

“We did it our Way.”

CONFRÉRIE  CLINIQUE
observance médicamenteuse et thérapeutique TRANSNATIONAL



ch, a.o. Novartis M Labs
e Projects, a.o. Knoll AG (BASF Pharma), Abbott
inical Trials & Real Practice Projects
DICCINE™, MEDICCINET™, TEMPOS™ projects

Joël Gebroers, PhD
Villem Kott, PhD
Executive Chairman & Technical Guru
Confrérie Clinique Transnational B.V.

12th Clinical Supplies Forum: “Regulatory Update.”

Contains Nonbinding Recommendations

Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 9, 2015.

This document supersedes “Mobile Medical Applications: Guidance for Food and Drug Administration Staff” issued on September 25, 2013.

This document was updated to be consistent with the guidance document “Medical Devices Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices” issued on February 9, 2015.

For questions about this document regarding CDRH-regulated devices, contact Bakul Patel at 301-796-5528 or by electronic mail at Bakul.Patel@fda.hhs.gov or contact the Office of the Center Director at 301-796-5900.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-7800.



U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Innovation OK! ... *Huhhhh?*



“How did you do it?”

“*Ehhh ... Therapy Adherence
Monitoring?*”

Problem: Therapy Mal-Compliance or Non-Adherence ...

(Infidelity vs. Therapy ...)

**If a patient does not comply to
the doctor's or pharmacist's instructions
concerning continuation, dosage and
interval of the medication, we speak of
“Mal- or Non-Adherence”**

Homo Sapiens ...?



Homo Sapiens ...?

Homo non adherent!



Medicines
don't work
in patients
who don't
take them.

Dr. C. Everett Koop

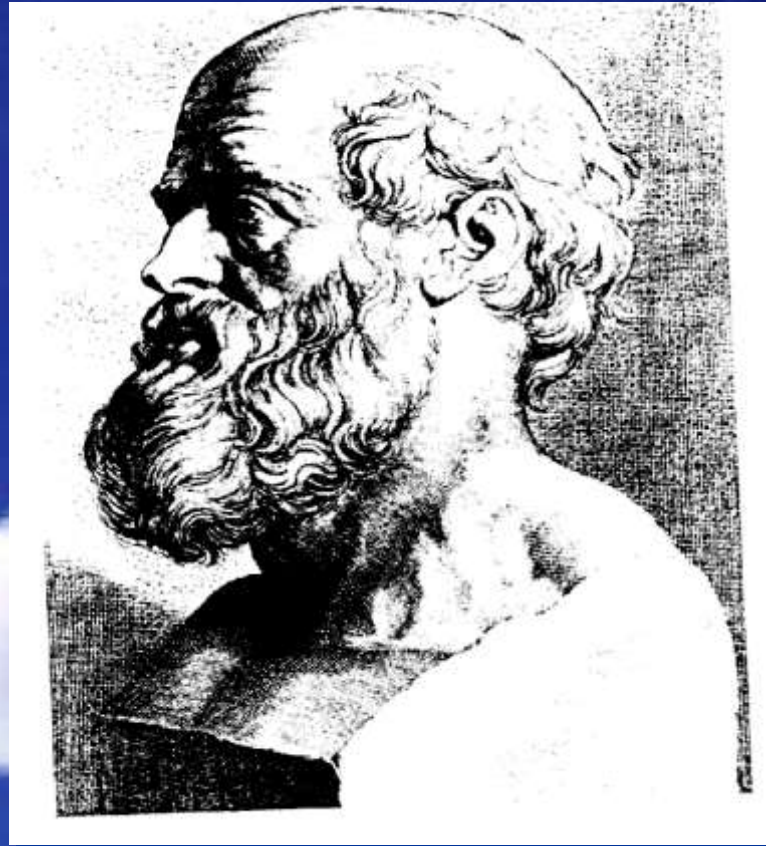




**Non-Adherence,
(*Infidelity vs. Therapy*)
is an Issue as old as Medicine ...**

Hippocrates (460-377)

Early Warning of the Non-Adherence Issue



Non-Adherence is a problem that predates Hippocrates, who advised his fellow physicians to *"keep watch for that fault in patients which makes them lie about the taking of things prescribed."*

Penicillin:



The Gift from the Gods ...

