

Non-Invasive Medical Devices Environmental Scan

Technology & Markets January 2007





Non-Invasive Technologies

Non-invasive medical devices can be defined as those which do <u>not</u> require insertion of the instrument through the skin or bodily orifice for diagnosis, monitoring or treatment of disease.

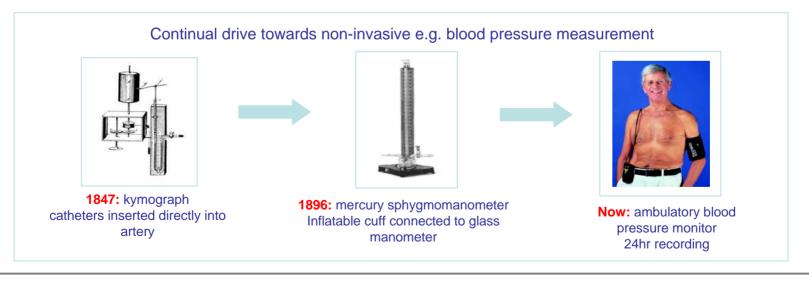




Move towards decreasing invasiveness

There is a clear trend towards decreasing the invasiveness of medical procedures and devices. This is largely driven by the numerous benefits non-invasive technology offers the consumer, end-user and payer:

Consumer:	pain-free
	earlier assessment / diagnosis
	improved health outcomes
End-user:	ease of use
	potential to increase measurement frequency utilisation away from bedside/out of hospital
	removes infection risk
Payer:	cost reductions



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E-Scan Aim

- The term 'non-invasive medical devices' encompasses several technologies, which have applications in numerous markets.
- The primary objective of this analysis is to identify sectors where emerging non-invasive technologies are likely to impact significantly the existing market.
- This environmental scan will highlight leading applications of cutting edge non-invasive technology within the life science sector.
- ITI Life Sciences may then chose to conduct a more in-depth analysis of identified technologies and associated market opportunities.



OE

PROJECT SCOPE	TECHNOLOGY SCOPE	
EMERGING TECHNOLOGIES		
MARKET DYNAMICS Size Growth 	MONITORS	
 Drivers, Challenges, Restraints KEY PLAYERS 	THERAPEUTICS	
IP LANDSCAPE	OTHER DEVICES	

LIMITATIONS

Limited to technologies within Life Sciences Sector.

Not to include imaging technology, which has been analysed during previous foresighting activities.



Strategic Analysis of the Non-Invasive Technology Landscape



Leading technology applications

4 application areas were identified, where recent advances in non-invasive technologies could impact the existing market:



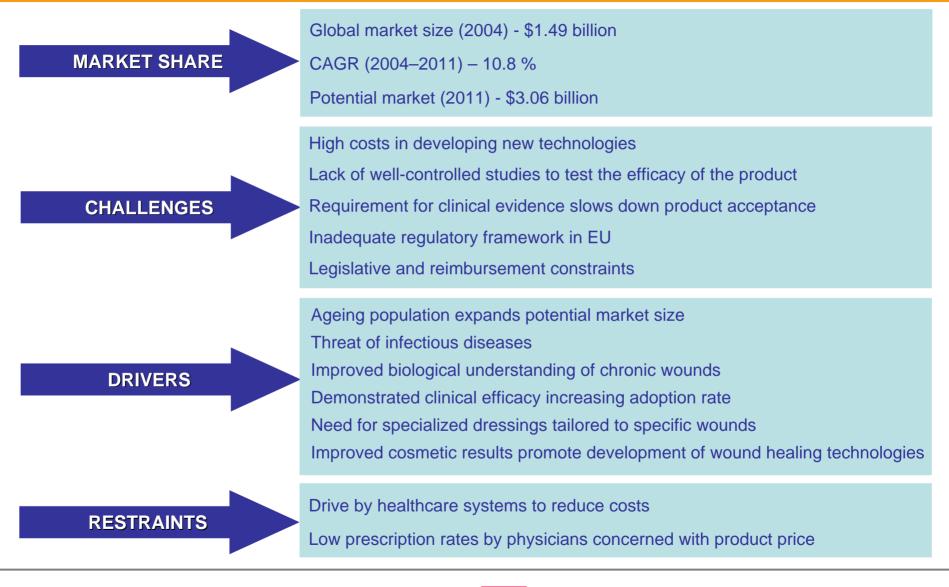


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Advanced Wound Healing



Advanced Wound Healing





Segmentation

MOIST WOUND DRESSING	ANTIMICROBIAL	ADVANCED THERAPIES	DEVICES
Alginate Hydrofibers Hydrocolloids	Silver Non-silver	Tissue engineering Biointeractive	Negative pressure therapy
Foam			Others
Hydrogels			
Transparent films			

