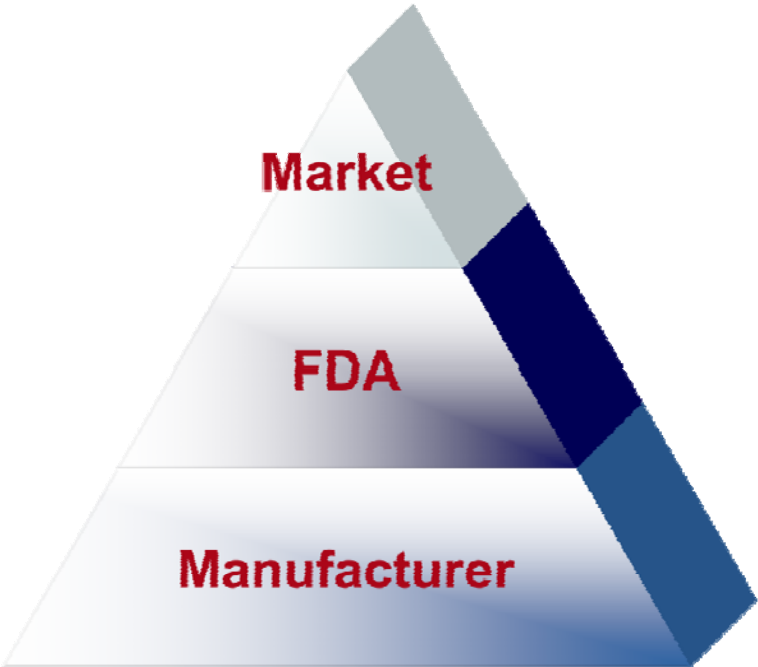
Understanding the Regulator

- Global ethical / legal framework
 - Nuremberg trials
 - Helsinki Declaration
- Local implementation
 - Culture
 - Language
 - Infrastructure
 - Economic pressures

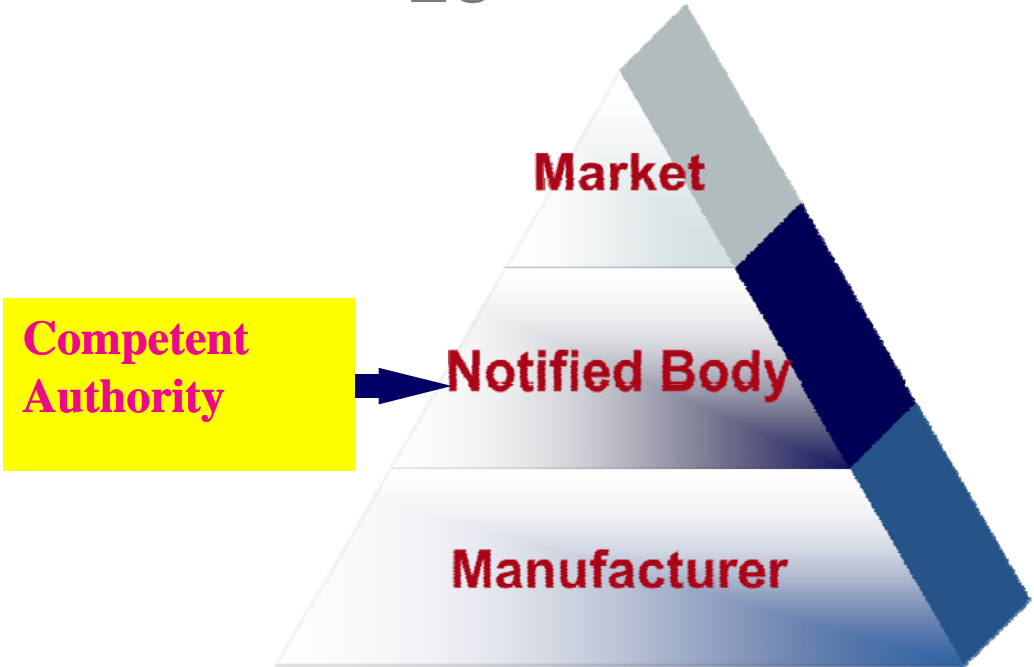


Regulatory Interactions

USA



EU



Global Trends in Clinical Trials Conduct

Observation (Cause?)

- 1980's – increased regulation in US (FDA)
 - FDA acceptance of European clinical data
- European Union Clinical Trial Directive (2001)

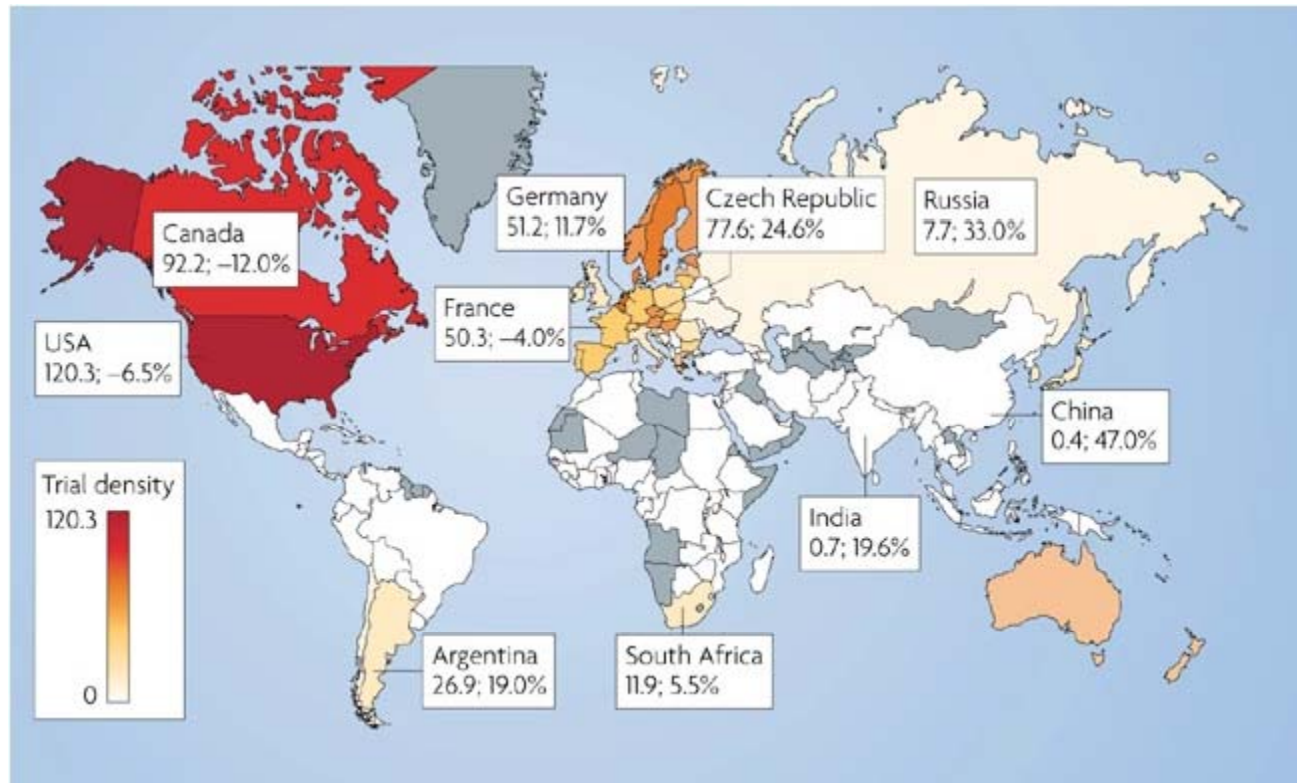
Observation (Effect?)

- Migration of clinical trials to Europe
- Migration of clinical trials to India, Russia and China
- Tassignon JP. The globalization of clinical trials. Applied Clinical Trials (2006)



ClinicalTrials.gov:

- >36,000 sites (through 1/07)
- 140 countries

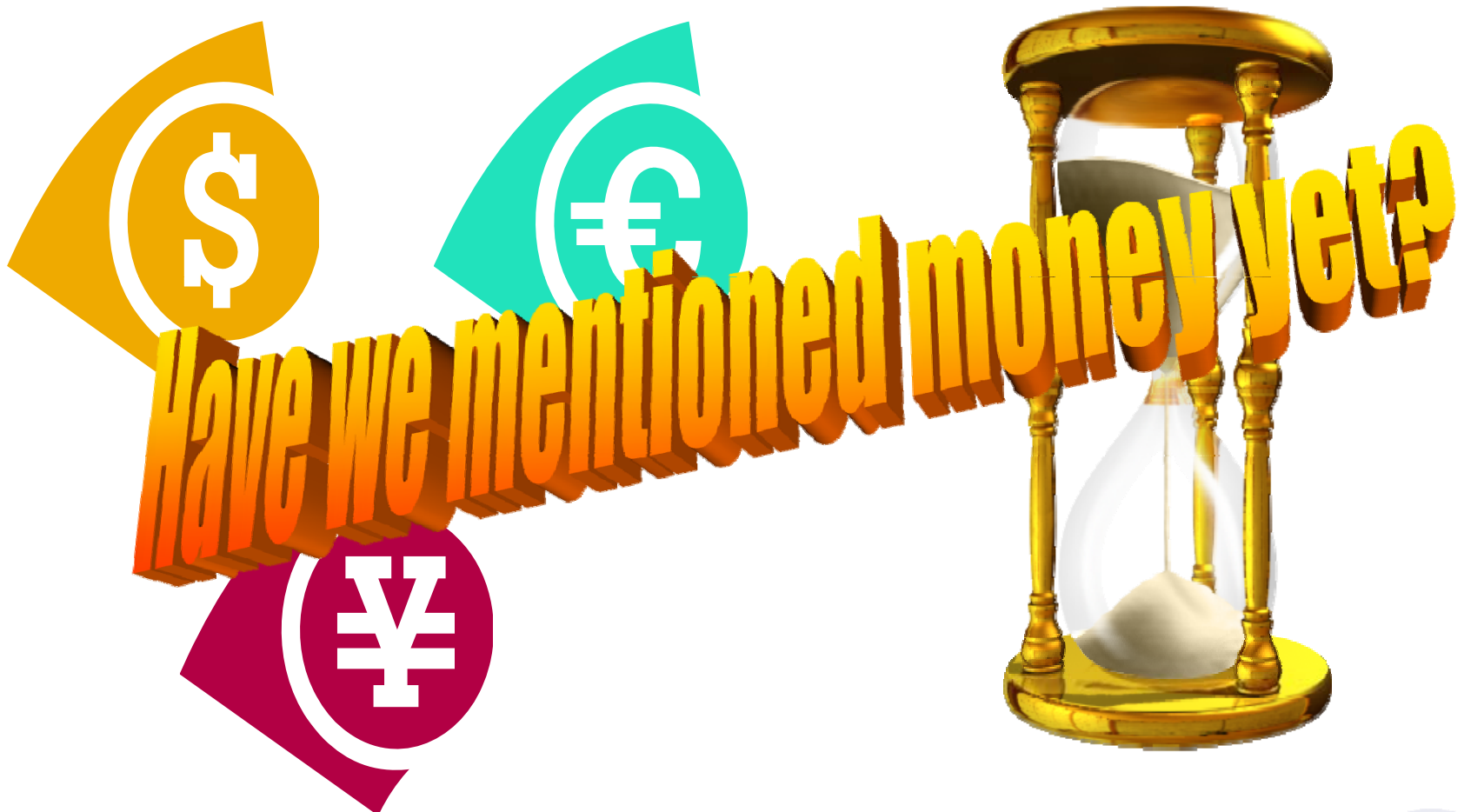


Ref: Trends in the globalization of clinical trials, Fabio A. Thiers, Anthony J. Sinsky & Ernst R. Berndt
Nature Reviews Drug Discovery 7, 13-14 (January 2008)

New Opportunities – Latin America

- Streamlined laws make Latin America attractive to sponsors
- October 2008 – 20% growth in the number of international clinical trials over four years

Country	Open Trials
Brazil	323
Mexico	292
Colombia	107



Economic Drivers

Increase regulation

- Increase
 - Costs
 - Investigators
 - Clinical environment
 - Monitors
 - Patient recruitment
 - Time
 - Longer
 - Effort
 - Higher

Move studies to:

- Less regulated countries
 - Time
 - Faster study initiation
 - Lower regulatory overhead
- Less expensive cost of living
 - Lower costs
- **However.....**

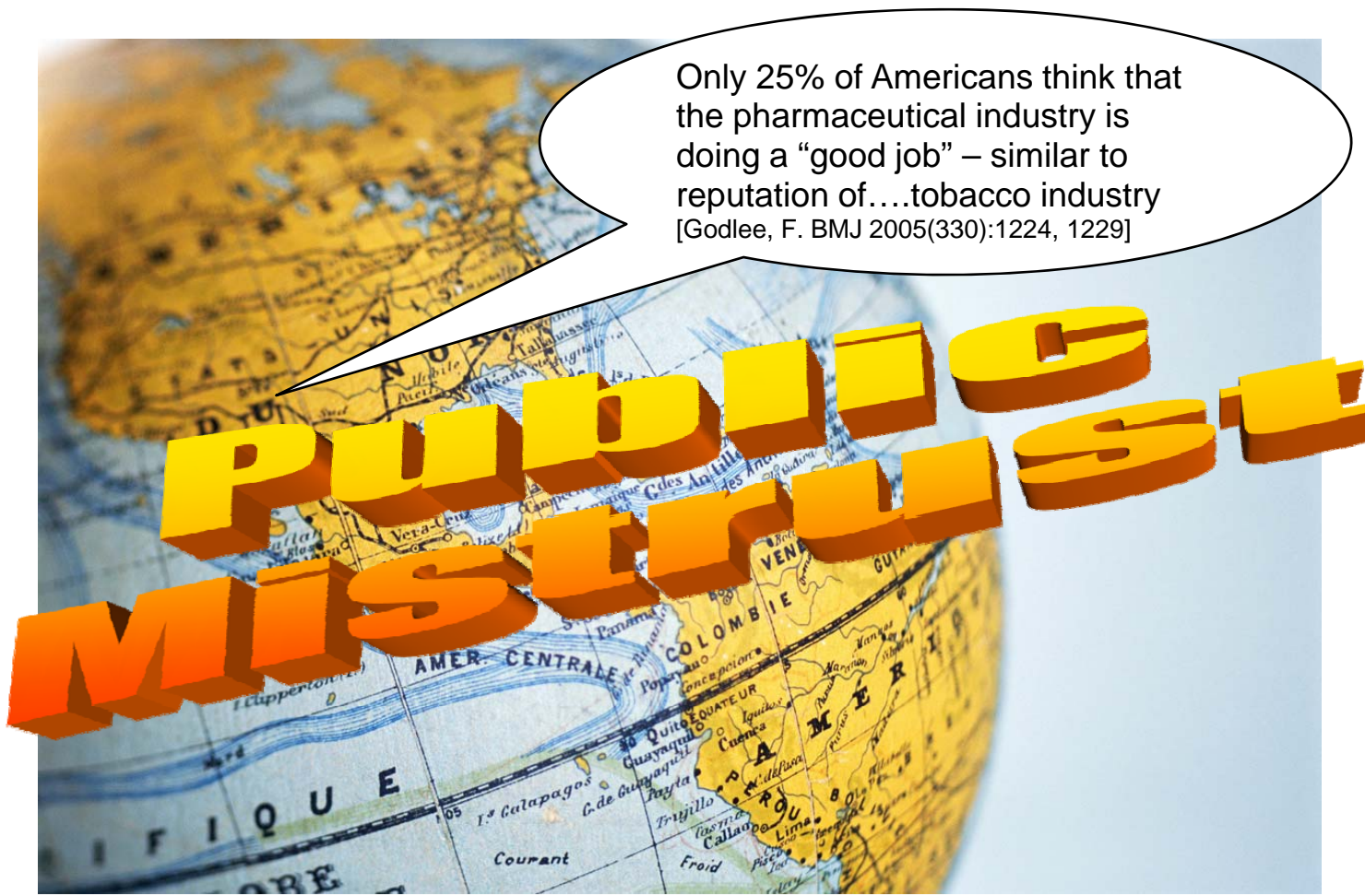


2004 – Clinical Trial Outcry (or Example #3)

- GlaxoSmithKline (GSK) Paroxetine treatment of depression in children
 - Attorney General of NY sued company
 - Allegation
 - Company selectively published positive partial results
 - Off-label promotion of drug by company
 - Settlement
 - GSK published all study results on Web
- 150 Scientists and organizations signed the Ottawa statement
 - Mandatory trial registration
- International Committee of Medical Journal Editors (ICJME) of 12 leading medical journals – no publication of unregistered studies
- Ministerial Summit on Health Research in Mexico
 - WHO
 - 52 Countries



Global Goals



Restoring Public Trust

Patient

- Full disclosure
 - Procedure
 - Alternatives
 - Risk / Benefits
 - Beneficiaries
 - Financial interests

Regulators

- Study approval
 - National regulatory authority
 - Local committee
 - IRB
 - Helsinki committee
- Complete and comprehensive information submittal
 - Related studies
 - Device safety

Community

- Clinical
 - Disclosure
 - Conferences
 - Publications
- Public
 - Registries
 - Patient groups

Clinical Trial Registration

- US FDA requirement – ClinicalTrials.gov
 - Established under FDAMA (1997)
 - First version – February 29, 2000
 - Initially mandated for only drug treatment of life threatening diseases
 - Expanded to include all trials conducted in US
 - October 2003 – 1000th study registered
 - Registration for non-life threatening treatments – RECOMMENDED!

- WHO International Registry

- Established 2004

- Enforcement

- FDA (limited to life-threatening treatments)
 - WHO (none)

Date	US Registration	WHO Registration
2003 (October)	1000	0
2004	13,000	0
2006 (June)	>40,000	12,000



WHO Clinical Trial Registry

- <http://www.who.int/ictrp/en/>
- Major components of trial including:
 - Contact information
 - Sponsor / source of support
 - Countries
 - Interventions
 - Key inclusion / exclusion criteria
 - Study type
 - Sample size
 - Recruitment status
 - Outcomes
- No requirement to report results



FDA Acceptance of Foreign Data (IND)

- Final Rule Published (effective October 27, 2008)
- 21 CFR Part 312
 - Non-IND foreign clinical studies
- Previous Requirement
 - Adherence to ethical principles stated in 1989 Helsinki Declaration (World Medical Association)
- Current Requirement – GCP
 - Includes review and approval by independent ethical committee (IEC)
 - Non-compliant studies
 - Have to be submitted
 - **Cannot be accepted as support**



FDA Acceptance of Foreign Data (PMA)

- 21 Section 814.15 (last amended December 2, 1986)
 - Valid data
 - Conformance with Helsinki Declaration or local laws and regulations
 - Whichever accords greater protection to the human subjects
 - If data is sole basis for submission:
 - Data applicable to US population and medical practice
 - Competent clinical investigators
 - Data can be audited and validated by FDA



Global Opportunities

- Potential Advantages of Foreign Clinical Studies (advertisement by an Indian CRO)
 - Diverse population
 - Genetically
 - Culturally
 - Socio-economically
 - Large numbers of target patients
 - Quicker studies
 - Regulatory approval
 - Medical infrastructure
 - Language
 - Costs

Remember Murphy*!

- Poor infrastructure
 - Clinical complications
 - Simple problems could become significant, severe and....expensive
- Poor regulatory infrastructure
 - May limit acceptability of data
- Poor study control
 - May jeopardize collection of data
 - May disqualify patients
- Hence....
 - **Regulatory submission denial**



*Anything that can go wrong...will!