The Gift from the Gods ...



However:

**“If there were a cure for non-adherence -
a pill that would make you take your other
pills - it would be a greater boon to health than
any medication since penicillin” ...**

“Medicine’s stealthiest problem”

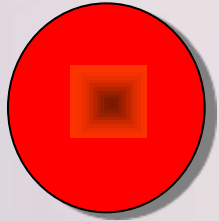
None, or less, therapeutical efficacy of the medication!

Negative Effects of Non-Adherence for Specific Drugs

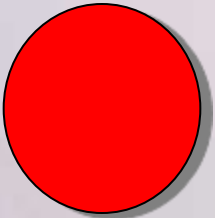
Antidepressiva	Serious Rebound Phenomena
Beta Blockers	Rebound Hypertension, Tachycardia
Ca-Antagonists	Reflex tachycardia at „restart“
Antibiotics	New „resistant“ infections
Antiarrhythmica	Life threatening arrhythmias
Anti Hypertensives	Stroke and myocardial infarction
Immunosuppressants in organ transplantation	Organ rejection
Anti Diabetica	Blood circulation problems

“In Flagrante Delicti ...”

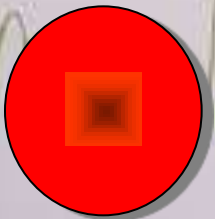
Noncompliance By Diagnosis		Noncompliance By Drug Type	
Alzheimer's Disease	.89%	Antiarrhythmics	.80%
Gastrointestinal Disease	.84%	Lipid-Lowering Agents	.72%
COPD	.80%	NSAIDs	.70%
Diabetes	.73%	Antihypertensives	.65%
Arthritis	.70%	Antidepressants	.61%
Glaucoma	.66%	Anticoagulants	.60%
Benign Prostatic Hypertrophy	.64%	Anticonvulsants	.54%
Osteoporosis	.60%	Antineoplastics	.53%
Schizophrenia	.60%	Anti-Parkinsonian Drugs	.52%
Migraine	.56%	Psychostimulants	.50%
Epilepsy	.54%	Nonsedating Antihistamines	.44%
Organ Transplants	.34%	Estrogen Replacement:	.40%



Counseling, education and behaviour modification techniques have achieved only limited success in boosting compliance ...



40% Of patients will experience treatment failure or a new medical problem as a result of improper use of medication ...



Of all medication prescribed, only 60% are actually consumed ...

Big savings from better compliance!

- “Research shows that many people with **chronic health conditions** do not take their medications as often as prescribed and that **noncompliance may cost as much as \$300 billion/year** to the **American healthcare system**”...

Changing old habits could save big on drug costs



[Julie Steenhuisen](#)

CHICAGO

Tue Apr 20, 2010 10:00am
EDT

Related News

[Why won't women
prevent breast
cancer?](#)

Tue, Apr 20 2010

(Reuters) - Making simple changes like getting people to take their medicines exactly as directed or to refill their prescriptions on time could save employers and their workers as much as \$163 billion a year in healthcare costs, U.S. researchers said on Tuesday.

Project `M-Lab` Smart Blisterpack

**Ilkka Siissalo
5.4.2002**

ICT Clinics

"Smart Blisterpack"

"Cardboard computer": battery, small computer, active RFID

- notes the time when a pill has been taken
- can sound a reminder voice
- can store answers to simple patient diary questions



