Introducing and Growing Medical Technologies: Pitfalls and Opportunities

February 5, 2009

Boston MedTech Advisors

Sullivan & Worcester

Program

- **Globalization of Clinical Trials - Promise and Reality**
  Zvi Ladin, PhD, Principal, Boston MedTech Advisors, Inc.

- **'Time-to-Adaptation' - Reimbursement as a Marketing Strategy Paradigm**
  David Barone, Principal, Boston MedTech Advisors, Inc.

- **Optimizing IP Portfolio Considerations for Early Stage and Growing Medical Technology Companies**
  Kimberly Herman, Partner, Sullivan & Worcester, LLP

- **Patient Monitoring and Informatics - New Opportunities for the Next Decade**
  Michael Imhoff, MD, PhD, Managing Director, Boston MedTech Advisors Europe, GmbH

Speakers

Zvi Ladin, PhD

Principal of Boston MedTech Advisors, Inc . Dr. Ladin has over 20 years of management experience in the medical industry, government and academia, focusing on clinical applications, regulatory affairs and reimbursement strategies. Experience includes establishing reimbursement and regulatory strategies for therapeutic and diagnostic medical device companies, submission of regulatory applications, including 510(k) and PMAs for products in Class I-III and drug-device combination products. Dr. Ladin represented companies in negotiations with the FDA, European and Asian regulatory agencies, and served for five years as a scientific advisor to the Food and Drug Administration. Dr. Ladin is a recipient of the Whitaker Fellowship and International Research Awards, and has taught mechanical and biomedical engineering at MIT and Boston University. Education: B.Sc., Aeronautical Engineering and M.Sc., Biomedical Engineering, both from the Technion, Israel Institute of Technology; Ph.D., Medical Engineering, MIT-Harvard Medical School / Division of Health Science and Technology.

David Barone

Principal of Boston MedTech Advisors, Inc. David Barone's background consists of over 25 years experience in the healthcare and medical industry, including general, technical, marketing, strategic planning and business development. David held senior management positions in a number of medical device companies, overseeing product development, marketing, clinical evaluations, regulatory affairs and intellectual properties. David Barone is also an accomplished entrepreneur, founding, financing and growing several healthcare service organizations. While leading these companies, David entered into clinical and business affiliations with many top-tier medical centers in the US, negotiated and successfully contracted with many of the national and regional health plans, and evolved high quality and efficient clinical delivery systems. David has consulted and assisted US and off-shore medical technology organizations, ranging from start-ups to Fortune 500 companies, in areas including market development, opportunity analysis, regulatory and reimbursement strategies, business development, financing and more. Education: B.Sc., Electrical Engineering, Technion, Israel Institute of Technology, M.Sc.; Bio-Medical Engineering and Master, Business Administration, both from Rensselaer Polytechnic Institute, NY.

Kimberly Herman, JD

Kimberly Herman is a partner in the Intellectual Property and Corporate Departments in the Boston office of Sullivan & Worcester LLP. Ms. Herman's practice spans across the United States, Europe and the Middle East and emphasizes the law and business of intellectual property with a particular focus on structuring and negotiating complex commercial agreements dealing with software, life sciences, biotechnology, pharmaceuticals, new media, the Internet, publishing and entertainment as well as patent, trademark and copyright matters on behalf of leading high technology, financial services, venture capital, banking, start-up and emerging companies. Member of the International Trademark Association, Computer Law Association and Massachusetts Bar Association. Education: B.A., cum laude, Northeastern University, J.D., Western New England College School of Law

Michael Imhoff, MD, PhD

Dr. Imhoff is the managing director of Boston MedTech Advisors Europe GmbH, based in Dortmund, Germany. Board certified in surgery and intensive care medicine, with 18 years of clinical experience in large medical centers and 16 years of strategic consulting for leading companies in the global medical technology markets, as well as start-ups in the US and Europe, focusing 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 lecturer in Medical Informatics, a member of the editorial boards of the Journal of Critical Care and of Care of the Critically Ill and a reviewer for several international journals. Education: Medical school: University of Bochum and Munster, Germany; PhD, Ruhr University, Bochum, Germany. 1991 Recipient of the Lederle Prize for Research.

Boston MedTech Advisors

Boston MedTech Advisors assists medical technology companies and healthcare organizations advance their business by providing:

- Market analysis and business strategy
- Business development
- Regulatory affairs and clinical trials management
- Reimbursement and contracting strategies
- Financing support

Boston MedTech Advisors provides practical business services to:

- Established and growing medical technology companies
- Healthcare providers
- Young organizations and entrepreneurs
- Private and institutional investors

Sullivan & Worcester

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Sullivan & Worcester's Clients benefit from:

- The resources and experience to take on and win the big ones.
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- More than 185 attorneys
- A full range of commercial legal services
- Experience with domestic and international clients ranging from emerging businesses to Fortune 500 companies and leading financial institutions
- Customized solutions that work for your business.
- Digging deep to understand clients and their industries in order to deliver solutions that, not only work on paper, but also make good business sense.
- Our lawyers work together in small teams, emphasizing close partner-client contact and collaboration.

Globalization of Clinical Trials
Promise and Reality

Zvi Ladin, Ph.D.

Boston MedTech Advisors

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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

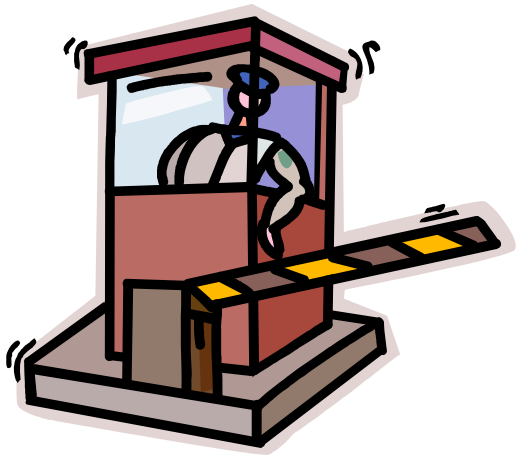
- Funding – from public to private
  - NIH ⟶ industry
- Nature – from single site to multi-center
  - Limited information to local IRB
- Size and numbers

1998 OIG Report – Revamping the IRB

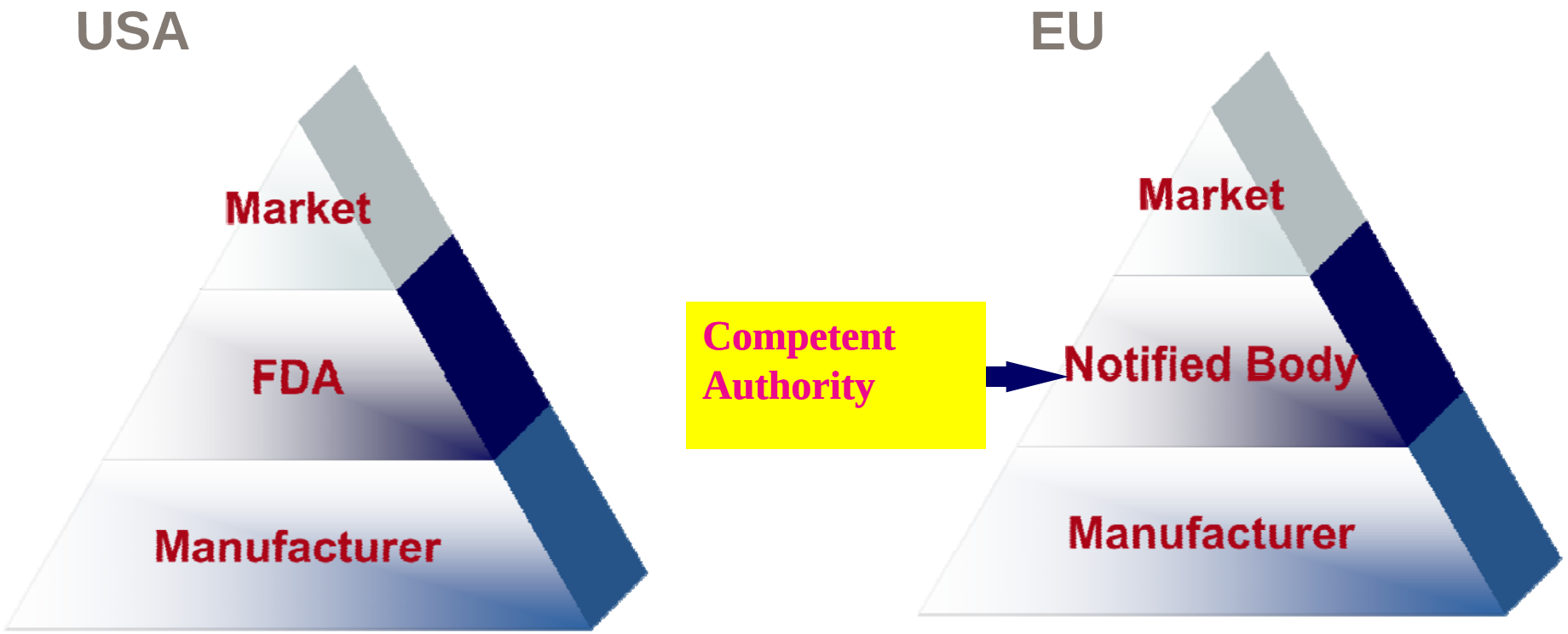
- Overwhelmed Local IRB
  - Time and expertise limiting review
  - New ethical issues (e.g. genetic screening)
- Evaluating IRB Effectiveness
- Conflict of Interest Inside the IRB
  - Part of the organization that gains from research
- Limited Training of IRB Members and Researchers

Understanding the Regulator

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



Regulatory Interactions



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)

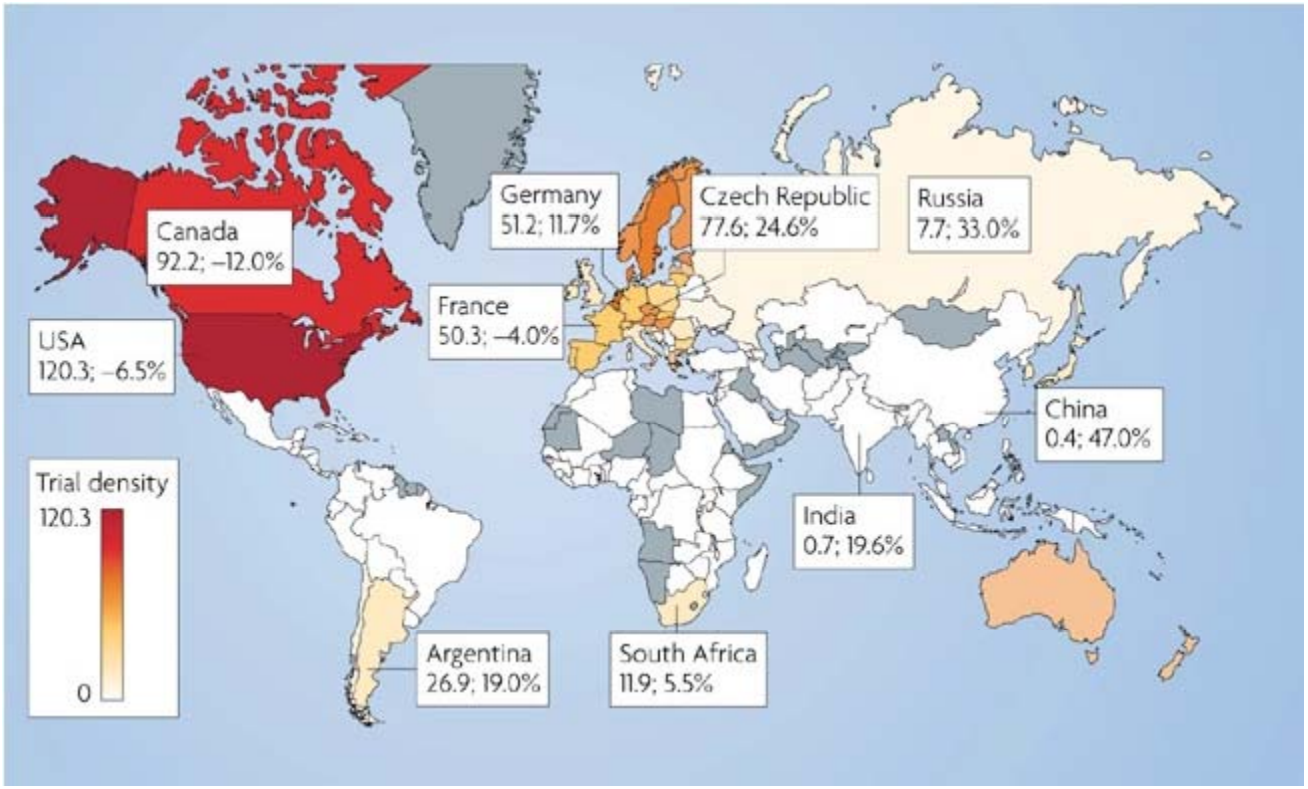
Observation (Effect?)