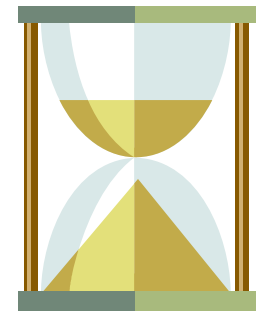


Global Challenges – I

- Regulatory Approval
- Medical Infrastructure
 - Addressing adverse events
 - Access to healthcare system
 - Access to specialists
 - Addressing complications
 - Training investigators

Global Challenges – II

- Language
 - Translation
 - Communication with patients, investigators
 - Validated questionnaires (e.g. QOL)
- Culture
 - Patient – clinician relationship
 - Collecting medical history (family, personal)
 - Medical tests
- Geography
 - Time
 - Distance
- Support



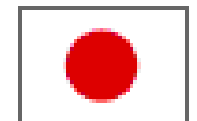
Global Limitations

- Review clinical plan with target regulators
 - In trial country
 - In target market
- Applicability of Clinical Data
 - Will target market accept trial data?
 - Regulators?
 - Clinical market?
- Validity of 'Pooling' Data
- Cost Information
 - Will it have any bearing on target market?
- Cost – Effectiveness Analysis
 - Is reimbursement an issue?



Global Trends

- Harmonization
 - Global Harmonization Task Force (GHTF)
 - Harmonize medical device regulations world-wide
 - Founding members (1992)
 - Regulatory authorities from Australia, Canada, EU, Japan and US
 - Five task forces, including one focused on clinical investigations
 - Global acceptance (and requirement) of GCP compliance
 - New FDA rule
- Opportunities
 - Site selectivity
 - It usually costs twice as much and takes three times longer (or vv)
 - If it is too good to be true....
- Challenges
 - Principal Investigator remuneration



Ethical Dilemmas (to ponder)

- Patient Enrollment
 - Monetary incentive
 - Clinician / patient trust (pressure?)
 - Full disclosure (risks, benefits, incentives)
- Study Conduct
 - Patient access to healthcare
 - Information dissemination to patients
 - Protocol requirements (tests, travel)
- Post-study
 - Availability of treatment



Thank You

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Time-to-Adoption

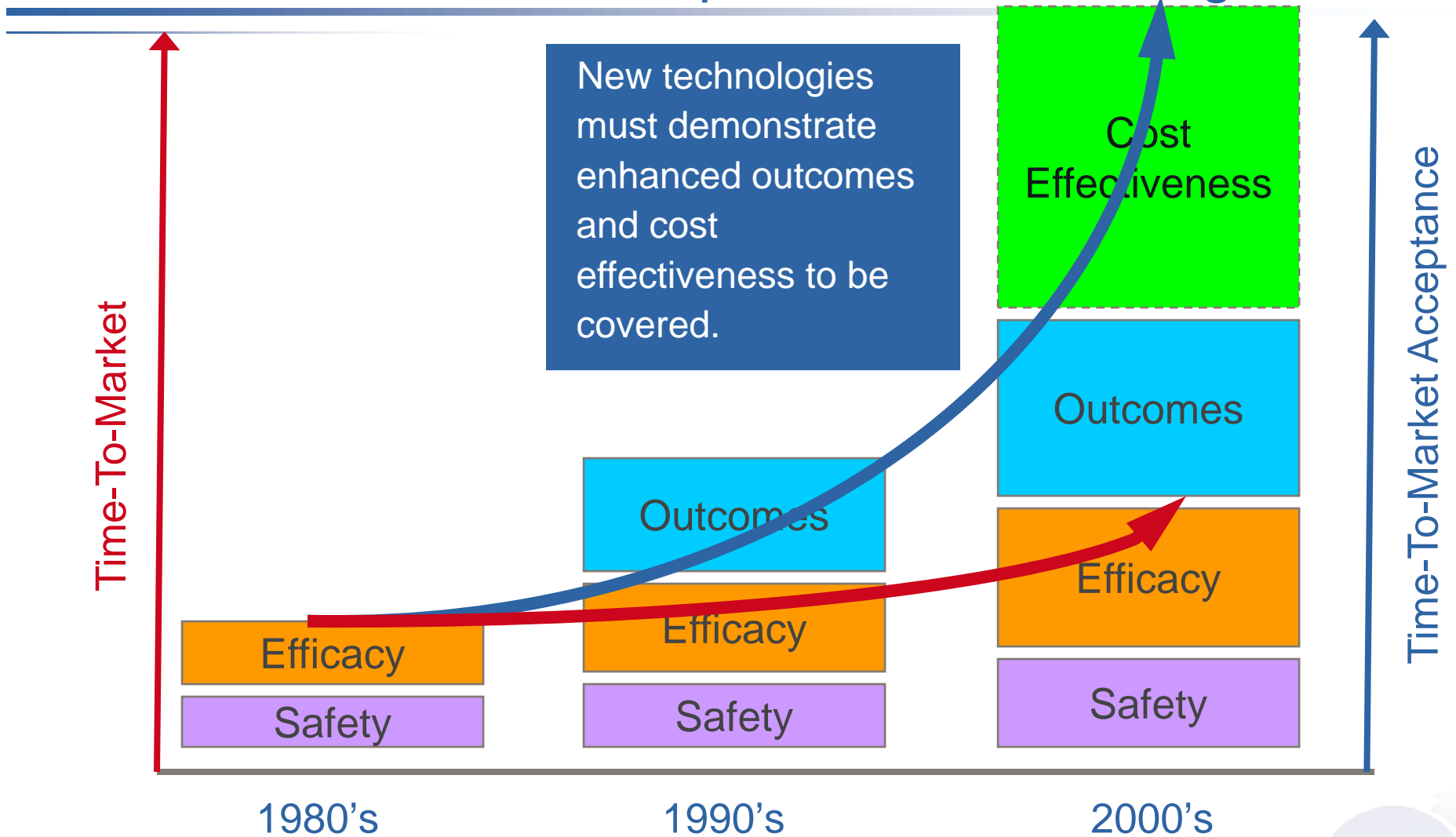
Reimbursement as a Marketing Strategy Paradigm

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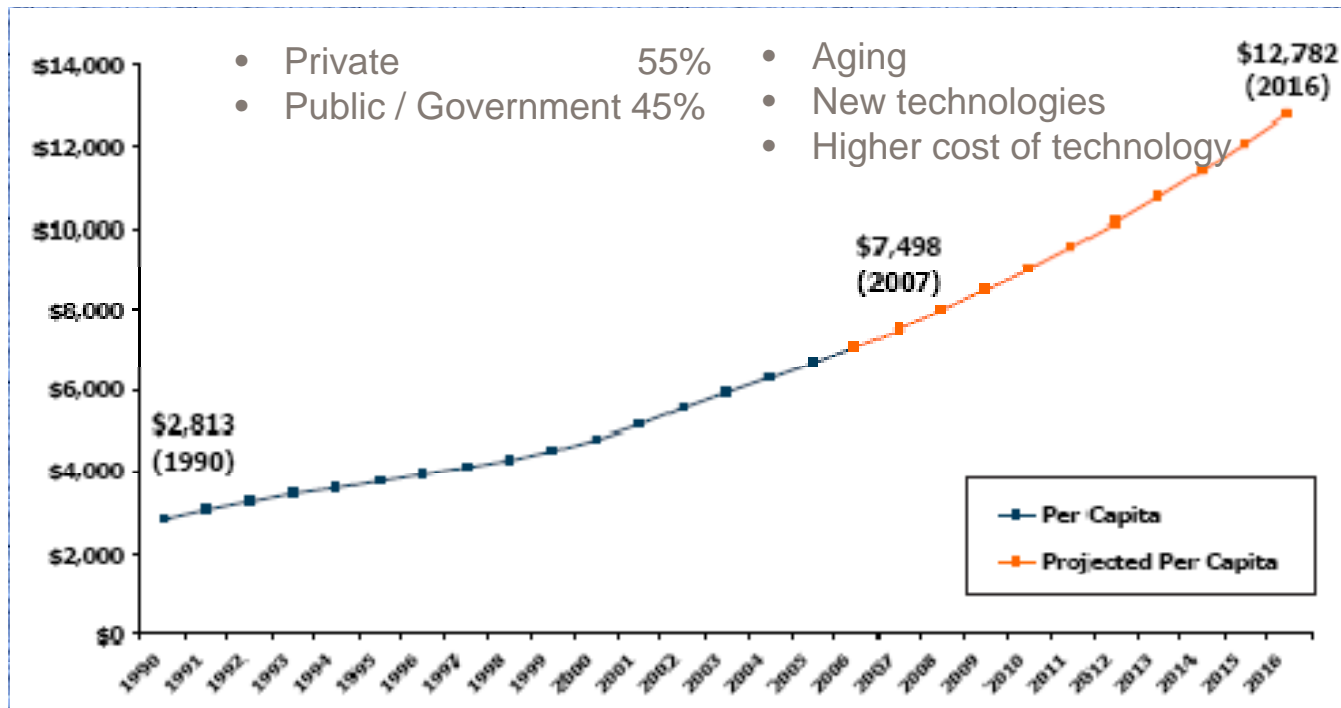
Time-To-'Market Acceptance' is Increasing



Considerable Implications

- Need additional funds and financing rounds
- Valuations are impacted
- Slowing business development initiatives
- Prospective distributors sit on the sideline
- Increased risk of new competitors