- Wound-care technologies are experiencing a shift from traditional wound management to active wound healing platforms
- Trend towards hybrid dressings, which combine aspects of existing products and may incorporate new technology
- A low-cost, acellular, non-animal based skin substitute that facilitates wound healing likely to disrupt the market



Negative Pressure Wound Therapy

- Negative Pressure Wound Therapy (NPWT) is a technology used to treat chronic, post-operative and hard-to-heal wounds by the application of sub-atmospheric pressure to an open wound.
- The market for NPWT is the fastest growing segment of the woundcare market. It has expanded rapidly in recent years and was estimated to be a global market worth \$1.2 billion in 2006. The market is growing at an annual rate in excess of 12% in the US and greater than 25% in non-US markets and is viewed as a threat by participants in the advanced wound management market.*



- The US company, Kinetic Concepts, Inc. (KCI) is market leader with its Vacuum Assisted Closure (VAC) technology but is now beginning to face competition from companies such as BlueSky, who were recently successful in their defence of a patent infringement suit by KCI.
- Smith & Nephew entered NPWT market in May 2007 through the acquisition of BlueSky Medical Group for an initial payment of \$15 million with further milestone payments of up to \$95 million related to revenues and other events.



Alternative Device Technologies

- Low Level Laser Therapy
- High-Frequency Pulsed Electromagnetic Stimulation
- Electrical Stimulation
- Non-contact Normo-thermic Wound Therapy (NNWT)
- Light Emitting Diodes



Deep Bleeder Acoustic Coagulation (DBAC) Program

Aim is to develop a portable, lightweight, non-invasive, automated system for the detection, localisation, and coagulation of deep bleeders that is operable by minimally trained personnel in the combat environment.

The DBAC system will cover the full range of life-threatening bleeders from the fast bleeder, which causes progressive shock in 30 seconds, to the slow bleeder, which causes progressive shock in 8 hours.

The Pentagon has reportedly committed \$51million over 4 years to this program. Two competing teams were awarded contracts in 2006 to develop the technology: one headed by Philips and the other by Seattle-based AcousTx Corporation (whose team also includes Siemens Corporate Research and Therus).

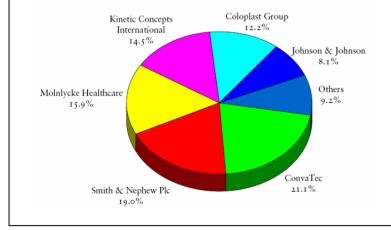


Ultrasonic tourniquets could stop blood vessels from bleeding out by noninvasively coagulating blood using focused sound waves. (Source: Philips Research)

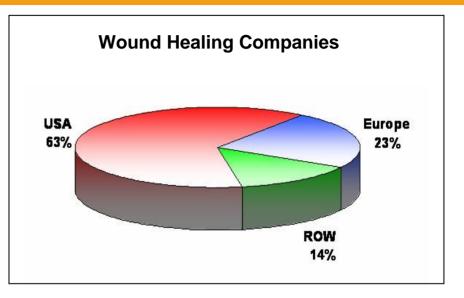
Players

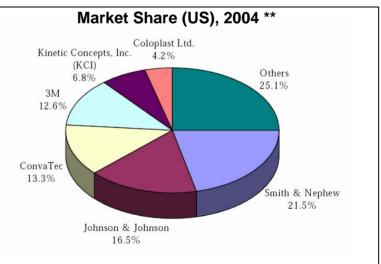
- Smith and Nephew
- Johnson and Johnson
- 3M Healthcare
- Molynlycke Healthcare
- Coloplast
- ConvaTec
- Covidien
- Kinetic Concepts
- B.Braun Medical

Market Share by Revenues (EU), 2005*



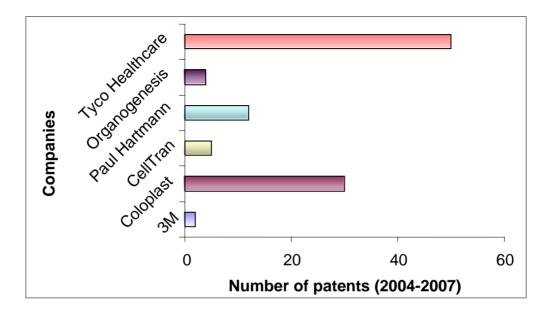
* Frost & Sullivan. European Markets for Advanced Wound Management (2006) ** Frost & Sullivan. Global Advanced Wound Management Markets (2005)