- 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

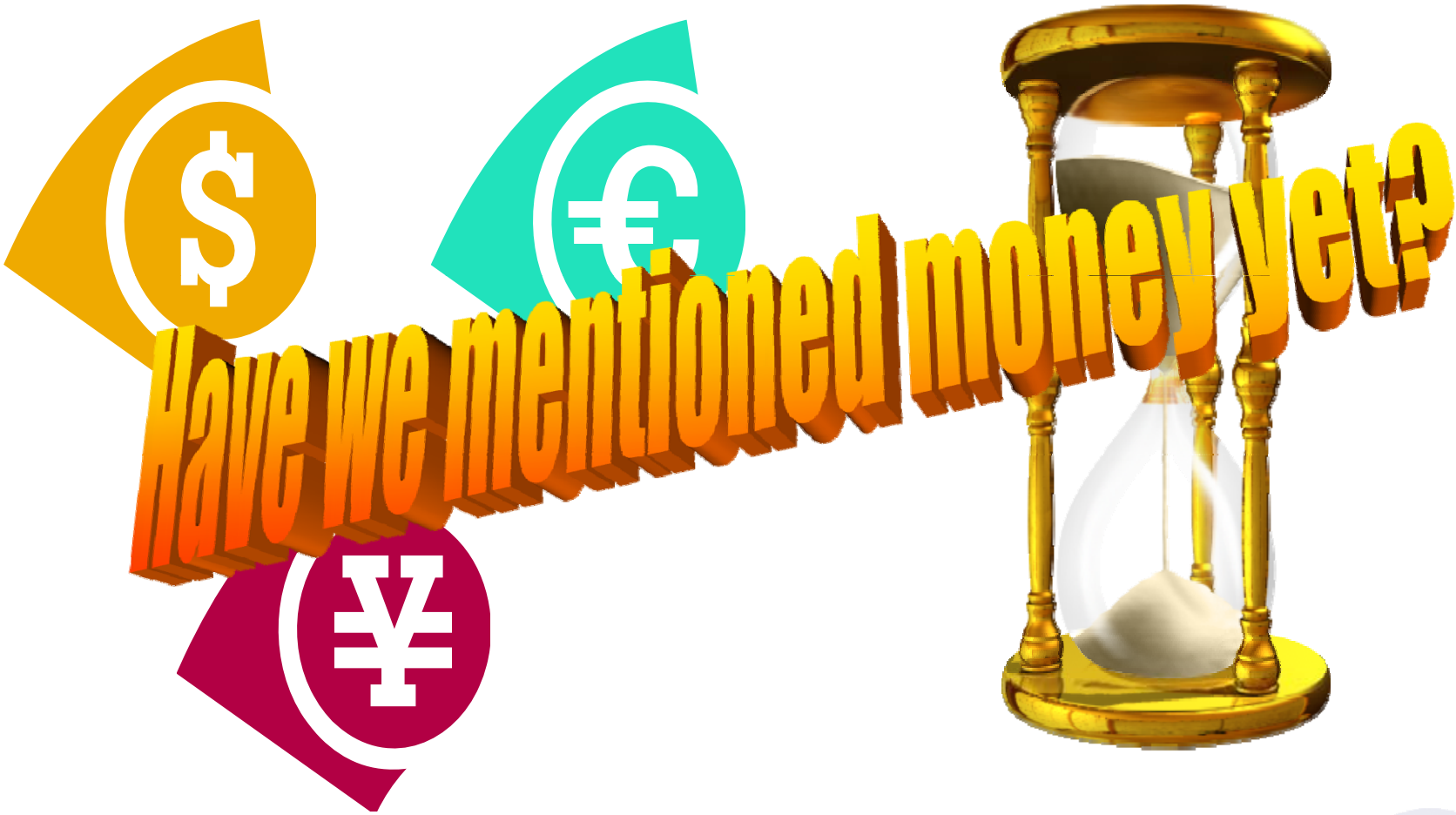


Ref: Trends in the globalization of clinical trials, Fabio A. Thiers, Anthony J. Sinskey & Ernst R. Berndt
Nature Reviews Drug Discovery 7, 13-14 (January 2008)

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


Have we mentioned money yet?

Economic Drivers

Increase regulation

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

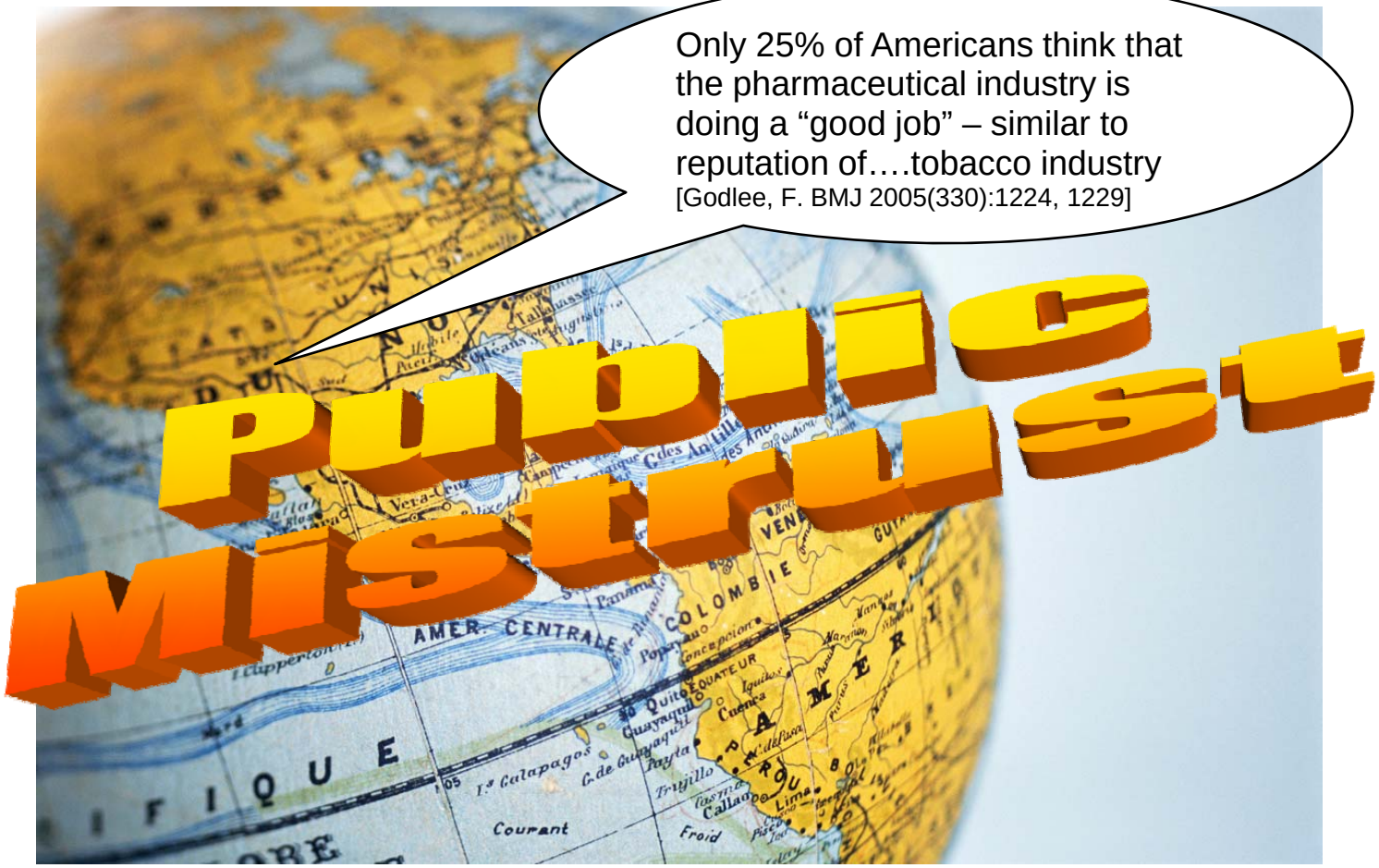
Move studies to:

- 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**

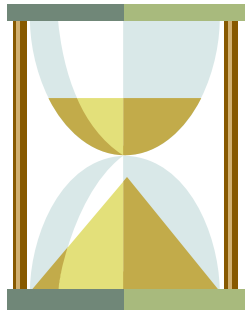
***Anything that can go wrong…will!**

Global Challenges – I

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

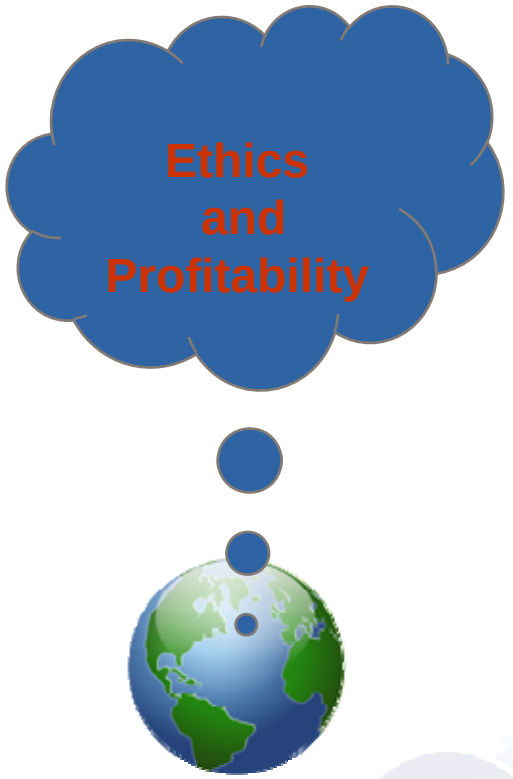
Global Challenges – II

- 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

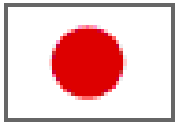


Global Limitations

- 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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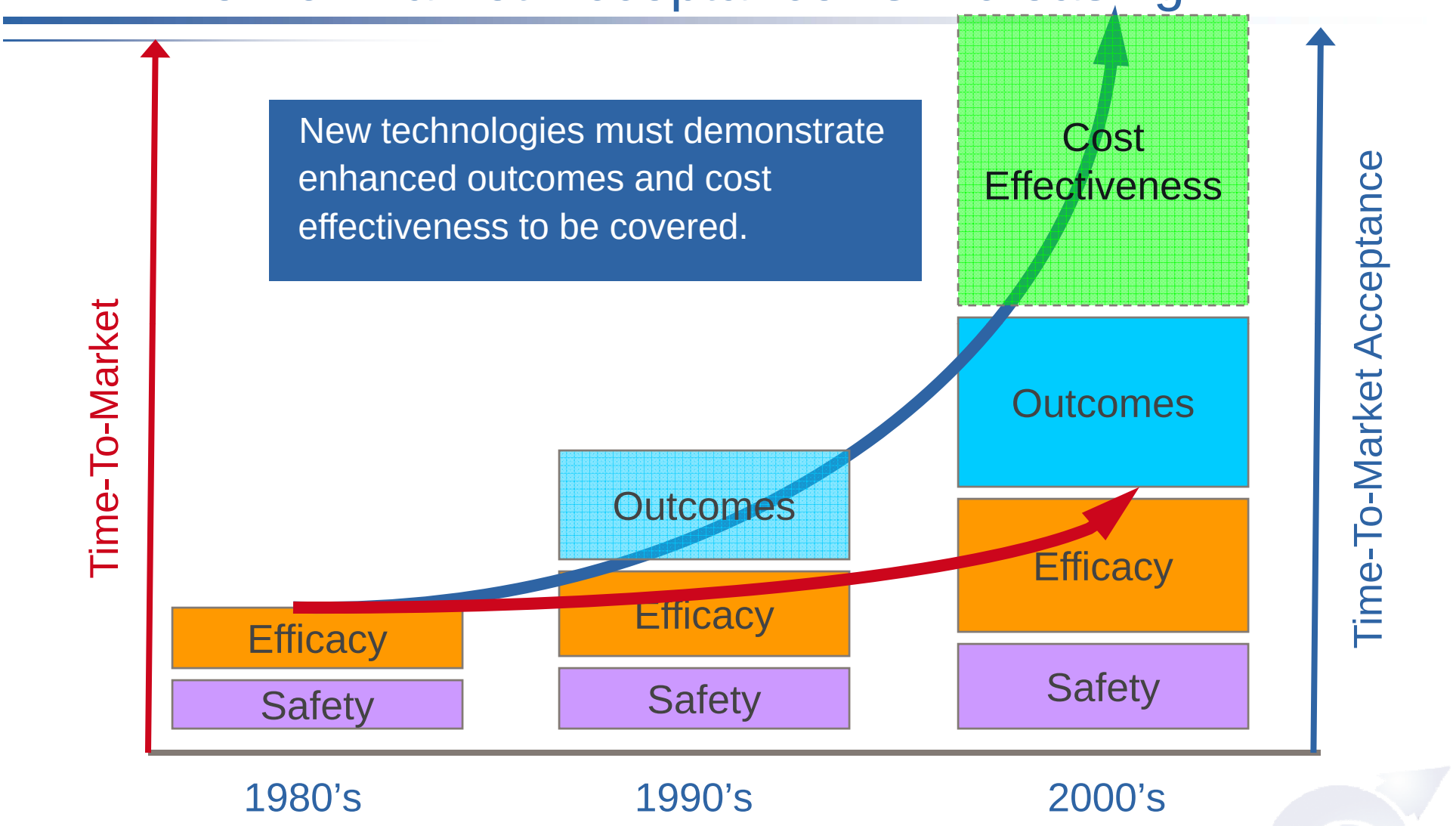
Decision to purchase and decision to use are not the same