Healthcare Expenditures Are Mounting

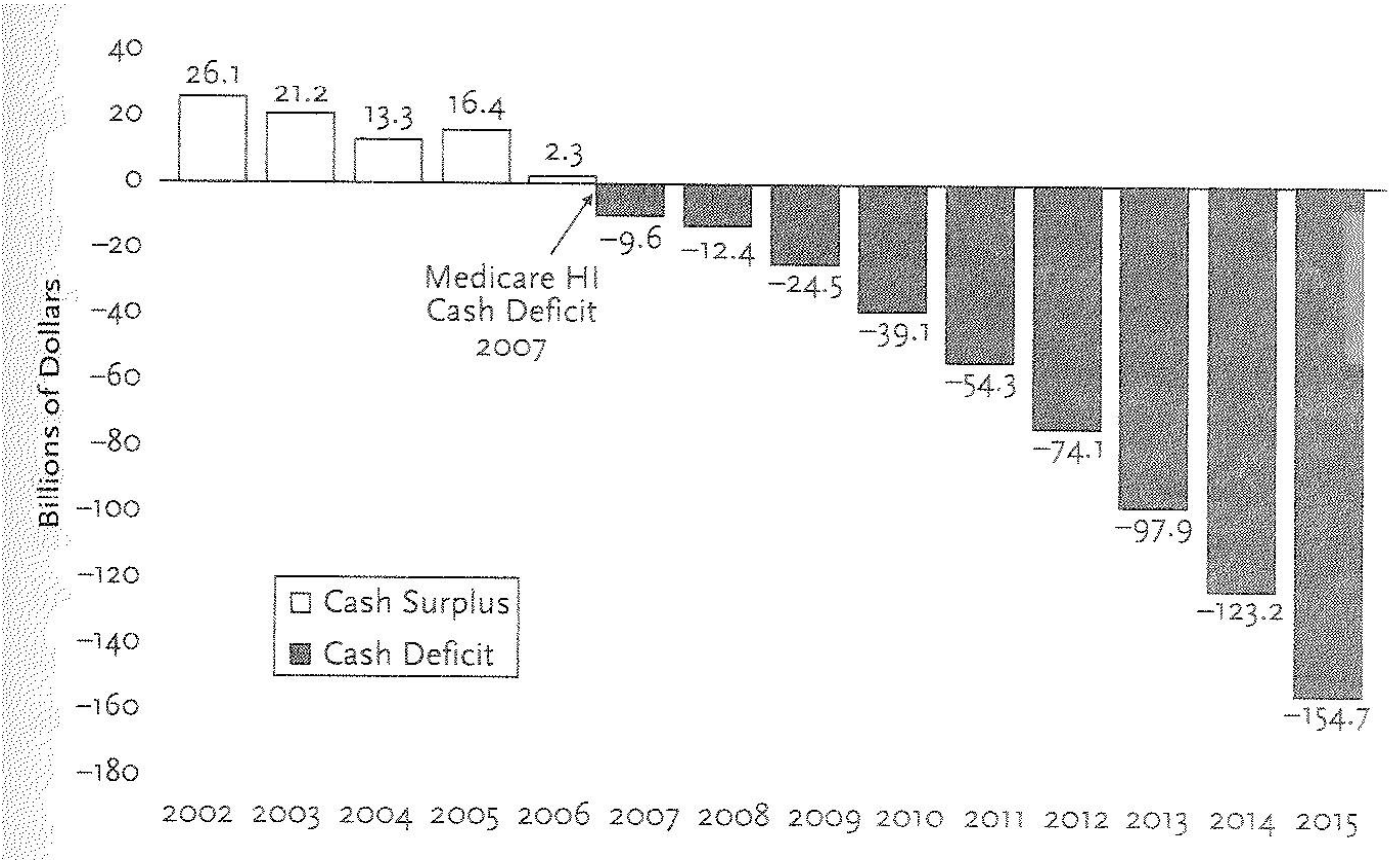


Demand for more care and new technology will continue to drive costs

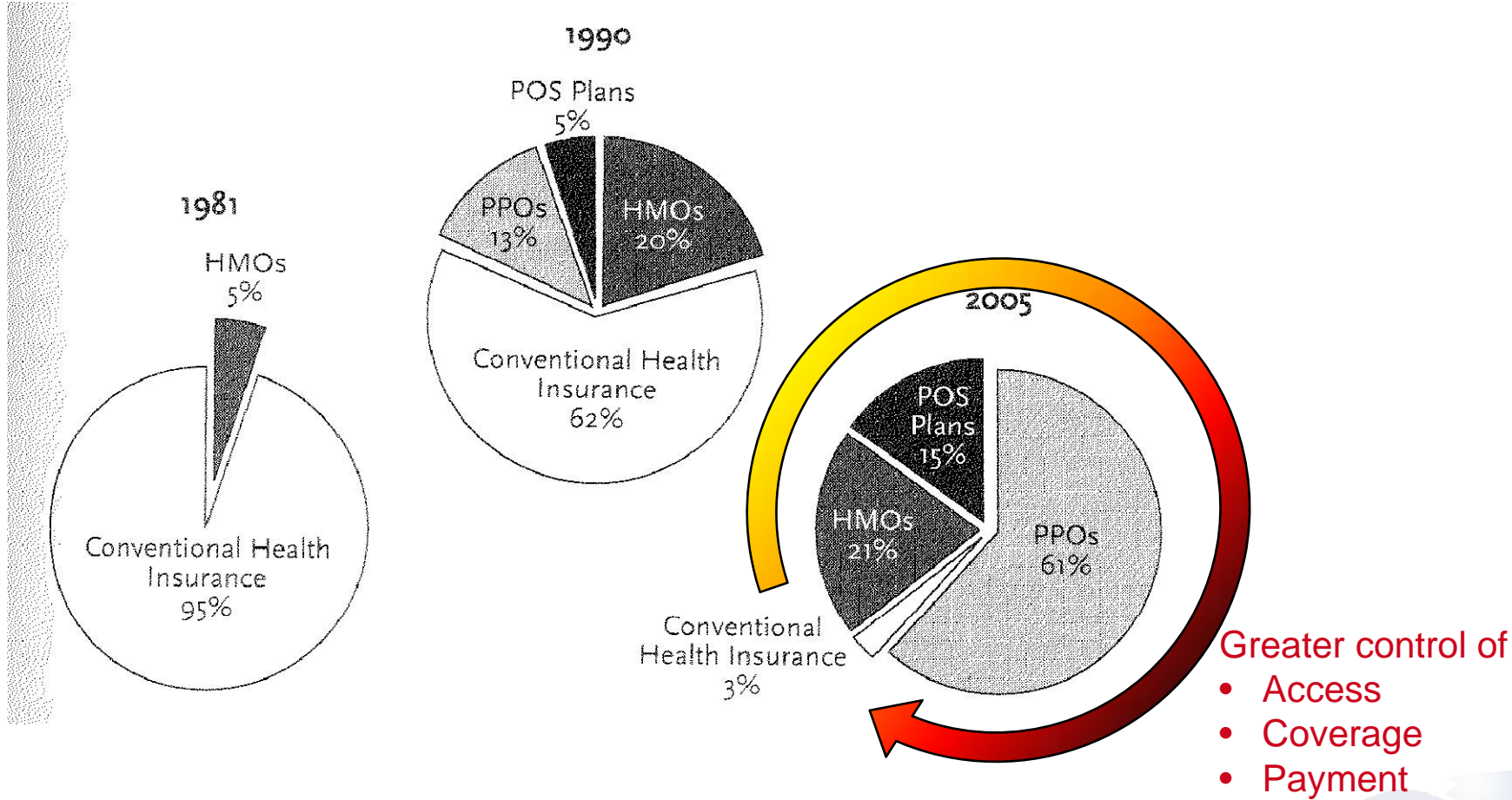
	1970	2007	2016 (p)
Annual cost per capita	\$356	\$7,498	\$12,782
Total Expenditures	75 billion	2.2 trillion	4.1 trillion
% of GDP	7.2%	16.2%	19.6%

Ref: Kaiser Family Foundation, Sep 2007

Net Cash Flow (Medicare) → Political Pressures



Market Response: Managed Care

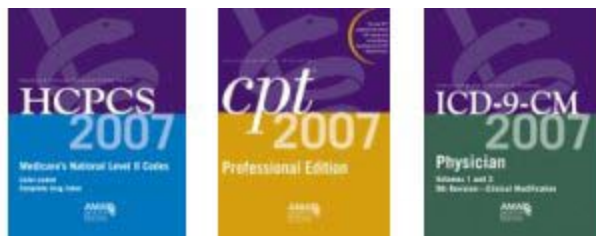


The Reimbursement Process

I. Coding ➡ II. Coverage ➡ III. Payments

Classifies patient conditions, services and supplies

- ICD-9 (~500)
- CPT (~8,000)
- HCPCS (~15,000)
- Drugs and Biologics



Defines when products & services are eligible for payment



Determines payment processes and amounts

Medicare Fees:

- Standardized
- Public
- Non-negotiable

Commercial Payers:

- Non-standardized
- Confidential
- Negotiable

Code \neq Coverage

Coverage \neq Payments

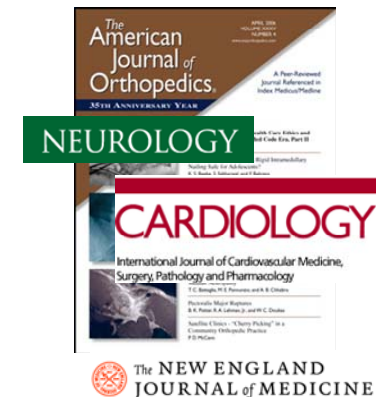
Obtaining a New CPT Code

Criteria

1. FDA approval for the specific use of the device / drug
2. Truly new service / procedure
3. The clinical efficacy has been well-established
4. The service is widely performed across the country
5. Used by many physicians or other healthcare professionals

Requirements

- ✓ Peer-reviewed literature
 - Published articles
 - Documenting improved health outcomes
- ✓ Specialty societies support



FDA and Payers are Looking for Different Benefits

FDA



Does the product do what it claims?