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IP Activity



- The figure indicates the number of wound healing-related first priority filed patents worldwide from 2004 to 2007.
- The patent issue pattern for key companies during the last three years suggests that the focus within wound healing has been across three major areas:
 - Foam-based wound healing devices
 - Gel based
 - Cell sheet development
- The patent pattern over the last 4 years suggests that while foam- and gel-based dressings are in vogue, the trend is shifting toward employing biomaterials to address chronic wounds.



Drug Delivery



Drug Delivery

Non-invasive technologies are also applicable to the drug delivery market, which can be segmented as follows:

Physical Devices / Approaches	Delivery Devices
 Electroporation, lontophoresis Implants Microspheres Nanospheres Needle Free Injection 	 Delivery from Stents Gastric Retention Devices Metered Dose Inhalers (mechanical and electrical) Microwave, Thermodynamic Heating, Ultrasonic Pump Delivery
Routes of Administration	Physiochemical
 Buccal, Sublingual and Transmucosal Gastrointestinal, Colonic, Rectal, Urogenital Nasal Ophthalmic Oral Parenteral Pulmonary (Inhalation)/ Respiratory Systemic Targeted Transdermal/Topical 	 Absorption, Solublizers and Bioavailablity Enhancers Aerosols Controlled and Sustained Delivery/Release Depot, Implantables and Biodegradables Encapsulation Taste Masking



Example: transdermal drug delivery

<u>Global</u>

MARKET SHARE

Current market size (2005) - \$12.7 billion

CAGR (2005–2010) – 11.1%

Bypassing the stratum corneum

Potential market size (2010) - \$21.5 billion

CHALLENGES

Increasing the spectrum of drugs that can be delivered through the skin Eliminating the impending risk of damage and contamination of the skin Assessment of molecular weight and increasing the speed of delivery through the transdermal route

DRIVERS

Preference and compliance of patients to alternative drug delivery methods Dosage control mechanisms in transdermal systems attract Elimination of side-effects and accelerating the curative process

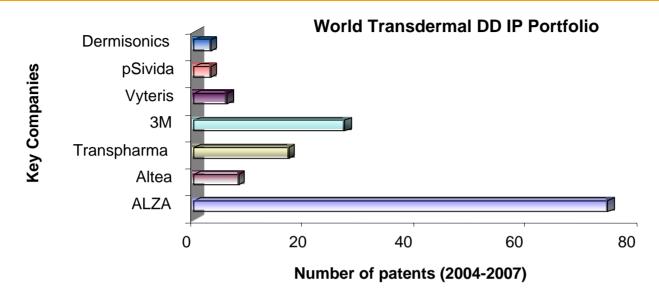


Transdermal DD Technologies

Microprocessor based	Vesicle and RF Patch	Ultrasound based	Nanotechnology based
Companies: ALZA Therapeutics ALTEA Therapeutics Vyteris	Companies: Phosphagenics Transpharma LCT Technologies	Companies: Dermisonics Sontra Medical	Companies: Nano-Vic Australia pSivida NanoPass Ceramisphere
Molecules: Fentanyl- Pain Management Insulin-Diabetes Lidocaine-Anaesthetic	Molecules: Insulin-Diabetes Morphine Diclofenac Growth Hormone Testosterone	Molecules: Insulin Heparin	Molecules: Insulin Drugs for Neurological disorders and Cancer
Advantage: Delivery of drug under control of the patient	Advantage: Delivery of large peptides	Advantage: Delivery of large peptides	Advantage: Reduce dosage frequency Passage via blood-brain barrier



Transdermal DD IP activity

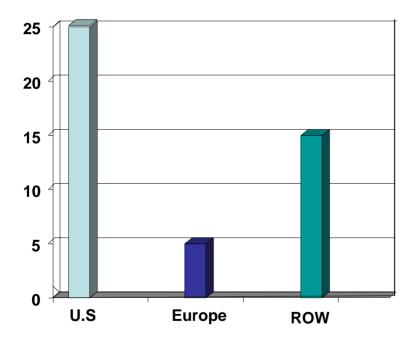


- The figure indicates the number of transdermal drug delivery-related first priority filed patents worldwide from 2004 to 2007.
- The patent issue pattern for key companies during the last three years suggests that the focus within transdermal has been across three major areas:
 - 1. Microneedle-based delivery
 - 2. Microprocessor embedded transdermal devices
 - 3. Nanoparticle- and ultrasound-based delivery
- The patent pattern over the last 4 years suggests that transdermal delivery of molecules through different processes is gradually increasing and there is space for new entrants in this area.