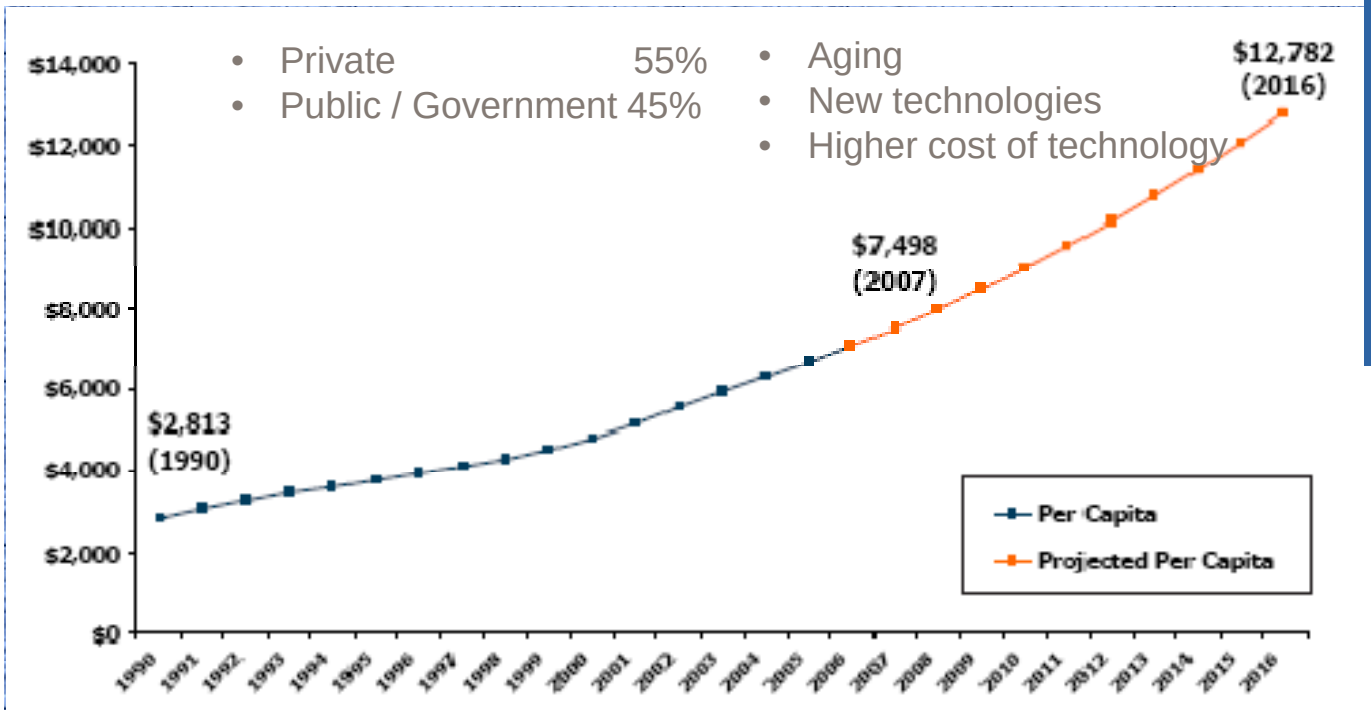
Time-To-'Market Acceptance' is Increasing



Considerable Implications

- Delayed revenue
- Need for additional funds and financing rounds
- Valuations are negatively impacted
- Business development initiatives are delayed
- Prospective distributors sit on the sidelines
- Increased risk of new competitors

Healthcare Expenditures Are Mounting

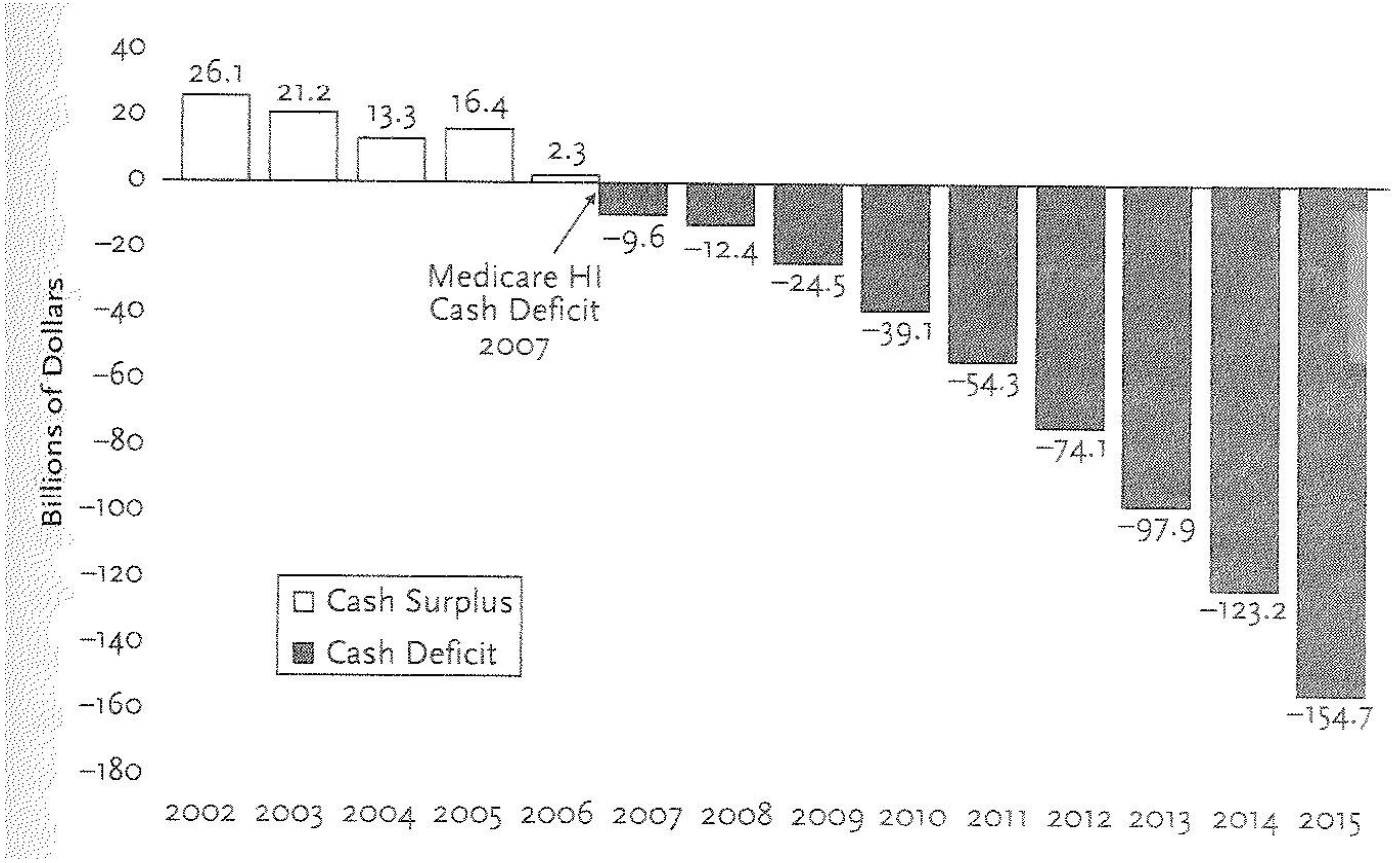


Demand for more care and new technologies will continue to drive costs

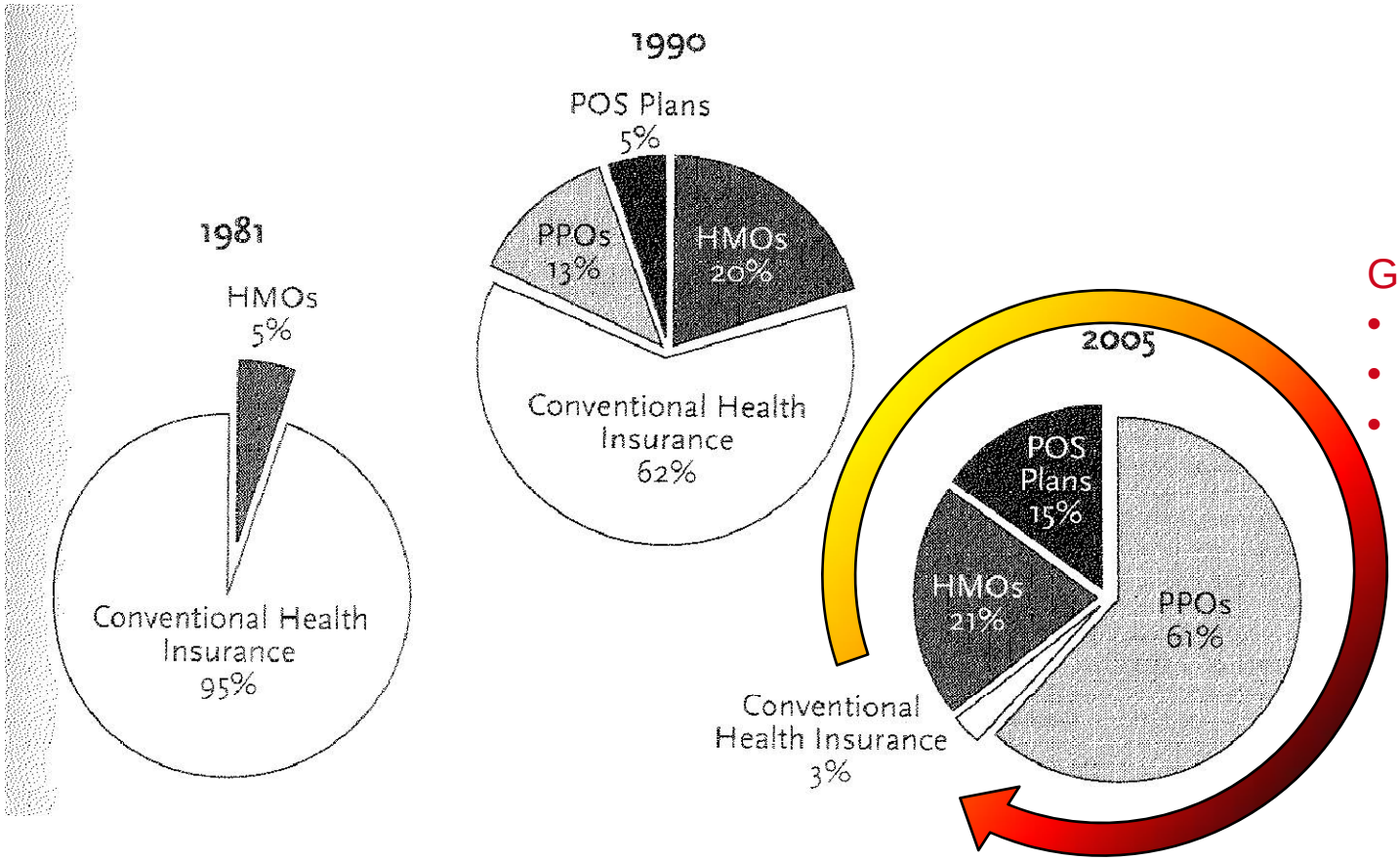
	1970	2007	2016 (p)
Annual cost per capita	$356	$7,498	$12,782
Total Expenditures	75 billion	2.2 trillion	4.1 trillion
% of GDP	7.2%	16.2%	19.6%

Ref: Kaiser Family Foundation, Sep 2007

Net Cash Flow (Medicare) → Political Pressures



Market Response: Managed Care



Greater control of
- Access
- Coverage
- Payment

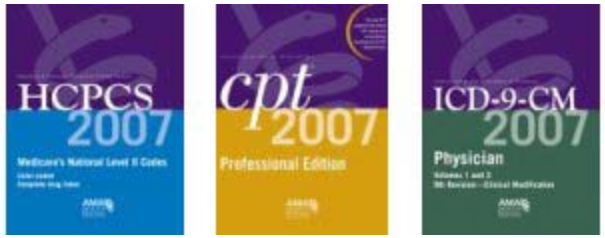
The Reimbursement Process

I. Coding ➡ II. Coverage ➡ III. Payments

I. Coding

Classifies patient conditions, services and supplies

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



II. Coverage

Defines when products & services are eligible for payment

III. Payments

Determines payment processes and amounts

<u>Medicare Fees:</u>

- Standardized
- Public
- Non-negotiable

<u>Commercial Payers:</u>

- Non-standardized
- Confidential
- Negotiable

Code ≠ Coverage

Coverage ≠ Payments

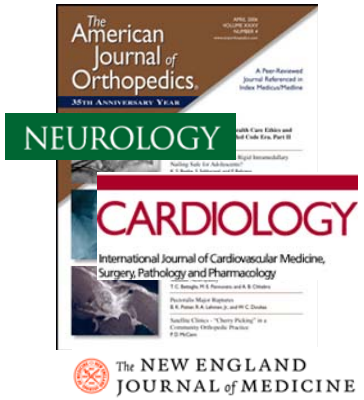
Obtaining a New CPT Code

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?