- Safety and efficacy
- Data generated in controlled setting
- Academic focused review / KOL
- Scientific method
- Substantial equivalence or comparison to placebo
- Intermediate or short-term outcome
- No cost considerations

Payers

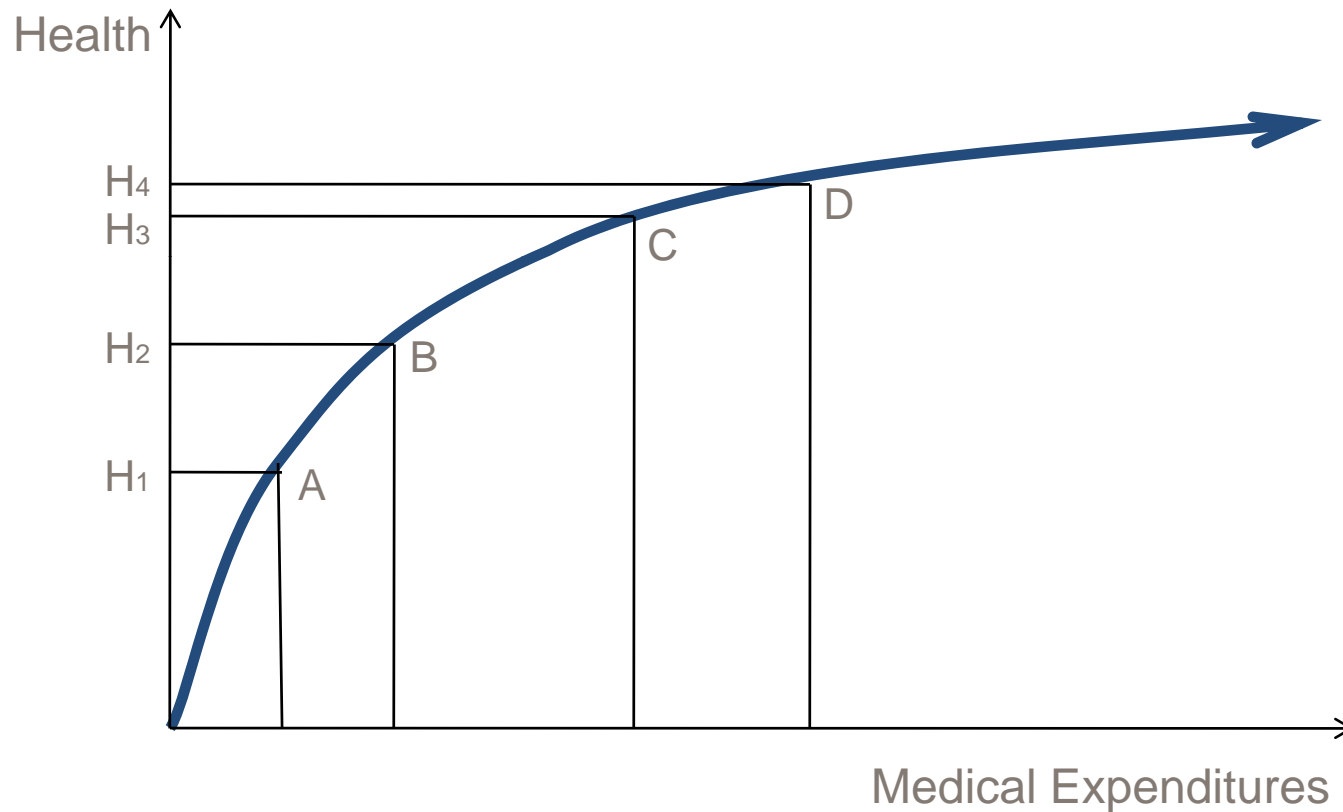


Does the product / procedure improve outcomes?

- ...Everything listed on the left, plus
- Reasonable and necessary
- Use in “real world” / general, non-academic and routine conditions
- Professional societies input is important
- No standard methodology for determining coverage
- Long term health outcomes
- Cost is often key consideration



Effect of Increased Medical Expenditures on Health



Ref.: Health Policy Issues, PJ Feldstein, 2007



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“Your insurance just called. They don’t cover ‘having a bad day’...”

Goals of Reimbursement Strategy

- Improving product development, regulatory and clinical studies/ plans
- Identifying proactive steps to remove or mitigate the effect of payment barriers
- Ensuring that customers of the product can obtain maximum reimbursement for the corresponding service
- Explore revenue generation options until full reimbursement is available (can take a few years)



Pre-Product Development Questions

Timing - during product development, and in conjunction with clinical, regulatory and sales and marketing planning

- Product / clinical positioning
 - Who will receive the product and who will be paying for it
 - Who will actually do the procedure and in what settings
 - What indications are most appropriate
 - Target population
 - Anticipated quality and/or efficiency benefits
- How will the product meet FDA “safe and effective” and payers’ “reasonable and necessary” requirements?
- If reimbursement exists, will it cover providers’ expense
- Reimbursement strategy
 - Available codes and coverage guidelines
 - Need to modify existing codes or establish new codes
 - Modifications to coverage guidelines
 - Justifications to payment increase
- Address payers needs when planning studies
 - What data represents evidence-based?
 - What will determine the amount they pay?



Reimbursement Planning

	Similar to Another Product	Expansion of Existing Technology	New / Innovative Technology
Development	Confirm existing codes and coverage	Modify coverage, coding and payments to include the new product	Create new coverage, coding and payment structure for the product
Evidence	FDA approval with same indications suffice for inclusions in existing coverage	1-2 studies	Randomized controlled study (2-4); cost effectiveness data; Registry data
Timelines (post FDA approval)	6 – 12 months	1 – 2 years	2 – 5 years

National or Local Coverage Decisions

NCD

- Risk assessment: “all or nothing” decision
- Positive decision leads to consistent coverage nationwide
- Risk of non-coverage decision or restricted access to treatment
- Private payers often follow national decisions

LCD

- No risk of “all or nothing” decision
- More flexibility in the process
- Standards of coverage vary
- Inconsistent LCD can lead to initiation of NCD



Validate your Reimbursement Early

Manufacturers may erroneously conclude that initial coverage suggests their device has been “approved” by a payer, when in fact, the payer may initially reimburse because it didn’t identify the product as new or with expanded indications. The product simply falls below the “reimbursement radar”.



Post Marketing Activities

- Cultivate support from KOL
- Seek position statements from specialty societies
- Educate employers and beneficiaries
- Improve the quality of evidence through additional studies (teaching and community settings)
- Document economic costs
 - Family, employer
 - Complications
 - Models estimating impact on societal healthcare costs
- Develop payers education packets specific to disease and patient population treated
- Follow legislative initiatives



Pre-Reimbursement Marketing

- Continue to develop supportive evidence
- Develop installed base in segments not/less sensitive to third-party payers
 - Early adaptors
 - Provider networks not affected by third party payers (e.g. VA, Kaiser)
 - Inpatients
 - Workers compensation
 - Self pay
 - Participation in covered clinical research (Coverage with Evidence Development)
- Local payers
 - Local opinion leaders
 - Significant providers
 - Use 'miscellaneous' codes or 'modifiers'
- Do not Induce utilization



Development

Clinical Studies

Regulatory

Reimbursement

Old Thinking

Development

Clinical Studies

Regulatory

Reimbursement

New Thinking



Decision to purchase and decision to use are not the same



Thank You

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Patient Monitoring and Informatics

New Opportunities for the Next Decade

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November 2008

Patient Monitoring and Informatics

New Opportunities

- Common Sense Approach
- Introduction into Patient Monitoring and Informatics
- Requirements from a changing healthcare environment
- Case study: Tight Glycemic Control
- Challenges and Opportunities

Patient Monitoring and Informatics

New Opportunities

Common Sense Approach

- Is there clinical need?
- Is there clinical benefit?
- Is there acceptance in the medical community?
- Is there financial benefit for the user?
- Where is the market?



Patient Monitoring and Informatics Definitions

Informatics

- Medical Informatics can be defined as any application of information management technology in healthcare [*Imhoff M et al, Intensive Care Med 2000*]

Monitoring

- Measurement of a parameter of a system (human being, aircraft, etc.)
- Continuous or semi-continuous measurement
- Automatic function over extended time periods (w/o user interaction)
- Warning capability – alarms
- Display of changes over time (e.g. trends)
- Timeliness of measurements in the clinical context
- No direct therapeutic effect



Benefits from Patient Monitoring

- Clinical benefit seems intuitive, but ...
 - Benefit could not be found
 - Pulmonary artery catheter [*Connors et al, JAMA 1996*]
 - Pulse oximetry [*Pedersen et al, Cochr Review 2003*]
 - Benefit could be found
 - ScvO2 / early goal directed therapy in sepsis [*Rivers et al, NEJM 2001*]
 - Cardiac output / perioperative hemodynamic optimization [*Boyd, JAMA 1993*]
 - Benefit depends on the translation of monitoring into therapy
-
- ➔ Process Control
 - ➔ Decision Support
 - ➔ Application of Informatics





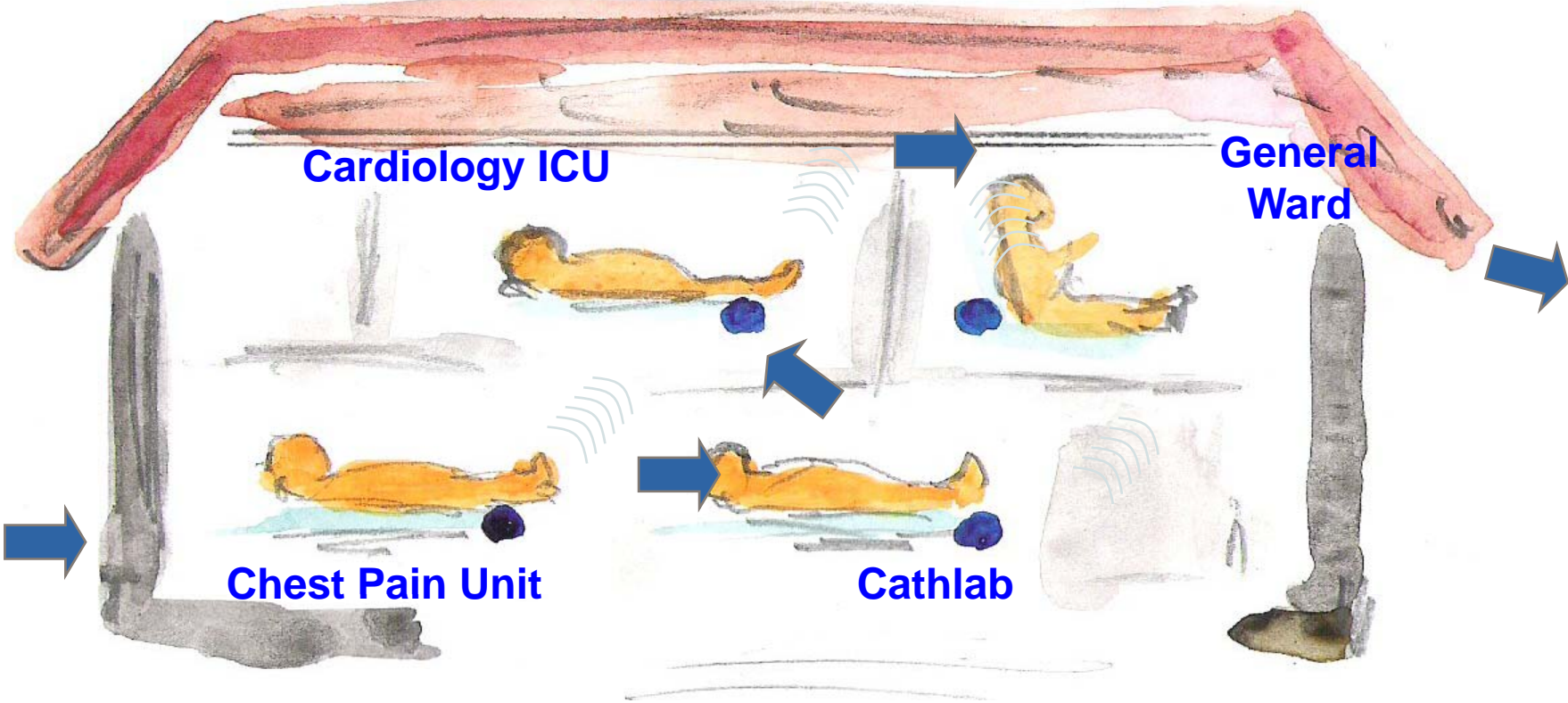


Changes in Hospital Care

- Increasing acuity
- Decreasing length of stay
- Increasing patient safety concerns
- Increasing liability challenges
- Shortage of ICU beds
- Shortage of qualified staff
- Implementation of intermediate care
- Telemetry units
- Critical care outreach (CCOT, MET, RRT, ...)
- Monitoring in general wards
- Improving informatics infrastructures