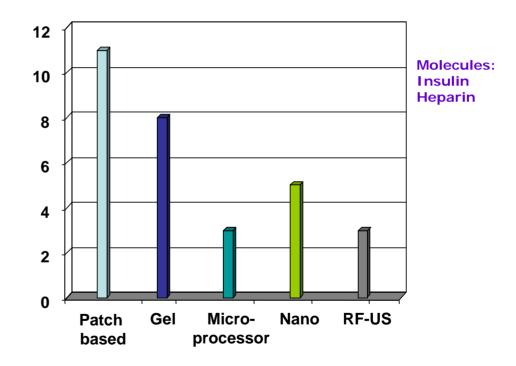


Transdermal DD Players

Global companies in transdermal drug delivery



Global company spread according to method of transdermal delivery



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Company Snapshot



Drug Delivery Technology

Broad array of technology platforms, including oral, transdermal, implantable and liposomal technologies.

Core technologies include a needle free solution for drug delivery of vaccines, small molecules and other biopharmaceuticals.

ALZA Corporation is a member of the Johnson & Johnson Family of Companies.

Transdermal Patch Technology

Developed a transdermal patch that uses short bursts of focused thermal energy to create tiny channels in the surface of the skin, which permit the rapid and sustained flow of proteins, peptides, carbohydrates, and small molecules into the body without the use of needles.

Completed a \$30 million Series C round in 2005 and won a 2007 Frost & Sullivan Technology Innovation Award. Based in Atlanta, Georgia.

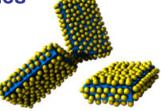
XstalBin Formulation of therapeutic proteins, peptides, DNA & vaccines

Has developed technology for preparing biomolecules as stable solid-state formulations. Particles may be engineered for a wide range of delivery options including parenteral, pulmonary, sustained release and transdermal routes.

The company started trading in 2002 and is based in Glasgow, Scotland.







Non-invasive Insulin Delivery

- Injection pain and needle phobia contribute significantly to the poor glucose control of a number of diabetic patients.
- Inhaled insulin offers both a non-invasive method to maintain blood glucose control for people with type 2 diabetes and a strategy to improving patient compliance.



Exubera is a rapid-acting, fine dry-powder insulin administered via inhalation developed by Pfizer in collaboration with Nektar Therapeutics (a company that specialises in developing drug delivery solutions). It offers the benefit of pain-free administration, which may aid treatment compliance.

- First non-injectable insulin product. Received FDA approval in January 2006.
- Annual sales predicted to be in the order of \$1B-\$4B. However, the product achieved sales of only \$12M in the first 9 months of 2007.*
- Pfizer discontinued Exubera in Oct 2007 after 11 years of development, less than one year of sales and at a cost of \$2.8B in pretax charges.*

"Exubera has failed to gain the acceptance of patients and physicians. We have therefore concluded that further investment in this product is unwarranted." Pfizer 3rd Quarterly Report 2007



In Jan 08, Novo Nordisk announced its decision to halt development of its inhaled insulin product AERx, costing the company \$0.3bn in charges. The product was in phase 3 trials but Novo Nordisk believed it unlikely to offer significant clinical or convenience benefits over insulin injections with pen devices. However, the company now plans to step up R&D activities targeted at inhalation systems for long-acting analogues of GLP-1 & insulin.

"[Patients] want very simple, very convenient devices for administering their insulin. This requires a whole new approach to inhalation of insulin." Novo CEO Lars Sørensen.



Is there a market for pulmonary insulin products?

Why did Exubera struggle?

- Poor marketing and sales strategy
- Inhaler is bulky, awkward, difficult and embarrassing to use
- More expensive to use than injectable insulin
- Requires a lung function test before prescription
- Difficult to calculate dosage



Does this signal the likely failure of all pulmonary insulin products?

- Not necessarily. Exubera perhaps best viewed as a pilot program offering lessons to be learnt.
- The development of bioavailable, stabilised insulin in powder form was a significant technical achievement. However, device design was poor. Success in this field requires development of both a clinically efficacious drug formulation and a consumer friendly device for non-invasive delivery. Development and implementation of a tailored marketing strategy is also required.
- There are a number of other companies also operating in this space.