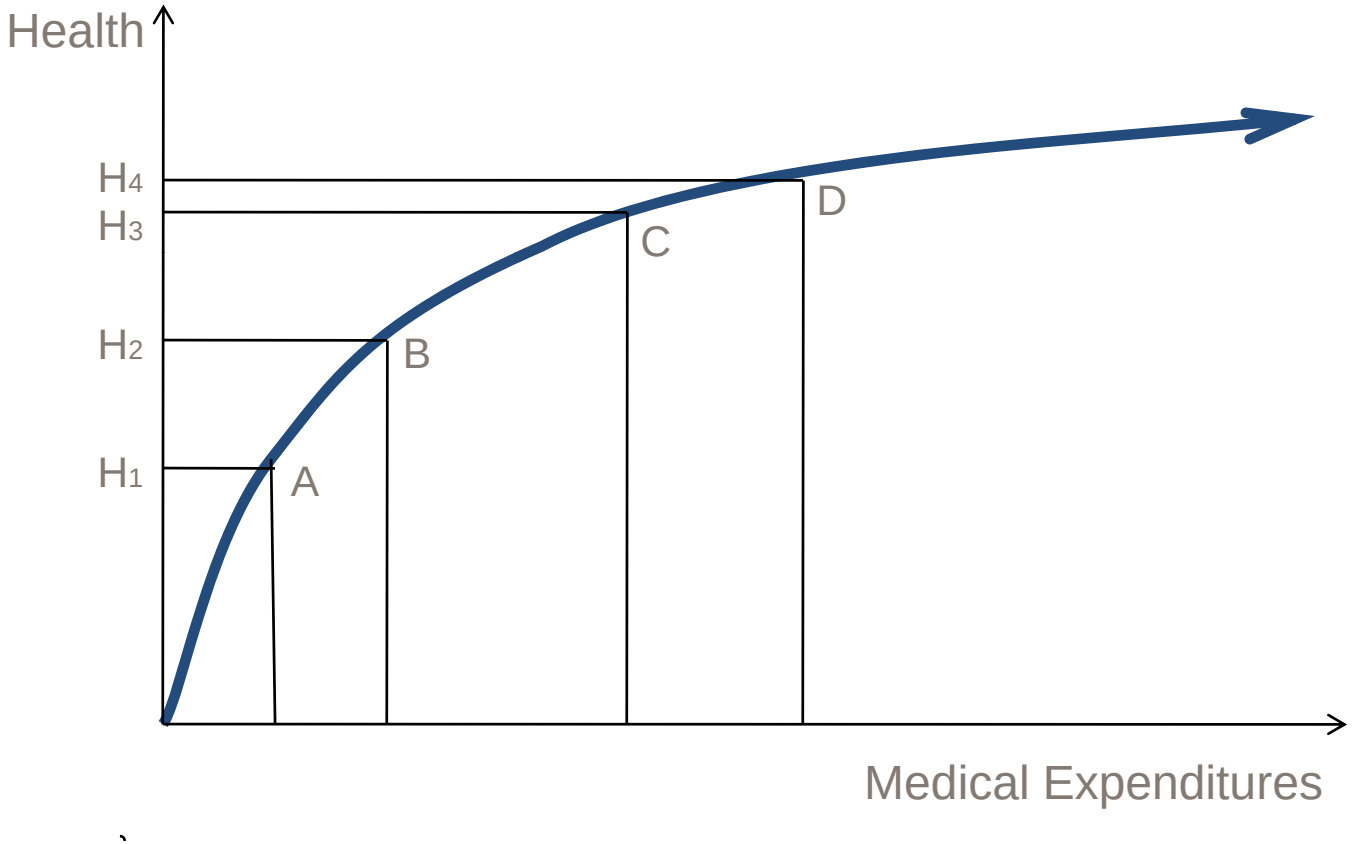
- Safety and efficacy
- Data generated in controlled setting
- Academic focused review / KOL
- Scientific method
- Substantial equivalence or comparison to placebo
- Intermediate or short-term outcome
- No cost considerations

Payers

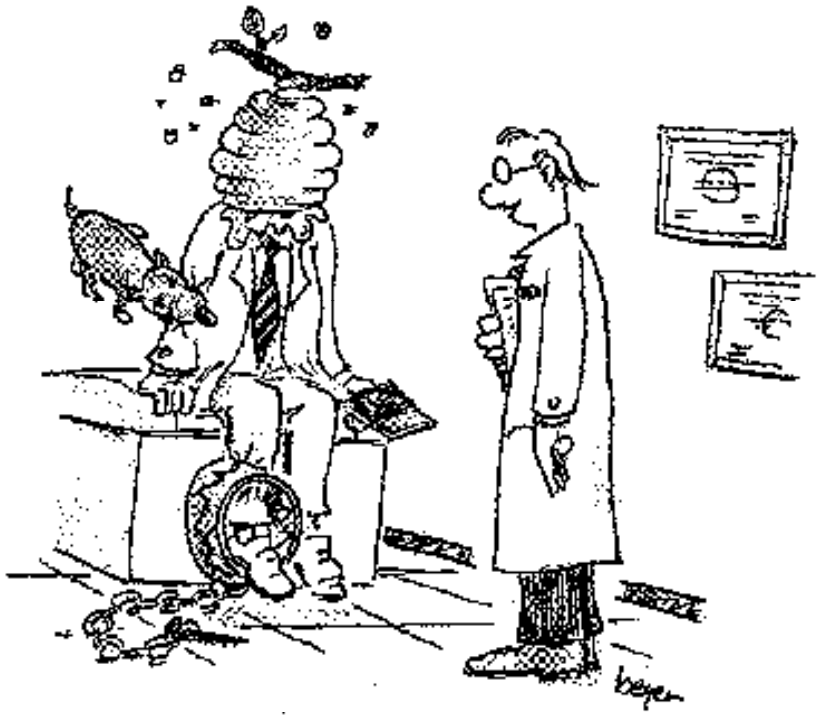
Does the product / procedure improves outcomes?

- …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



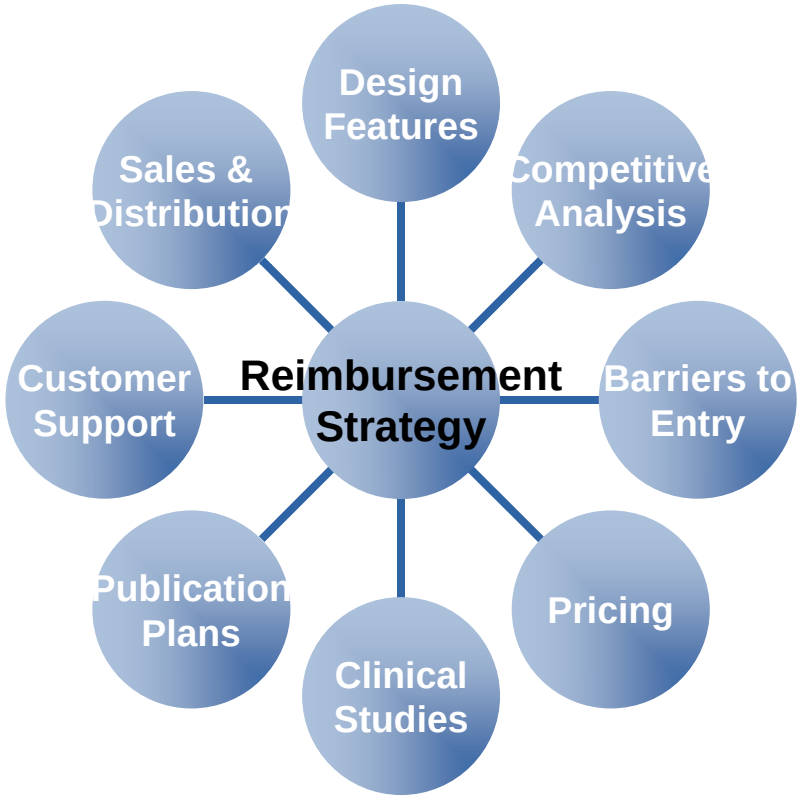
Ref.: Health Policy Issues, PJ Feldstein, 2007



“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)



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

Early 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?

Post Market Launch Activities

- Cultivate support from KOL
- Seek position statements from specialty societies
- 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

National or Local Coverage Decisions?

NCD

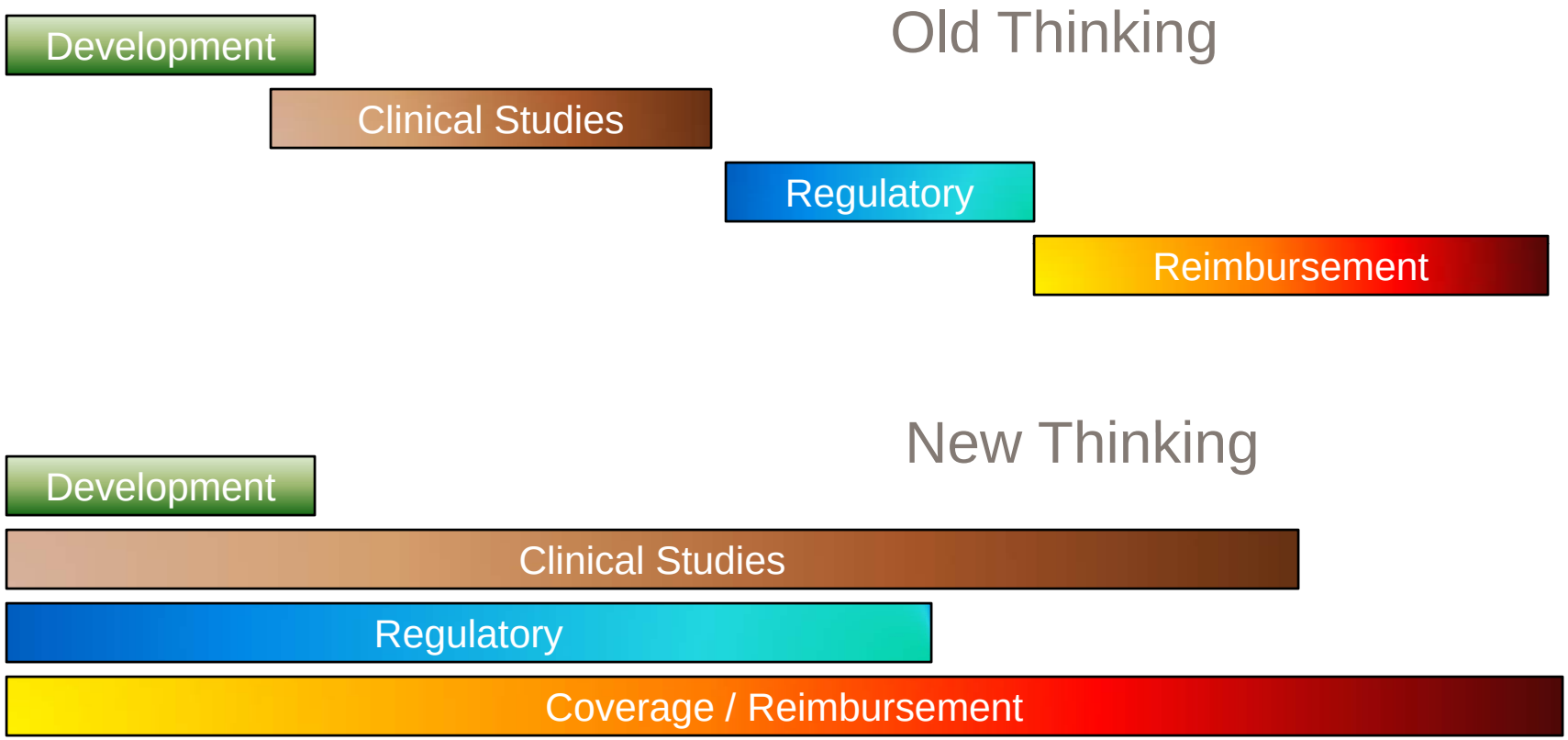
- Risk assessment: “all or nothing” decision
- Positive decision leads to consistent coverage nationwide
- Risk of non-coverage decision or restricted access to treatment
- Private payers often follow national decisions

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

Pre-Reimbursement Marketing

- 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
- Seek coverage from local payers
  - Local opinion leaders support
  - Significant providers
  - Use ‘miscellaneous’ codes or ‘modifiers’
- Do not induce utilization


Old Thinking
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Freedom to Operate Opinions: Surveying a Crowded Marketplace

By Kimberly B. Herman
Partner, Sullivan & Worcester LLP

February 5, 2009

Patent rights in a "nutshell"

- Patent rights
  - A patent gives the owner the right to stop others from making, using, and selling in a specific jurisdiction.
  - A patent, however, does not give the owner the right to practice the invention if it infringes on third party IP rights.