Continuum of Care Continuous Monitoring



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Monitoring in the Hospital

“Traditional” Monitoring (ICU/OR)

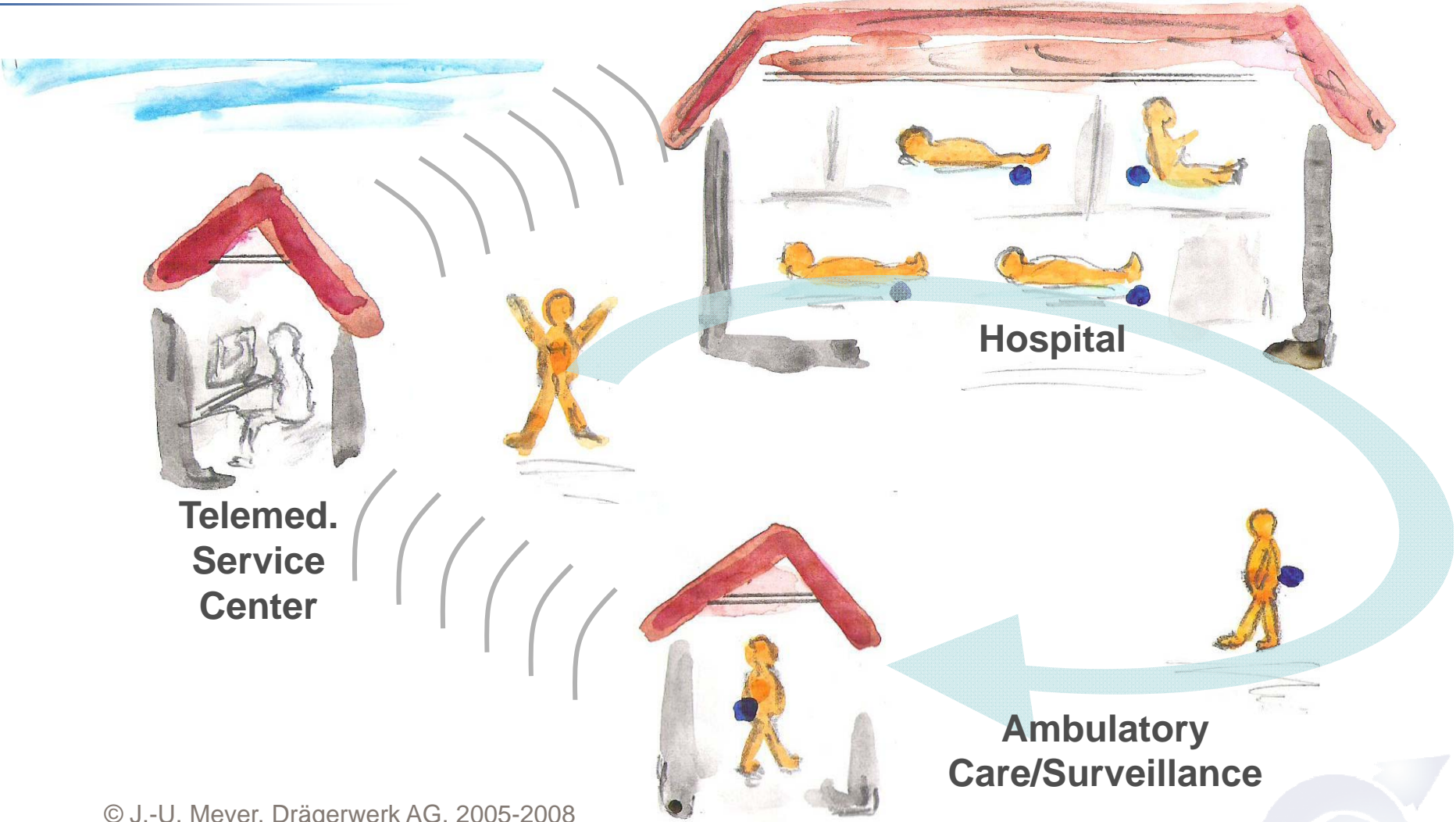
- Immobile patients
- Invasive monitoring
- Cables and lines are “acceptable”
- Patient comfort not a primary concern
- High risk of immediately life-threatening changes
- High nurse/patient ratio
- Caregiver presence

“Extended” Monitoring (outside ICU/OR)

- Potentially mobile patients
- Non-invasive monitoring
- Cables and lines are not acceptable
- Patient comfort highly relevant
- Less risk of immediately life-threatening changes
- Low nurse/patient ratio
- Limited caregiver presence



Continuum of Care Continuous Monitoring



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Monitoring Outside the Hospital

- Mobile, active patients
- Monitoring during activities of daily living
 - non-invasive, non-obtrusive, no cables, ...
 - patient comfort!
- Easy handling, application and operation without help
- No caregiver presence
- Alarms cannot be answered immediately!
- Early warning, before a situation becomes life-threatening
- ➔ Monitoring devices and sensors
- ➔ Data communication and analysis
- ➔ Remote services and patient support



Tight Glycemic Control

- Tight Glycemic Control (TGC)
 - *TGC in intensive care:*
Maintenance of blood glucose levels 80-110 mg/dl (4.4-6.1 mmol/l) with IV Insulin infusions (and IV glucose infusions)
 - *TGC (intensive insulin therapy) in diabetes care:*
Frequent insulin injection (>3/d or continuous) and frequent blood glucose measurements
 - ➔ Integration of Patient Monitoring and Informatics
- Management of Diabetes mellitus type 1 and type 2
 - better long-term outcomes (complications, survival)
 - significant DM type 1 populations (0.2-0.5%/pop., constant)
 - huge DM type 2 populations (4-8%/pop., increasing)
- Intensive Care Medicine
 - improved outcomes (survival, organ failure)
 - “low cost” intervention
- ➔ Opportunities for new technologies
- ➔ Significant perceived market potential



Tight Glycemic Control New Opportunities

Common Sense Approach

- Is there clinical need?
 - TGC without monitoring and decision support is barely feasible
- Is there clinical benefit?
 - Clinical studies
- Is there acceptance in the medical community?
 - Guidelines, best practice
- Is there financial benefit?
 - What is the cost of current practice?
 - What is the cost of the new technology?
- Where is the market?



Hyperglycemia and In-Patient Outcomes

- Hyperglycemia is associated with increased hospital mortality
 - Surgical and non-surgical patients
 - Especially in patients without prior diabetes
- Numerous studies and reviews
 - Capes SE, et al.; Stroke 2001
 - Systematic review of 32 studies
 - Acute hyperglycemia is associated with increased mortality after stroke.
 - Umpierrez GE, et al.; J Clin Endocrinol Metab 2002
 - Observational study with 2,030 patients
 - Hyperglycemia is an independent marker of in-hospital mortality
 - Krinsley JS, et al; Mayo Clin Proc 2003
 - Observational study with 1,826 patients
 - Hyperglycemia is associated with hospital mortality.
- ***Does control of hyperglycemia change outcomes?***



TGC Studies, Leuven I

van den Berghe G, et al.; NEJM 2001

- Seminal study into glucose control
 - Prospective randomized controlled trial
 - 1548 patients (mostly post cardiac surgery)
 - maintenance of blood glucose in normal range (80-110 mg/dl)
- Results
 - Significant reduction of mortality, complications, and cost
 - But only in patients with ICU LOS > 5 d
 - No differences in patients with shorter LOS.
 - Only surgical/open heart patients, no projections to medical patients



Tight Glycemic Control Best Practice Guidelines

- No “official” guidelines but several strong recommendations
 - Surviving Sepsis Campaign (SSC) Sepsis Bundles
 - Institute of Healthcare Improvement (IHI)
 - Volunteer Hospital Association
 - Many intensivists want to implement TGC, but
 - Target glucose levels: 80-110 mg/dl?
 - Which patient groups?
 - Glucose measurements intervals 1-4 hours (or less?)
- ➔ Significant hype about TGC



Tight Glycemic Control

The Challenges and Opportunities

- **Monitoring of blood glucose levels**
- **Administration of insulin and glucose**
- **Decision support for dosing and titration**



Glucose Monitoring

Current State of the Art

- Manual arterial/venous blood sampling
 - Central lab
 - Stat lab in the ICU (near POC)
 - Test strip (at POC)
- Manual capillary blood sampling
 - (Central lab)
 - Stat lab in the ICU (near POC)
 - Test strip (at POC)
- Finger prick
 - Test strip (at POC)



Glucose Monitoring Clinical Requirements

Glucose Monitoring Technologies can enable TGC

Requirements for ICU Glucose Monitoring (unproven!)

- Automatic
- Fast: less than 2 min measurement time
- Short intervals: 10 min or less
- High precision: higher precision than for ambulatory diabetes control
- Invasiveness: Invasive – Minimally invasive – Non-invasive?