Developed powdered insulin with aerodynamic properties that enable it to be dispensed from small, simple inhaler. This is a disposable device, discarded after 1 month's use. AIR insulin is in phase 3 trials



MannKind Corporation

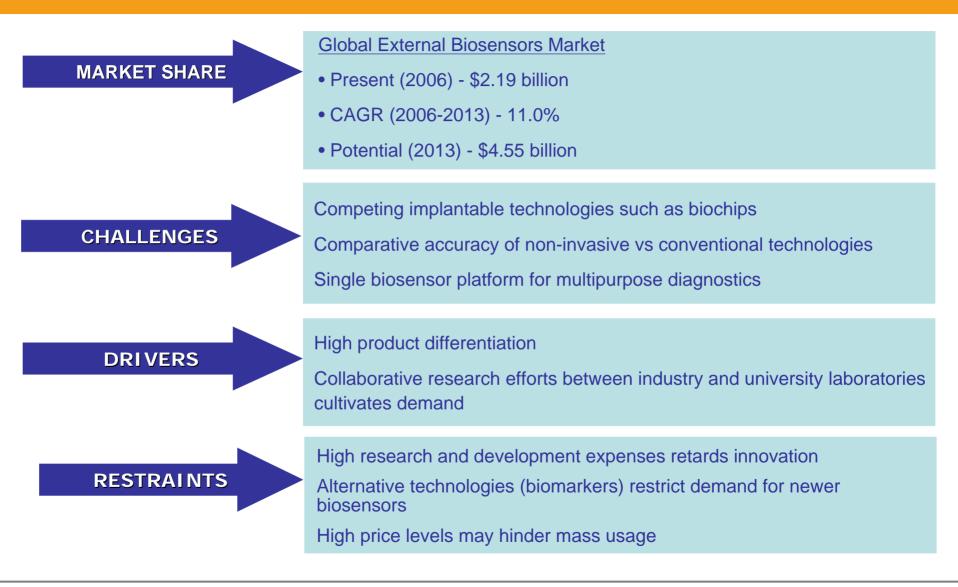
Developed a small, palm-sized device for use with its reportedly superior 'Technosphere' formulation. Now in phase 3 trials.



Non-Invasive Sensing



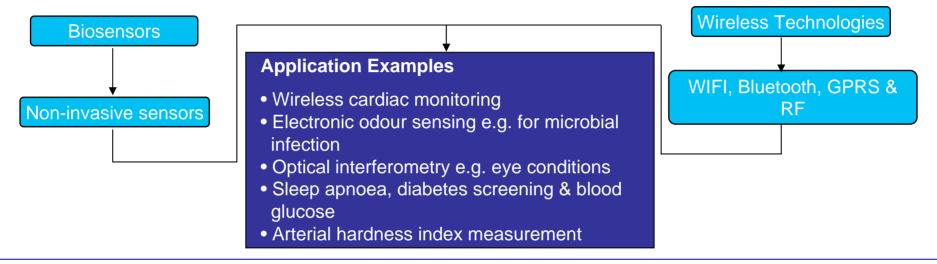
External Biosensors Market





Technology

Non-invasive sensing technology is viewed as having significant potential to disrupt the existing sensing market and moderate potential to lead to incremental improvements in devices currently in the marketplace.



Non-invasive Glucose Sensing

- The global market for glucose monitoring is reportedly \$7B with room to grow. The market is significantly underpenetrated with patients testing on average 1.5 times a day compared to the 4-6 times a day recommended.* This is at least partly due to the pain experienced on testing although inconvenience and embarrassment also play a role. Non-invasive sensing technology could address these barriers to use.
- However, the non-invasive glucose monitoring field has a high attrition rate and is now viewed by investors with much skepticism. While the market need is clear, the technology has failed to deliver. The market has yet to see a low-cost, conveniently sized, non-invasive device, which has comparable performance to traditional technologies and has a business model with revenue potential similar to that of the razor-blade approach associated with current finger-stick devices.

* Windhover Information. Start-Up 2007; 12: 14



Company Snapshot

VeraLight

Sense

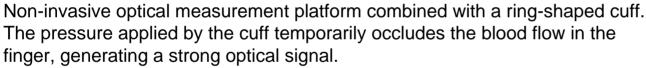
Non-invasive diabetes screening

Employs fluorescence spectroscopy to non-invasively measure advanced glycation end-products (AGE) in the skin.