Dealing with third party patent rights

- Example
  - New spray coating technology for boats
  - But the equipment used to apply coating is covered by several patents
  - Do you have freedom to operate?
  - Potential resolutions
    - *Take a license*
    - *Undertake freedom to operate study to find "white space"*

Patent thickets

- Freedom to operate opinions survey and map patent thickets.
- A “patent thicket” is a group of patents in the same technological space usually owned by several players.

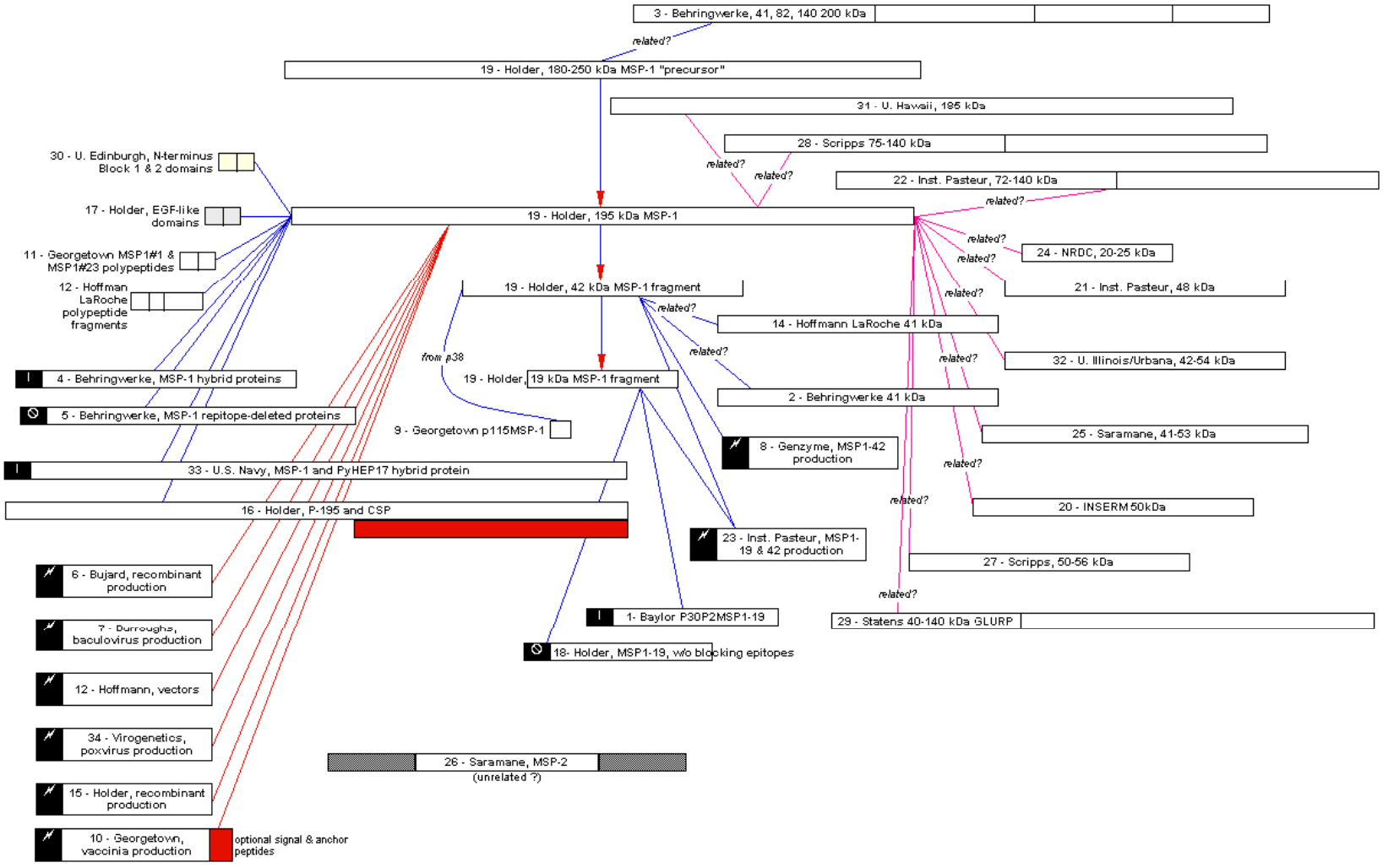
Objectives of FTOs

- Freedom to operate opinions evaluate two key issues:
  - The degree to which there is “white space” available for new patent claims.
  - Your freedom to practice i.e. what is your infringement risk?

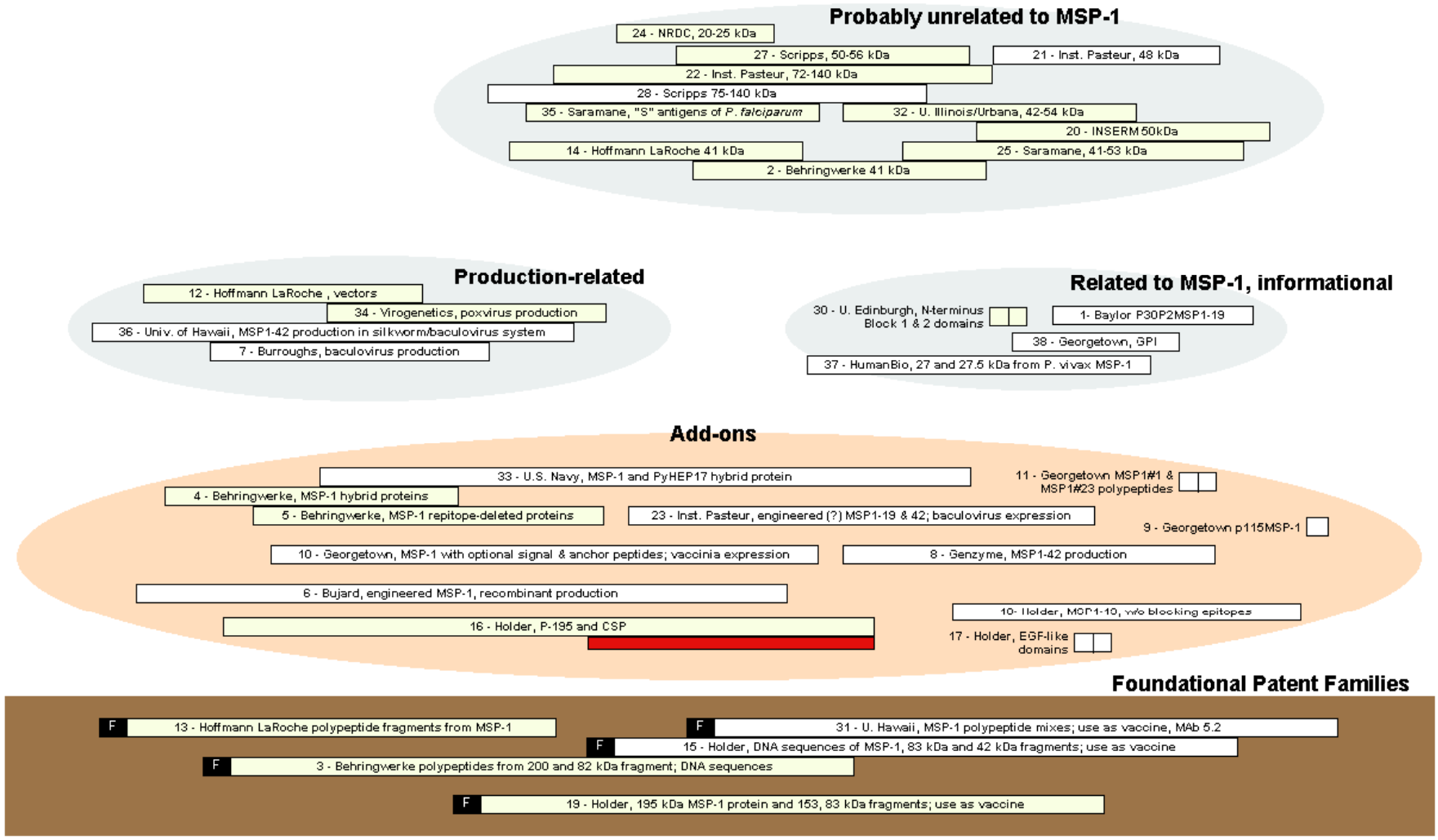
How do FTOs accomplish objectives?

- How do FTO opinions work?
  - Identify all existing IP rights within the jurisdiction relating to the invention – patent mapping.
  - Distinguish between the relevant and the peripheral.
  - Among the relevant, determine at what level the rights are held.
  - Determine extent of rights held.

A FTO takes a patent thicket …



And sorts it into a tidy patent garden…



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A case study

- The Malaria Vaccine Initiative's FTO assessment:
  - Program's goal was to identify promising vaccine development projects and fund them.
  - FTO search was performed to determine which projects may face freedom to operate issues.
  - Patent search results used to choose most viable vaccine projects and aid R&D in navigating the patent thicket.

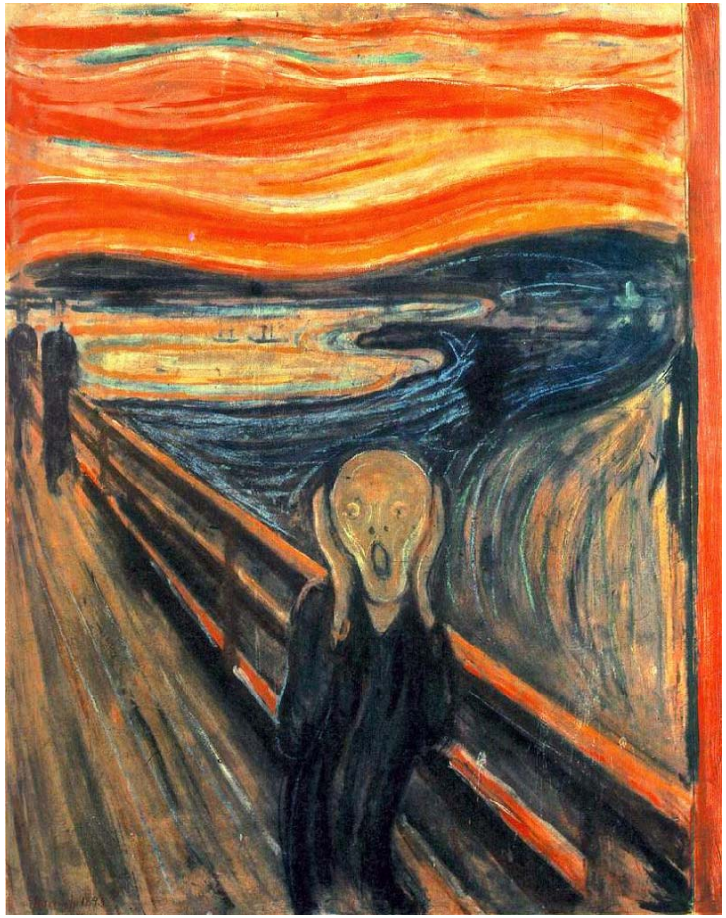
A case study

- Initial results of patent search found a muddied, complex landscape.
  - Among other problems, difficult to distinguish between highly technical, esoteric patent claims.
- FTO sorted existing patents into categories based on the content of the claims.
  - E.g., “foundational,” “production,” “add-on,” and so on.
- Result: a more navigable patent landscape.
  - MVI able to factor FTO’s IP considerations into decision to fund.
  - Also able to advise R&D sector on how to make projects commercially viable.