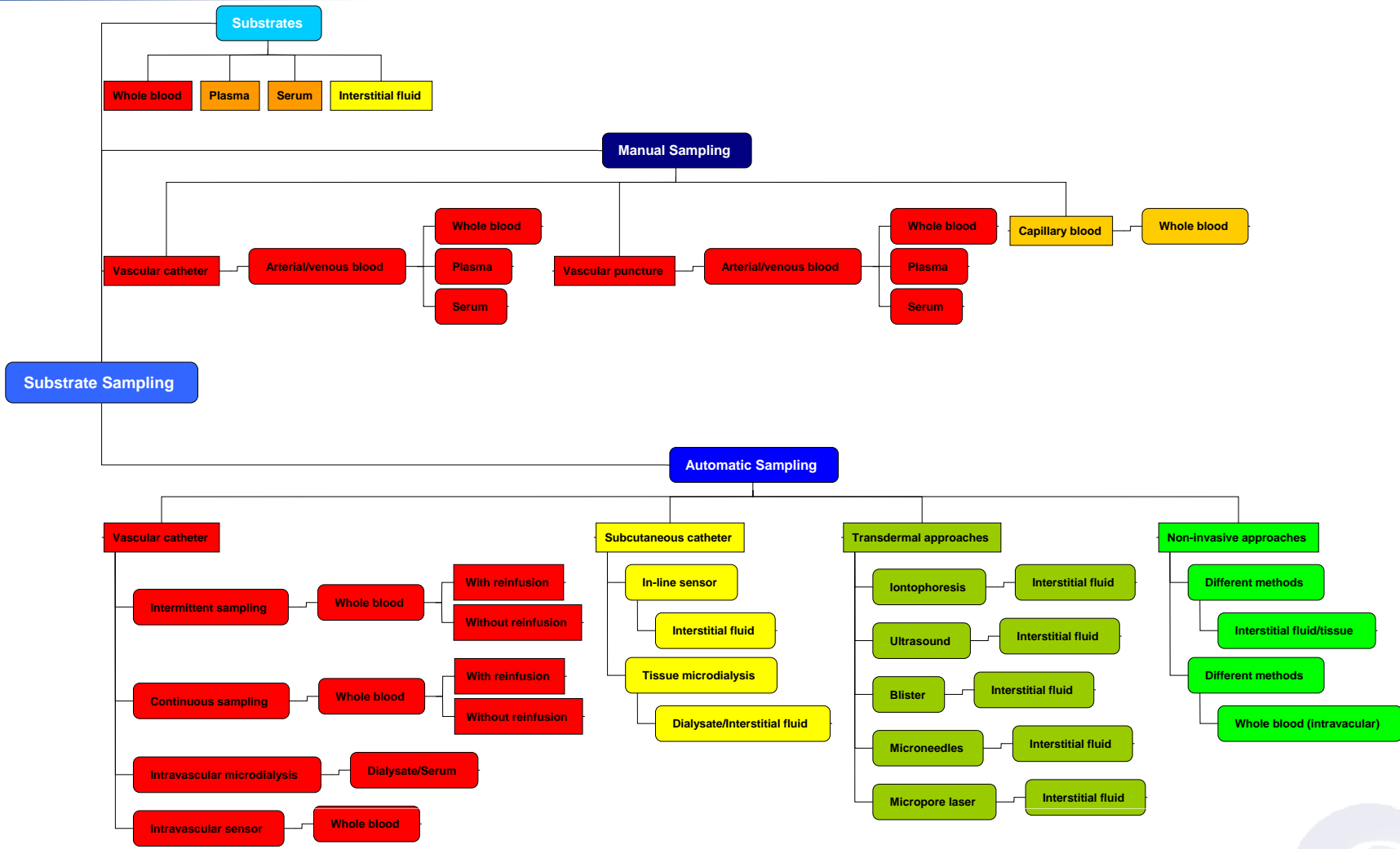
Two challenges

- Substrate sampling
- Blood glucose measurement



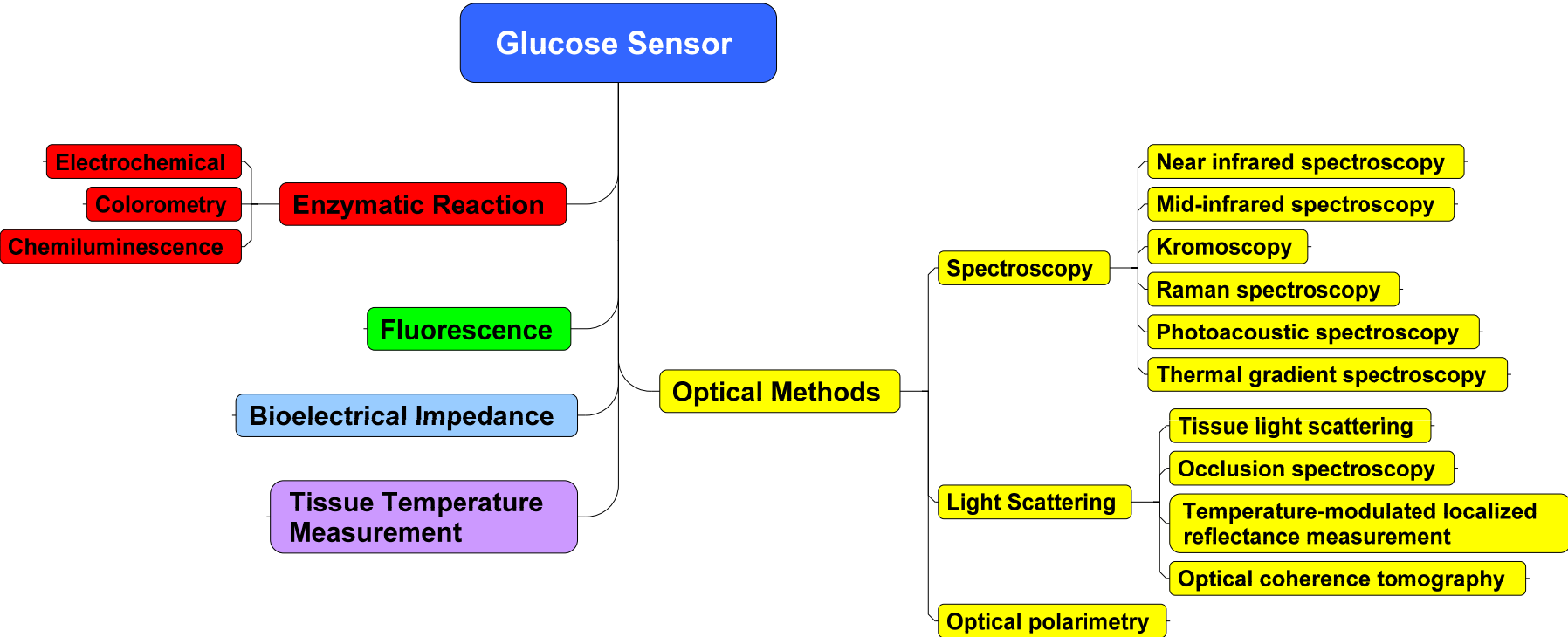
Continuous Glucose Monitoring Technologies