Skin AGEs have been shown to relate to the development of type 2 diabetes.

Company raised \$17.5M in a series B financing in 2006 and is based in New Mexico.







The company is based in Israel and received a technology innovation award from Frost & Sullivan Dec 2006.

IDM S' Non-invasive caries detection device

Uses electrical impedance to detect the early stages of tooth decay at which point the decay process is capable of being arrested or reversed.

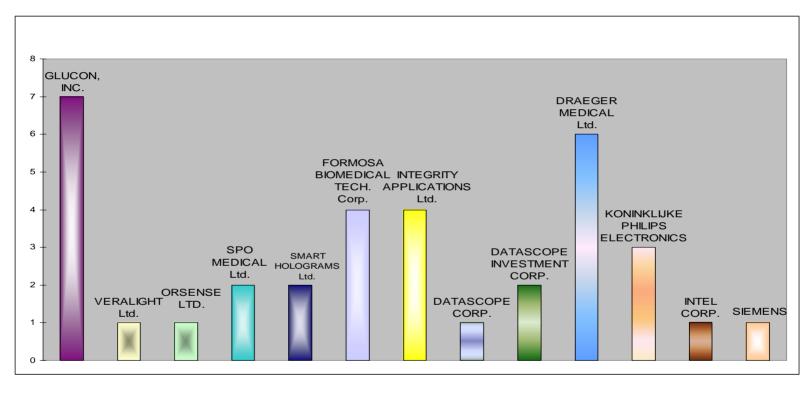
Company floated on AIM in Nov 2004 and have a long term collaborative agreement with Dentsply International. Based in Dundee, Scotland.

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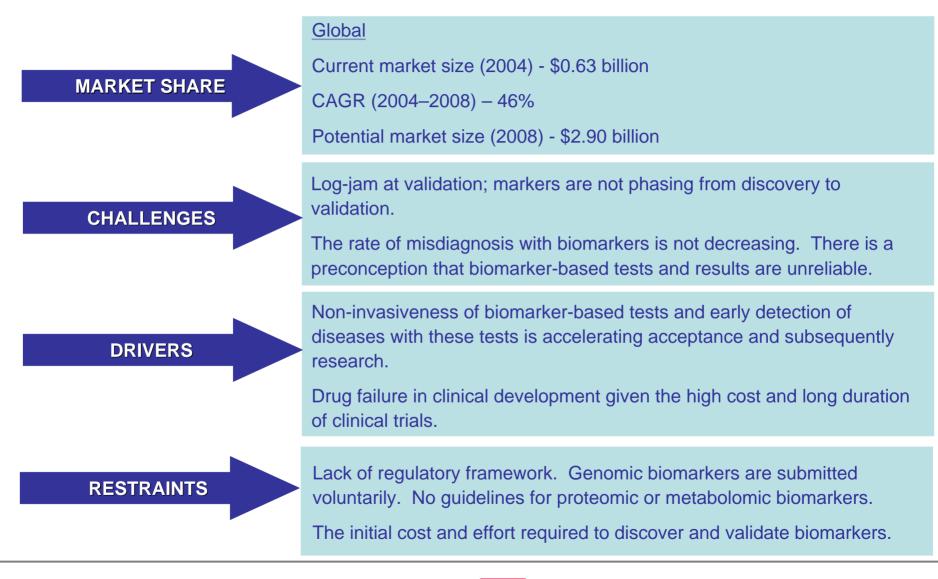
IP Activity

Number of Patents (2006-2007)





Influencing technology: biomarkers





Biomarkers

GENOMICS

PROTEOMICS

METABOLOMICS

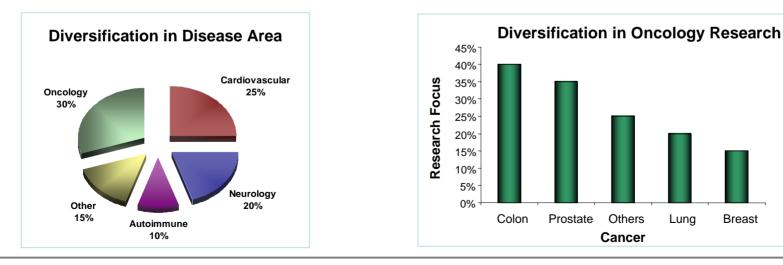
BIO-INFORMATICS

• The most commonly used technologies for biomarker identification and measurement are the 'omics' platforms and imaging techniques.