Problems typically encountered

- Large number of patents
- Different terminology used
- Uncertain ownership relationships
- Extent to which patents are valid and enforceable
- Which patents expired or are about to expire
- Submarine patents

A word about investors



- Perform FTO assessment <u>before</u> entering the market, or otherwise risk:

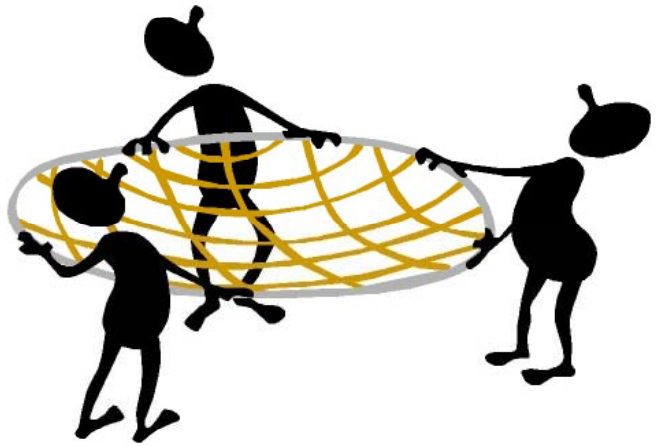
SPOOKING INVESTORS

FTO assessments and investors

- FTO opinions reassure (or not) investors because:
  - Confirm value of technology to be invested in.
  - Help minimize the risk that the invention will be rendered useless by pre-existing patents.
  - Maximize the utility of the invention by identifying area available to be claimed.
  - Reduce potential liability if invention later found to infringe pre-existing IP rights.

The law that says so

- FTO opinions *may* reduce liability for patent infringement
  - *Broadcom Corp. v. Qualcomm Inc.*, No. 2008-1199 (Fed. Cir. Sept 24, 2008)
  - Failure to obtain a non-infringement opinion (equivalent to FTO opinion) from qualified independent legal counsel may be circumstantial evidence of an intent to commit patent infringement.

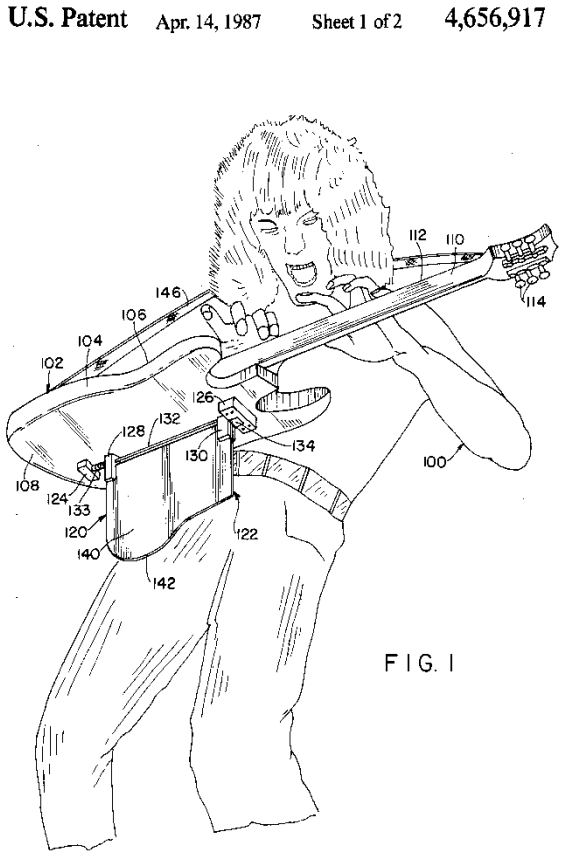


The law that says so

- *Broadcom Corp. v. Qualcomm Inc.* further explained:
  - Infringement may be found even when willfulness is absent.
  - Failure to seek non-infringement opinion is relevant to whether the accused infringer "knew or should have known" that its acts would cause actual infringement.
  - No requirement that patentee produce direct evidence of intent to infringe—circumstantial evidence alone may suffice.

Timing of FTO assessments

- When to investigate:
  - At start of product development
  - Then, at critical stages in development process
- …before you're ready to rock & roll.



Wait a minute:

- Should you secure patent rights in the first place?
- Weigh patent protection against trade secret protection.
- Avoid waiving IP rights:
  - If patent, file patent application before you publicly disclose.
  - If trade secret, or if patent application not yet filed, execute NDAs before disclosing to business partners, collaborators.

On the one hand, on the other:

- Patent protection
  - Patents disclose and teach invention to public
  - But, public is barred from practicing invention
  - Patent protects invention for minimum of 20 years, but not indefinitely
  - Protects against reverse engineering
- Trade secret protection
  - Invention and method kept secret from public
  - But, if invention lawfully discovered, public not barred from practicing
    - *Remedies available for espionage, breach of NDA, etc.*
  - Protects invention indefinitely, but for no minimum period of time
  - Does not protect against reverse engineering

Inventions must be “novel”

- Novelty requirement for patents
  - Invention must not be part of prior art
  - Not previously disclosed or part of public domain

Don’t shoot yourself in the foot

- Acts that could constitute public disclosure of the invention and loss of novelty:
  - Display of invention at industry convention or forum.
  - Publication of technical paper or article discussing the invention.

And don't take too long

- U.S. has one-year statutory bar on patent applications.
- 35 USCA § 102(b): Patent application is barred if, more than one year prior to the application:
  - 1) the invention is patented or described in a printed publication available anywhere in the world; or
  - 2) the invention is in public use in the U.S.; or
  - 3) the invention is on sale in the U.S.

Especially in first-to-file Europe

- European and most foreign patent law regimes have an absolute novelty requirement
  - Patent application must be filed before any enabling disclosure is made public.
  - Can backdate foreign filing date to previous U.S. filing date if within one year.
  - However, if you file a foreign patent application first, only one year to file in the U.S.

To summarize

- Take-away points about FTO opinions
  - Patents do not grant positive rights, only negative--must make sure space to practice invention exists.
  - FTO opinions can reduce liability exposure and maximize an invention's profitability.
  - Investors are more likely to back inventions backed by FTO assessments for these reasons.
  - Along with obtaining FTO assessment, prudent to weigh advantages of patent versus trade secret protection for the particular invention.

Patient Monitoring and Informatics
New Opportunities for the Next Decade

Michael Imhoff, MD PhD

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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

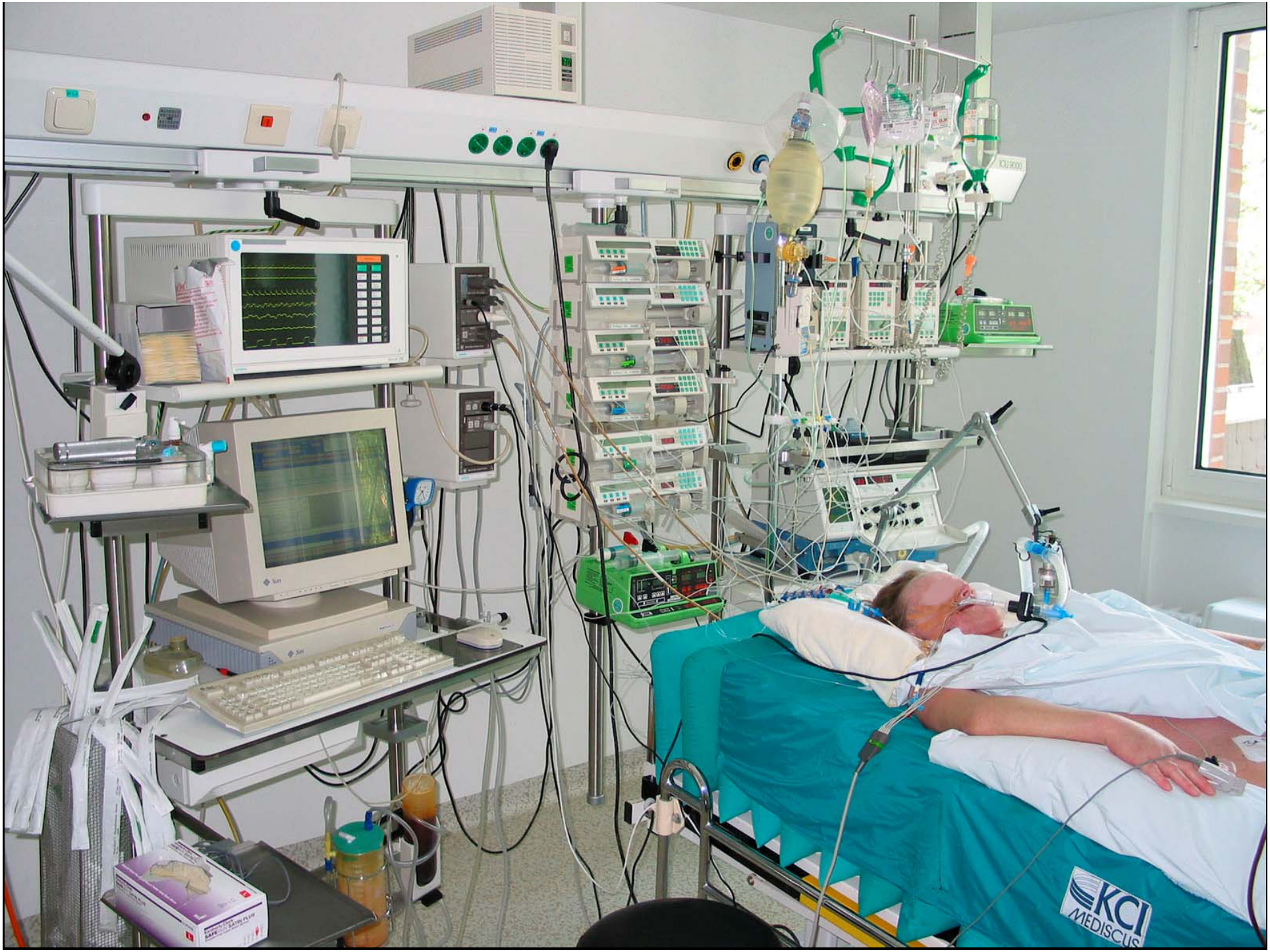
Monitoring

- Measurement of a parameter of a system (human being, aircraft, ...)
- 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
  - Pulse oximetry
- Benefit could be found
  - ScvO2 / early goal directed therapy in sepsis
  - Cardiac output / perioperative hemodynamic optimization
- Benefit depends on the translation of monitoring into therapy