Substrate Sampling



Continuous Glucose Monitoring Technologies

Sensor Technologies



Tight Glycemic Control

Administration of Insulin and Glucose

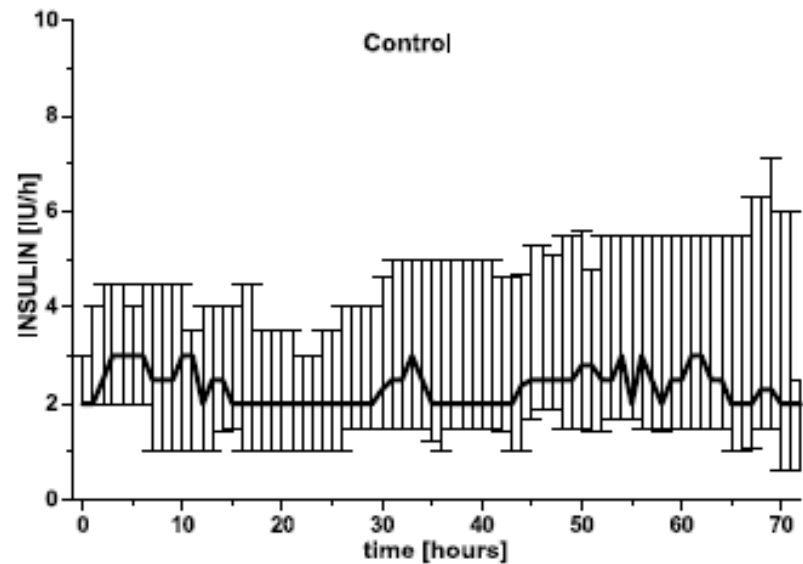
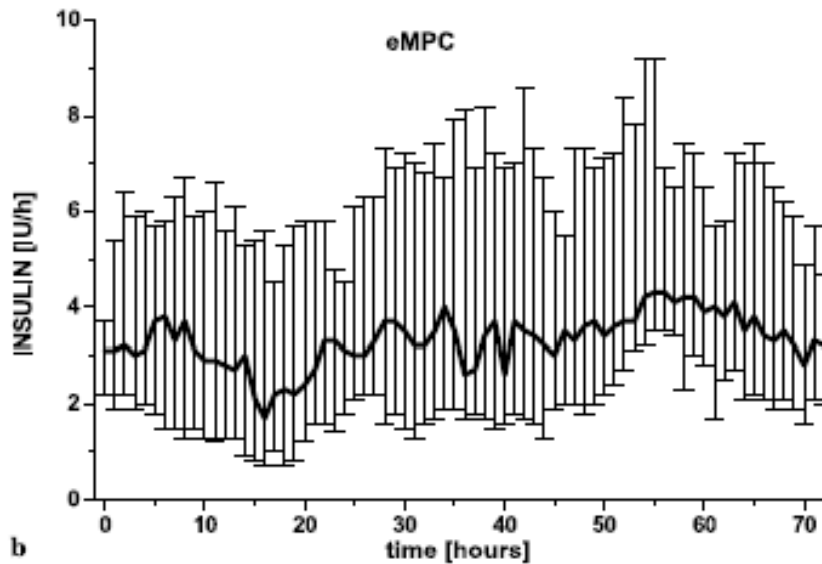
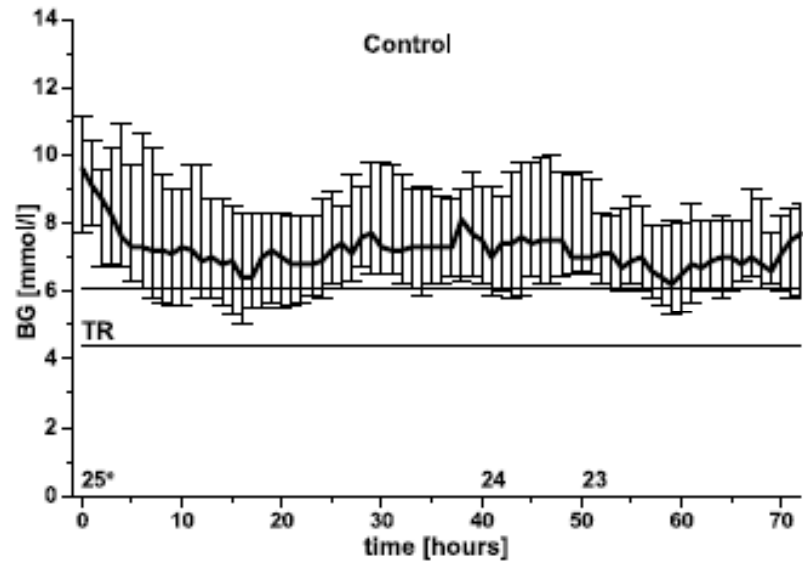
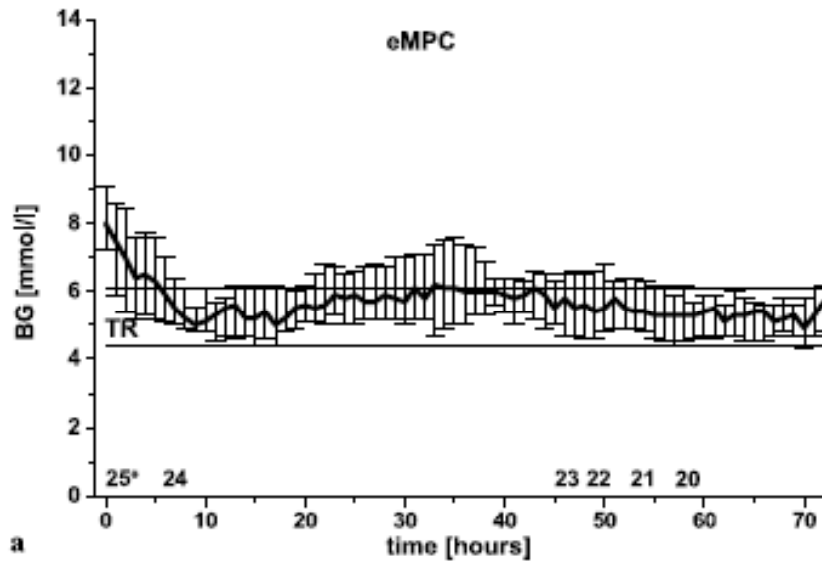
- Standard infusion systems and syringe pumps
 - Manual control
 - Bi-directional interfaces to computer systems (CPOE, CDSS)
- Pumps/pump controllers may serve as computer platform for DSS algorithms



Tight Glycemic Control Decision Support

- TGC algorithms for clinical care
 - Several protocols tested in clinical studies
- TGC decision support software
 - Systems for clinical studies
 - Commercial PC-based solutions
 - Integration into CPOE/HCIS/CDSS
- Closed-loop control = Holy Grail



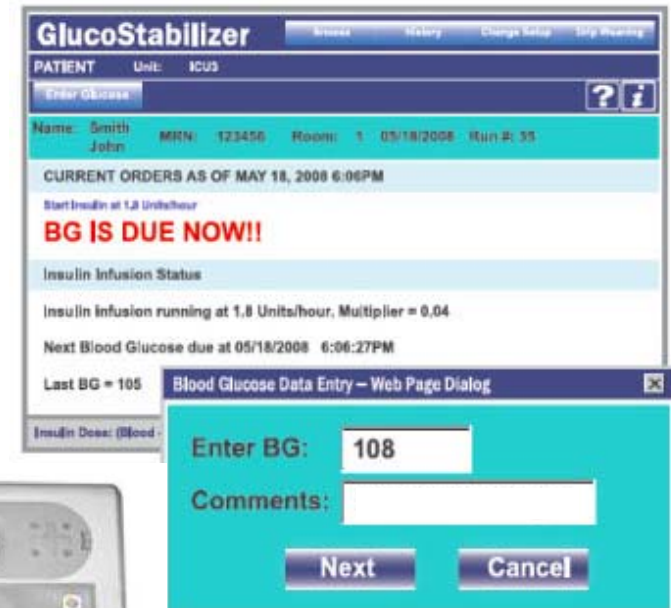


Pachler et al, Intensive Care Med 2008

www.clinicip.org

Tight Glycemic Control Commercial Decision Support Tools

- MD Scientific, LLC
 - Endotool Glucose Management System
 - www.mdscientific.com
 - Acquired by Hospira 10/2009
- MDN Medical Decisions Network
 - GlucoStabilizer
 - www.mdnoutcomes.net
- GlucoTec, Inc.
 - G+™ Model 2020
 - Tablet PC based solution
 - G+™ Analytics
 - posthoc analysis software
 - www.glucoTec.com
- Clinical utility?
- Cost effectiveness?
- Integration with CIS/EMR?



**ICU
Patient**



1. Glucose Measurement

Manual Blood Sampling
Bedside Glucose Meter



**Physician /
Nurse**

2. CLINICIP system

Enter glucose level
Confirm insulin infusion
Await next sample reminder



Market Potential

Acceptable Cost for Glucose Monitoring

- Assumptions
 - Blood gas analyzer on ICU
 - 4-8 blood gas analyses required per day
 - Glucose protocol requires measurement q1h (24 measurements/d)
 - Blood sampling takes 5 minutes nursing time (= 120 min/patient; 30€/h)
 - Blood gas disposables/reagents ~1€ (glucose test strip ~0.30-0.50€)
- Total cost for glucose monitoring with blood gas analyzer
 - 24 € disposables
 - 60 € working time
 - minus 8 blood gas measurements
 - 8€ disposables
 - 20€ working time
- Effective cost of glucose monitoring: 56€/d
- A new monitoring technology should not be much more expensive



Market Potential

TGC in Intensive Care

- Worldwide 10+M ICU admissions per year
- Surgical critical care
 - 10-50% of all ICU patients
- Non-surgical critical care ??
- Pediatric critical care ??

- 1M patients eligible for TGC/year (mean ICU LOS 3 days)
 - US\$200 over 3 days
 - US\$200M per year worldwide

- Global high-acuity monitoring market: US\$2-3B
- Global glucose test strip market: > US\$10B



TGC Studies, Leuven II

van den Berghe, et al., NEJM 2006

- Continuation of 2001 study in non-surgical patients
 - Prospective randomized controlled trial: 1200 patients
 - mixed medical ICU patients in a tertiary referral center
 - maintenance of blood glucose in normal range (80-110 mg/dl)
 - Results
 - Overall mortality unchanged
 - Reduced mortality in patients with ICU LOS > 3 d
 - **Increased mortality in patients with ICU LOS < 3 d!**
- ➔ Case for TGC is not as clear as often thought
- ➔ More studies needed



TGC Studies, VISEP, Glucontrol, NICE-SUGAR

- VISEP study
 - TGC arm stopped after 488 patients
 - Hypoglycemia 12.1% vs. 2.1%
 - No differences in mortality or complications
- Glucontrol (<http://clinicaltrials.gov/show/NCT00107601>)
 - Stopped at interim analysis (05/2006) after 1,101 patients (3,500 planned)
 - High rate of hypoglycemia in TGC group (8.6% vs. 2.4%)
 - No difference in mortality
- NICE-SUGAR (<http://www.clinicaltrials.gov/ct/show/NCT00220987>)
 - 95% patient enrolment (of 6,100 patients)



Tight Glycemic Control

Where is the Market?

- Patient populations for TGC not sufficiently defined
 - Market size remains unclear
- Contradicting study results
 - Market acceptance may take much longer (if any!)
- Therapeutic ranges?
- Complications and side effects?
- Compliance with guidelines [*Brunkhorst et al, Crit Care Med 2008*]
 - TGC: 66% perceived compliance vs. 6% actual compliance
- ***The hype may be over!***



Tight Glycemic Control

Large MedTech Vendors

- Are they active in this area?
 - Is the market large enough?
 - Does a new technology match the current/future portfolios?
 - Can it be sold through the existing sales organizations?
 - Can it be harmful to their current businesses?
 - Is the business model suitable?
 - Electromedical/imaging companies expand into biochemical diagnostics
- Philips
 - Own biochemical developments (lab on a chip)
 - Integration of monitoring & IT
 - Cooperation preferred with “brand names”
 - Siemens
 - Acquisition of 3 lab companies
 - World leader in central labs and blood gas analyzers
 - Strong integration of imaging, biochemical diagnostics and informatics



Large MedTech Vendors

New Opportunities

How do large companies look at new market trends/opportunities?

- Excellent knowledge of their markets and their customers
- Significant expertise in marketing, sales, R&D, production
- They tend to be conservative and slow
- But large vendors may also try to expand into new markets
 - hospital monitoring → home monitoring
 - electromedical technologies → biochemical technologies
 - hospital beds → in-patient monitoring
 - These may be great opportunities for start-ups
- New players enter the medical market



Patient Monitoring and Informatics

New Opportunities

Traditional high-acuity monitoring?

Inpatient monitoring outside high-acuity settings!

Monitoring outside the hospital!

- Wearable devices (spot-checking, self-testing, continuous monitoring)
- Implants
 - Monitoring of the patient
 - Monitoring of the implant
- Sensors – new sensor technologies, new biosignal/data analysis
- Energy supply and management
- User interfaces
- Communications, networks
- Decision support, data management and analysis
- Patient-centered services



Thank You

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