• These strategies will only provide candidate biomarkers. Sophisticated bioinformatics technologies are required to validate these candidate biomarkers, analyze the data and assign statistical significance.

• Oncology is currently the biggest industry focus for biomarker cancer research worldwide. The figure below shows the main current focus across the R&D community in oncology, with colorectal biomarkers receiving the highest industry focus (40%). Other areas include pancreatic, liver and ovarian cancer (25%).

 Research trend analysis indicates that the highest research focus (investment) is on the oncology field (30%). Cardiovascular (predominantly heart disease) and neurology disease groups (including hereditary disease and neurodegenerative disorders such as Alzheimer's disease) are also being extensively studied (25% and 20%, respectively) as well as autoimmune disease (with a focus on human immunodeficiency virus). The remaining 15% is predominantly focused on the treatment of arthritis.



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Biomarkers players

KEY PLAYERS (GLOBAL)

OMICS / BIO-INFORMATICS APPROACH

Gene Express, Inc. **Epigenomics Caprion Proteomics Proteome Sciences Proteome Systems Banyan Biomarkers Digilab BioVision Metabolon Biotrin Nonlinear Dynamics**

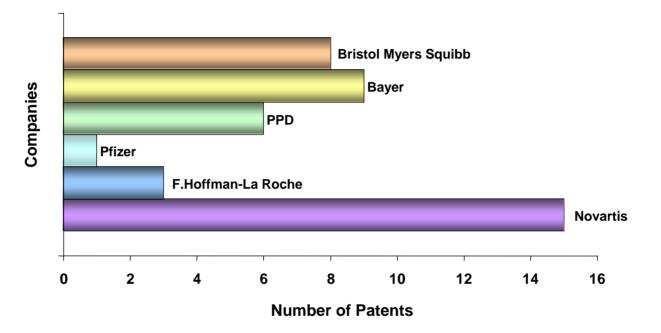
BIOMARKERS IN CLINICAL APPLICATIONS

Novartis AG F.Hoffman-La Roche Ltd Pfizer Inc. PPD Inc. **Bayer AG Biosite / IMI Bristol Myers Squibb Company Biogen IDEC Inc.** GlaxoSmithKline Seattle Genetics Inc. **AVEO Pharmaceuticals Inc.** Vermillion Inc.



Biomarker IP activity





- The figure indicates the number of currently enforced biomarker-related first priority filed patents worldwide from 2004 to 2007. Biomarker IP volume is currently low compared to overall R&D portfolios.
- The patent pattern over the last 4 years suggests an increase in proteomic marker identification and markers in neurology and inflammatory disorders.

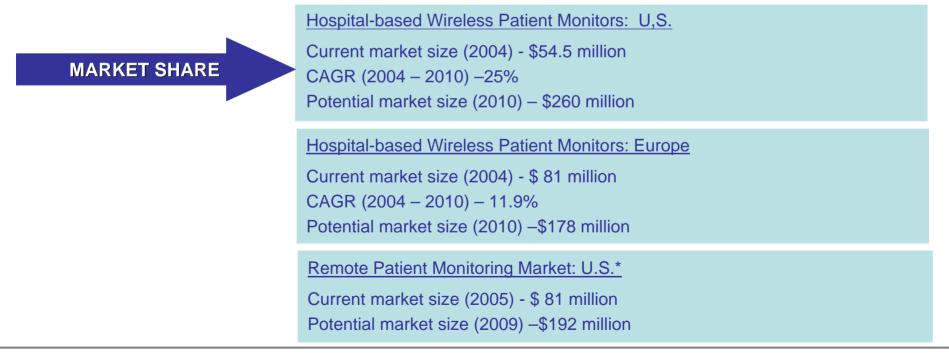


Wearable Patient Monitors



Wearable Patient Monitors

- Wearable patient monitoring (WPM) devices is an emerging non-invasive technology, which is likely to influence the more established wireless patient monitoring market and may open up the remote patient monitoring market.
- Current devices typically measure a range of pulmonary, cardiac, posture and activity signals and so are limited to physiological measurements though offerings will expand as non-invasive sensing technologies that enable non-invasive biomarker measurements advance.
- WPM market is nascent at present and so market forecasts cannot be made easily. Examining the market size of both the wireless patient monitoring market and the remote patient monitoring market provides some insight into its market potential.