➔ Process Control
➔ Decision Support
➔ Application of Informatics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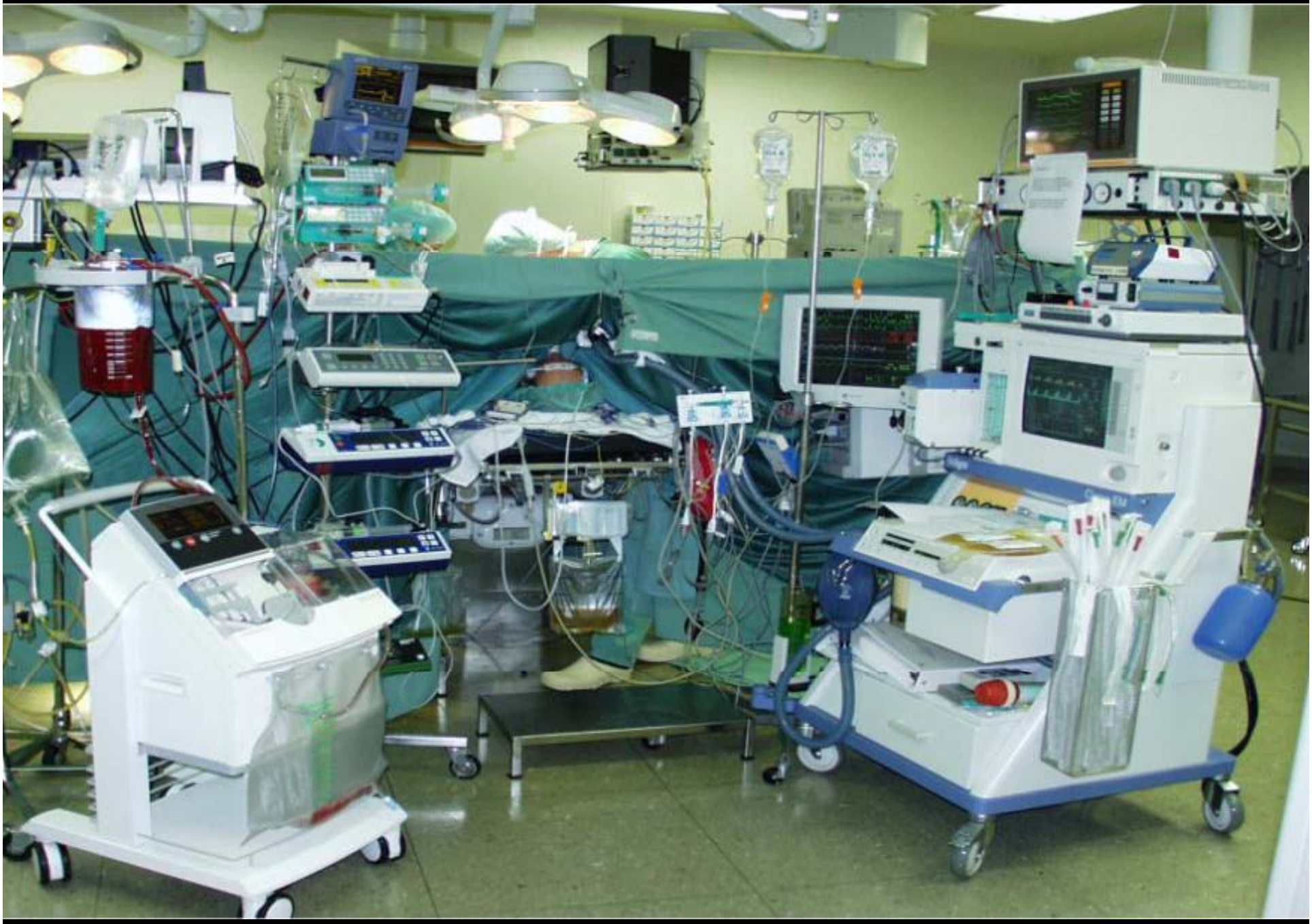


Changes in Hospital Care

- Increasing acuity
- Decreasing length of stay
- Increasing patient safety concerns

- Shortage of ICU beds
- Shortage of qualified staff

➔ Implementation of intermediate care

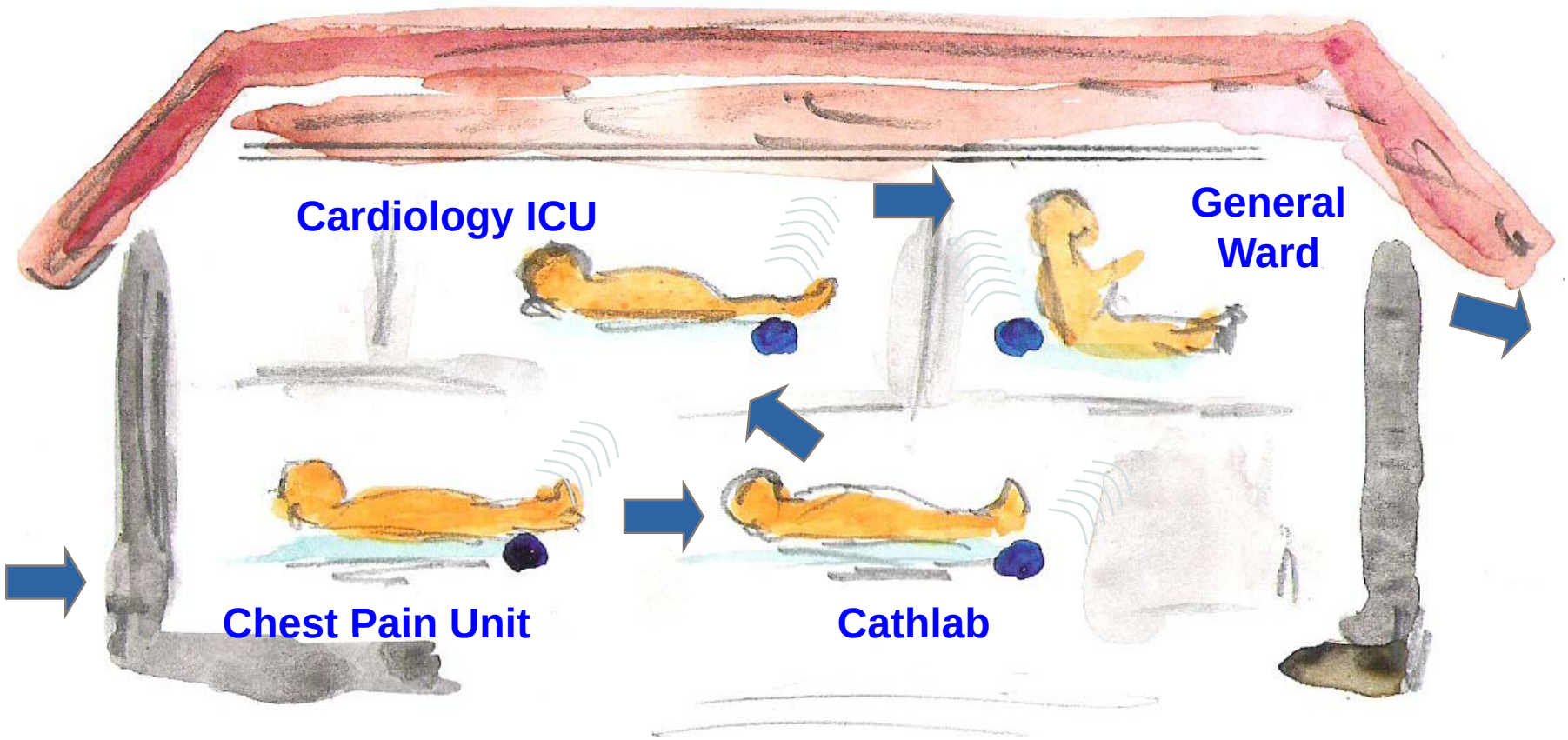
➔ Telemetry units

➔ Critical care outreach (CCOT, MET, RRT, …)

➔ Monitoring in general wards

- Improving informatics infrastructures

Continuum of Care
Continuous Monitoring



Monitoring in the Hospital

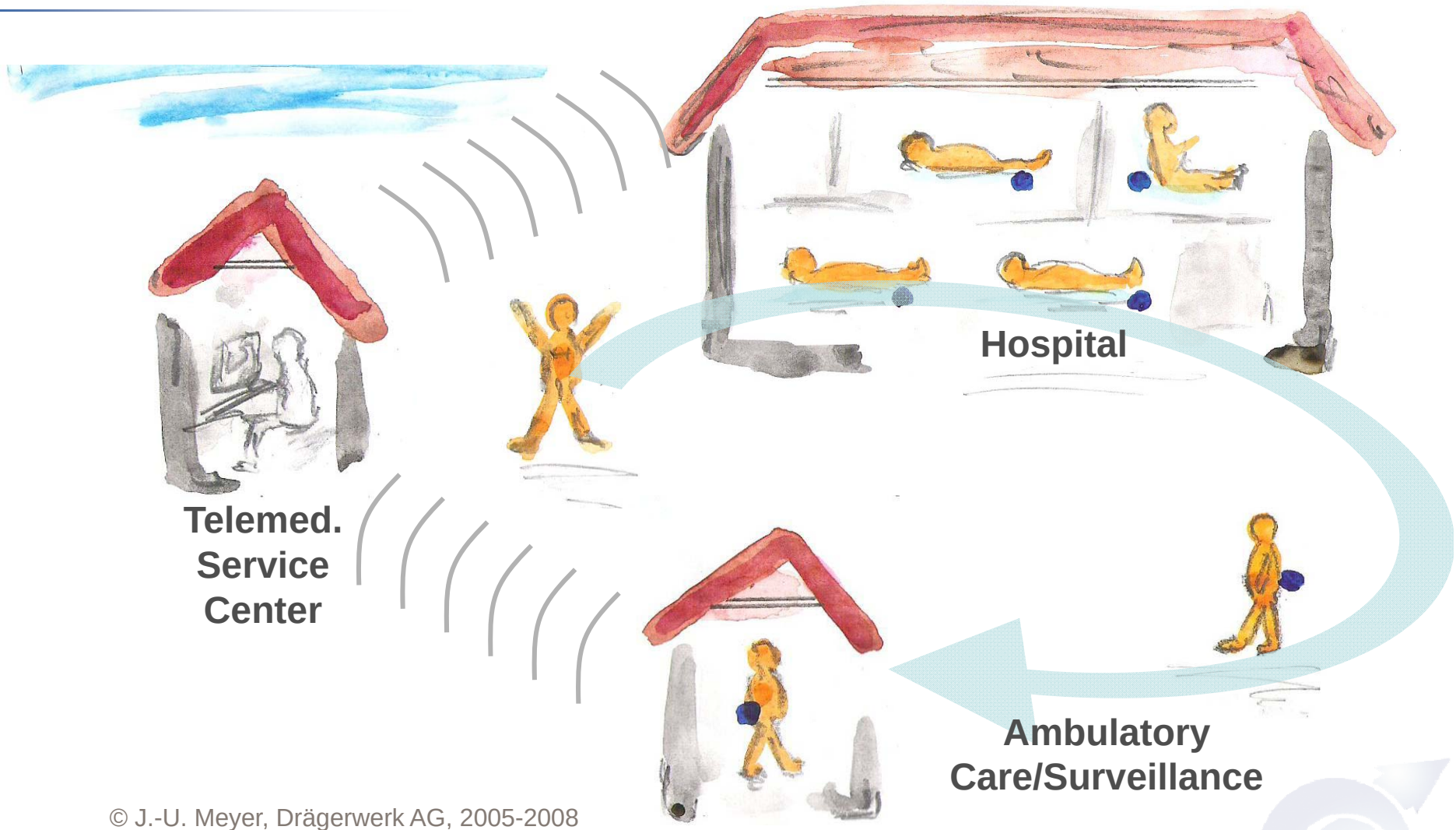
“Traditional” Monitoring (ICU/OR)

- 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



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 - IIT) 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?)