Wearable Patient Monitors

CHALLENGES

Reliability and robustness of technology platform

Standardisation and ubiquitous integration of platform technologies

Data security

Miniaturization of sensors and power sources

Obtaining reimbursement

Currently limited to physiological monitoring though offerings will expand as advances are made in non-invasive sensing

Promoting consumer out-of-pocket payment for wellness offerings



Growth of the remote patient monitoring market

Associated cost benefits given the decrease in health/disease management costs

Improved disease management - better and faster clinical diagnosis

Consumer interest in personalised health monitoring driven by increased concern about health and healthcare costs



Company Snapshot

BODYMEDIA" Wearable Body Monitoring Products & Services

BodyMedia's products provide accurate and actionable information about the health and behaviours of people outside of the traditional clinical setting (eg caloric burn, caloric intake, sleep, physical activity duration). The company's technology platform consists of clinically-validated hardware, algorithms, and software. BodyMedia is based in Pittsburgh, Pennsylvania.





Non-invasively Monitoring Life



VivoMetrics focuses on developing ambulatory physiologic monitoring devices for first responders, pharmaceutical clinical trials and academic research. Pharmaceutical companies use its technologies to improve the speed and economics of clinical research. The company's offerings also enable academic researchers to discover new clinical signatures of disease, and government agencies to protect the lives of military and civilian first responders. Opportunities in sports and fitness sector are also being explored. Vivometrics is based in Ventura, California.

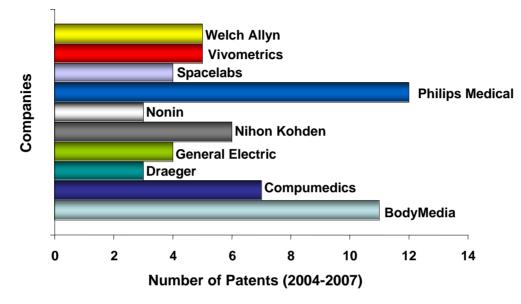
PALtechnologies Quantifying Free-living Activity

PAL technologies is a Scottish based company that develops and markets activPal, which provides an accurate measurement of free-living physical activity for the healthcare, fitness and veterinary markets. This technology allows clinicians and other professionals to assess patient compliance with exercise and treatment protocols and patient response to novel treatment interventions. The activPAL professional is worn discretely on the thigh and attached using a PALstickie[™].



Wireless & Wearable Patient Monitors IP Landscape

World WPM IP Portfolio



- The figure indicates the number of wireless patient monitoring-related first priority filed patents worldwide from 2004 to 2007.
- The patent issue pattern for key companies during the last three years suggests that the focus within wireless patient monitoring has been across three major areas:
 - 1. Cardiac monitoring
 - 2. Body activity and energy expenditure
 - 3. Multiparameter monitoring of vital signs
- The patent pattern over the last 4 years suggests that an increase in wireless-enabled health monitoring systems is on the increase with increasing emphasis on metabolic activity in the individual.



Conclusions & Next Steps



- This environmental scan has highlighted a number of non-invasive technology applications, which are of interest given their innovation potential and market opportunities.
- There is a clear move towards developing technology that enables **non-invasive delivery** of drugs. There is scope for innovation in non-invasive routes of administration such as pulmonary and transdermal delivery.
- There are also opportunities for non-invasive technology within the **wound-care** market. ۲ NPWT, a non-invasive wound healing device, has experienced considerable growth in the past 2-3 years. Alternative non-invasive device-based technologies also exist, although their efficacy remains unproven.
- Development of **non-invasive sensing technologies** with comparable performance to ۲ conventional technologies is likely to disrupt the diagnostics market. Several opportunities do exist, although there are technical and financial obstacles to commercial realisation as evidenced by activity in the glucose monitoring field.
- Development of wearable monitoring devices is likely to open up the remote patient monitoring market. The technology can also be exploited in other fields such as wellness, sports and defence sectors.



Next steps

- ITI Technology and Markets team will progress a number of the areas highlighted in this scan to a full foresighting analysis in order to gain further insight into the market opportunities. Wound Healing and Drug Delivery will be addressed in the first instance.
- Furthermore, it became clear while conducting this analysis that opportunities relating to minimally invasive technologies may also exist, where a reduction in invasiveness is sufficient to offer benefits over conventional technology despite a completely noninvasive solution not being achieved.

ITI Life Sciences will also conduct an environmental scan to map this space. This will include technologies associated with the following markets:





We very much welcome dialogue with our Members in this area.

If you would like to discuss the scan findings and related opportunities with us further, please contact ITI Life Sciences at:

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For more information on ITI Life Sciences, please visit:

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