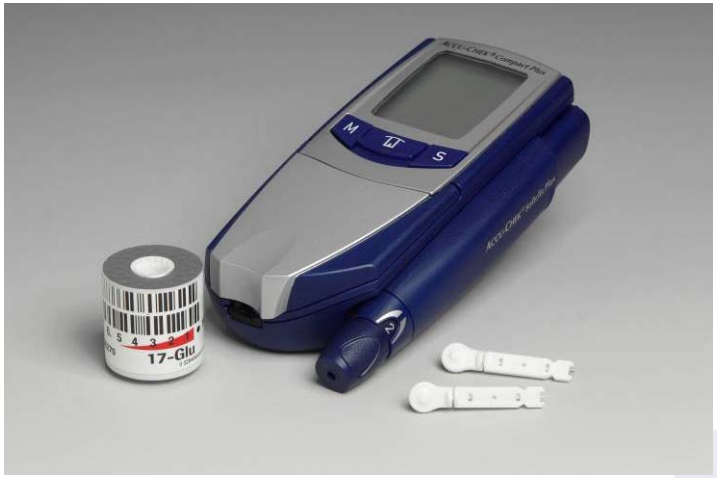
➔ Significant hype about TGC

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

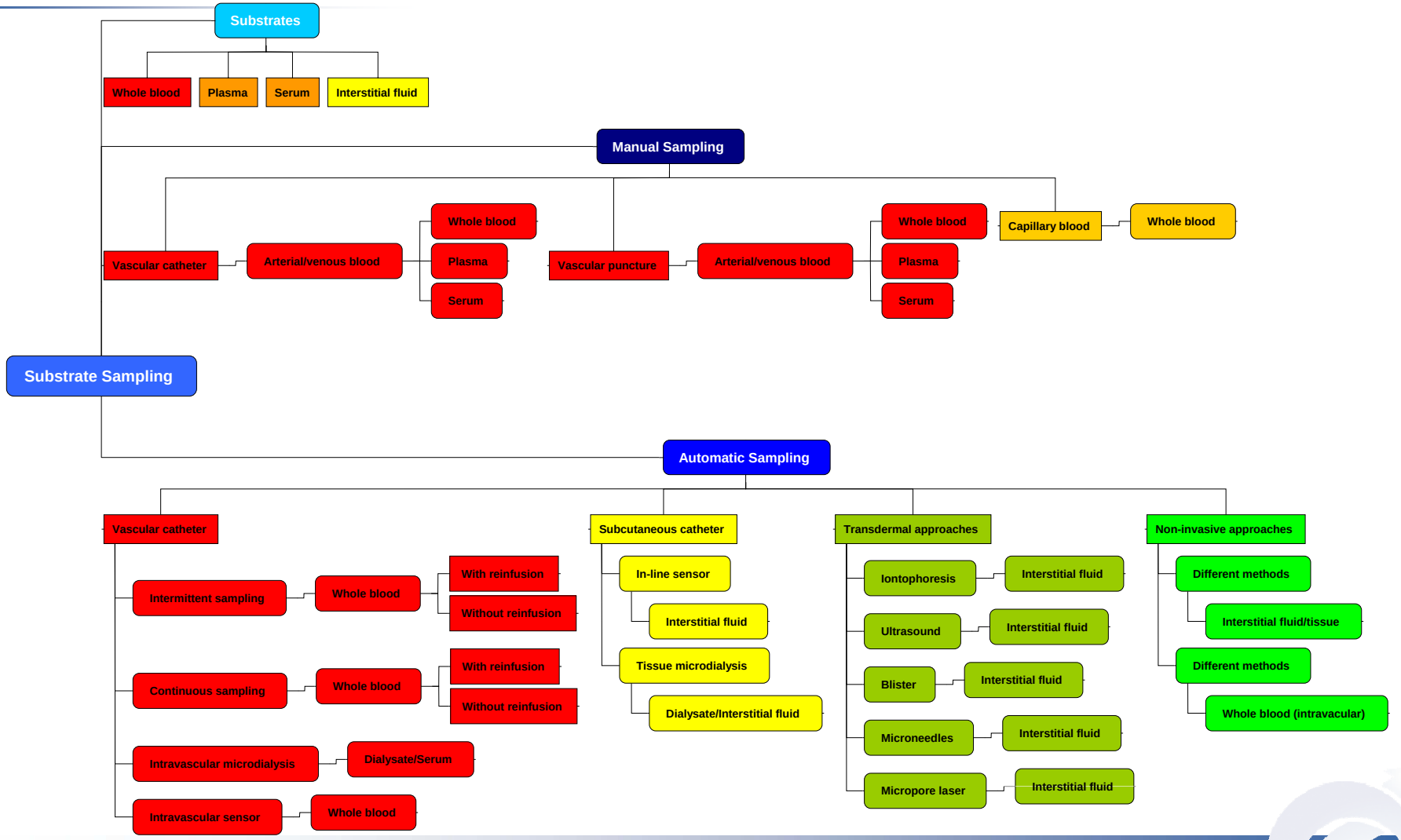
Requirements for ICU Glucose Monitoring (unproven!)

- 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?

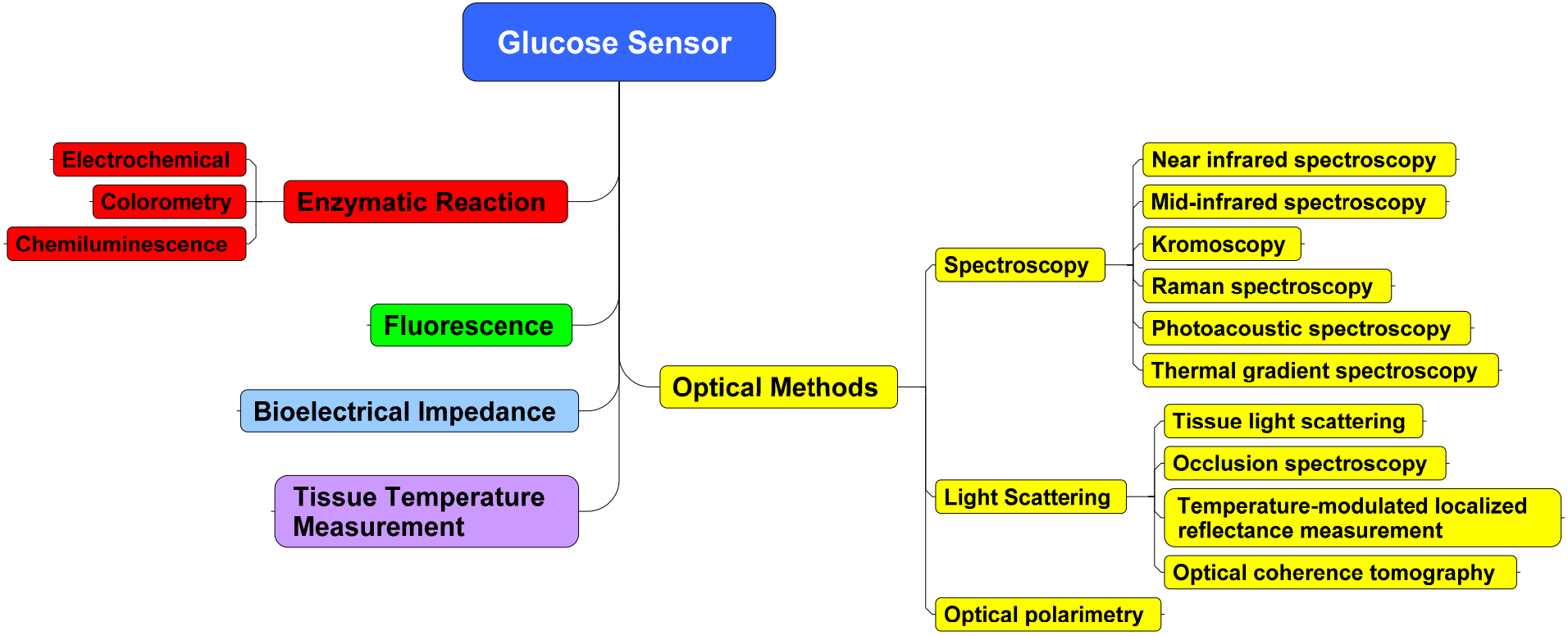
Two challenges

- Substrate sampling
- Blood glucose measurement

Continuous Glucose Monitoring Technologies
Substrate Sampling

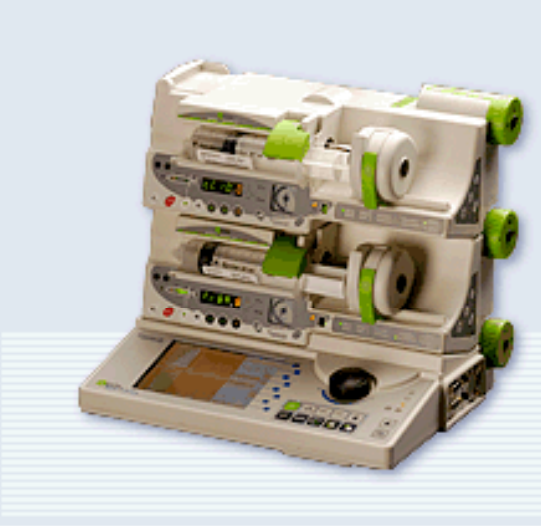


Continuous Glucose Monitoring Technologies
Sensor Technologies



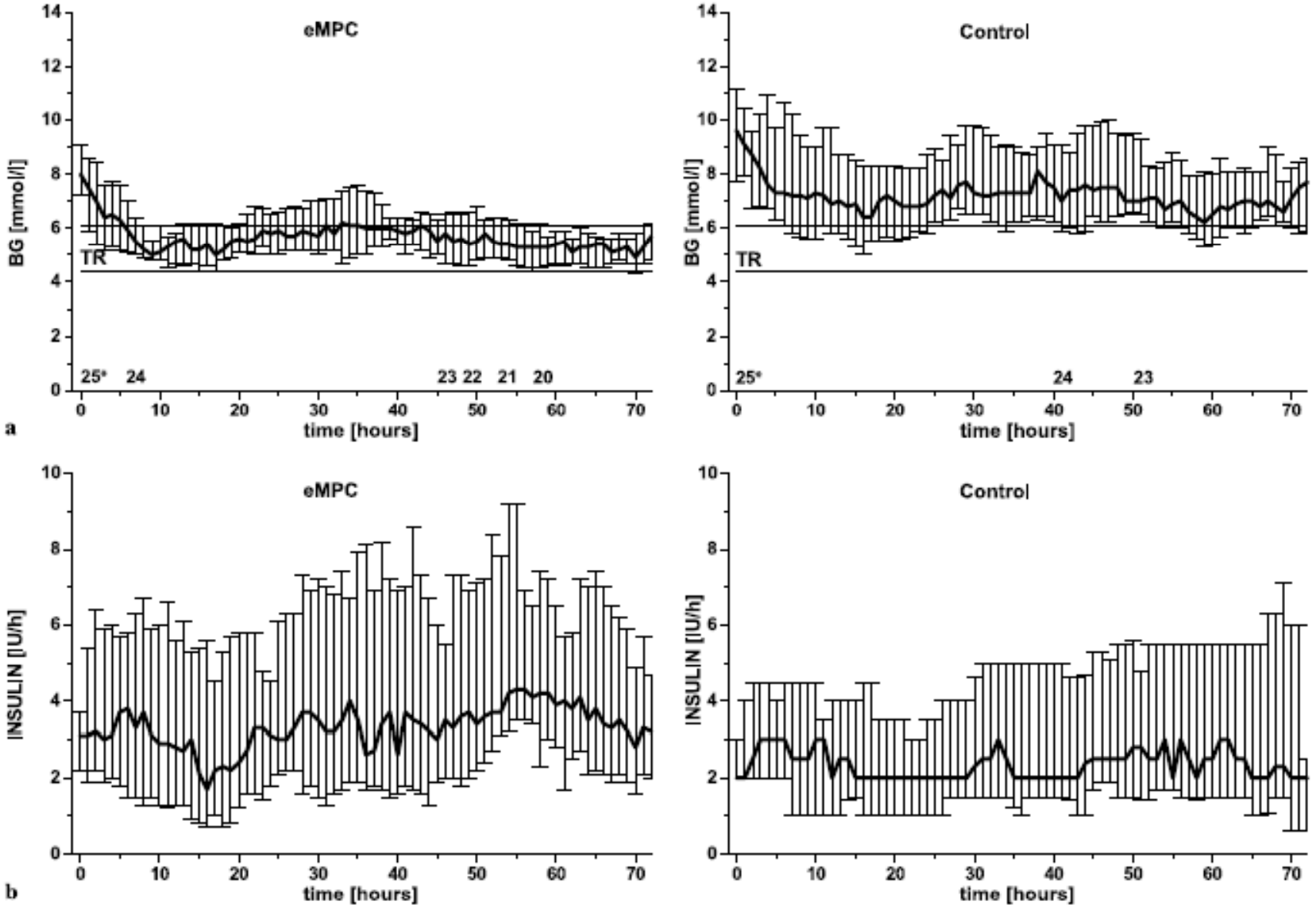
Tight Glycemic Control
Administration of Insulin and Glucose

- 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

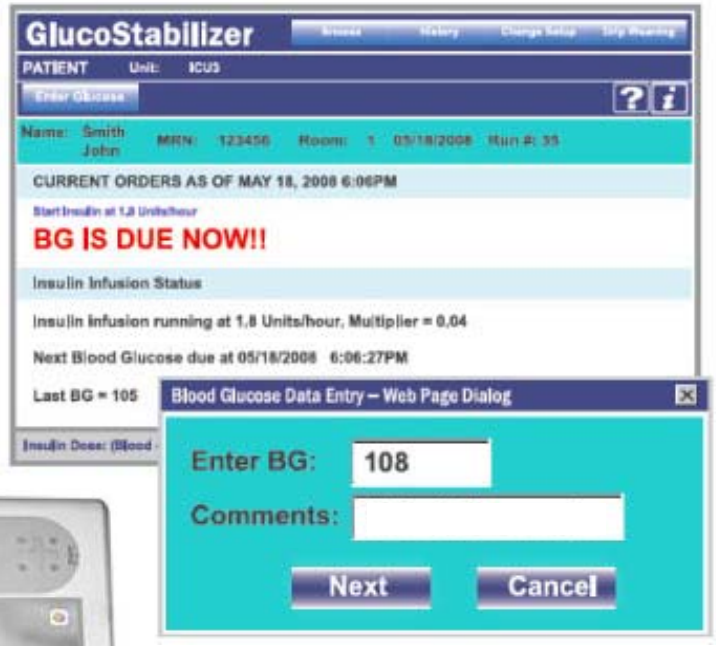


Pachler et al, Intensive Care Med 2008

Tight Glycemic Control
Commercial Decision Support Tools

- MD Scientific, LLC
  - Endotool Glucose Management System
  - Acquired by Hospira 10/2008
- MDN Medical Decisions Network
  - GlucoStabilizer
- GlucoTec, Inc.
  - G+™ Model 2020
    - Tablet PC based solution
  - G+™ Analytics
    - posthoc analysis software

- Clinical utility?
- Cost effectiveness?
- Integration with CIS/EMR?



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
  - 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
  - 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
  - TGC: 66% perceived compliance vs. 6% actual compliance
- ***The hype may be over!***

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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