Normal blister packs

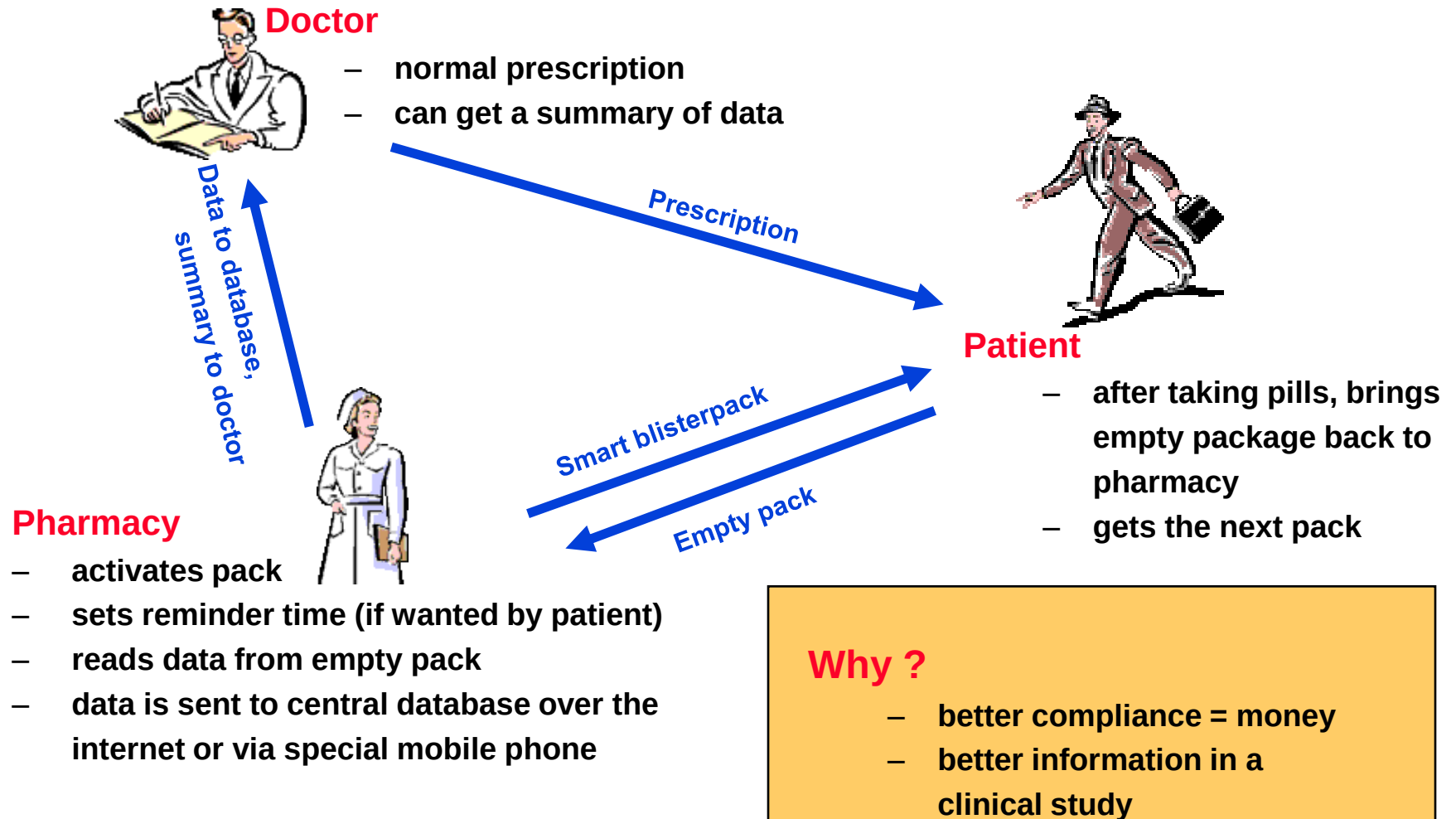
- no packaging change = no regulatory problem
- up to 2 packs
- taking pill breaks a circuit

Patient QoL question

- after taking a pill beeps until question is answered by pressing a button
- can be omitted to fit 2 blisterpacks

ICT Clinics

"Smart Blisterpack"



"Smart Blisterpack" Diovan pilot in Holland



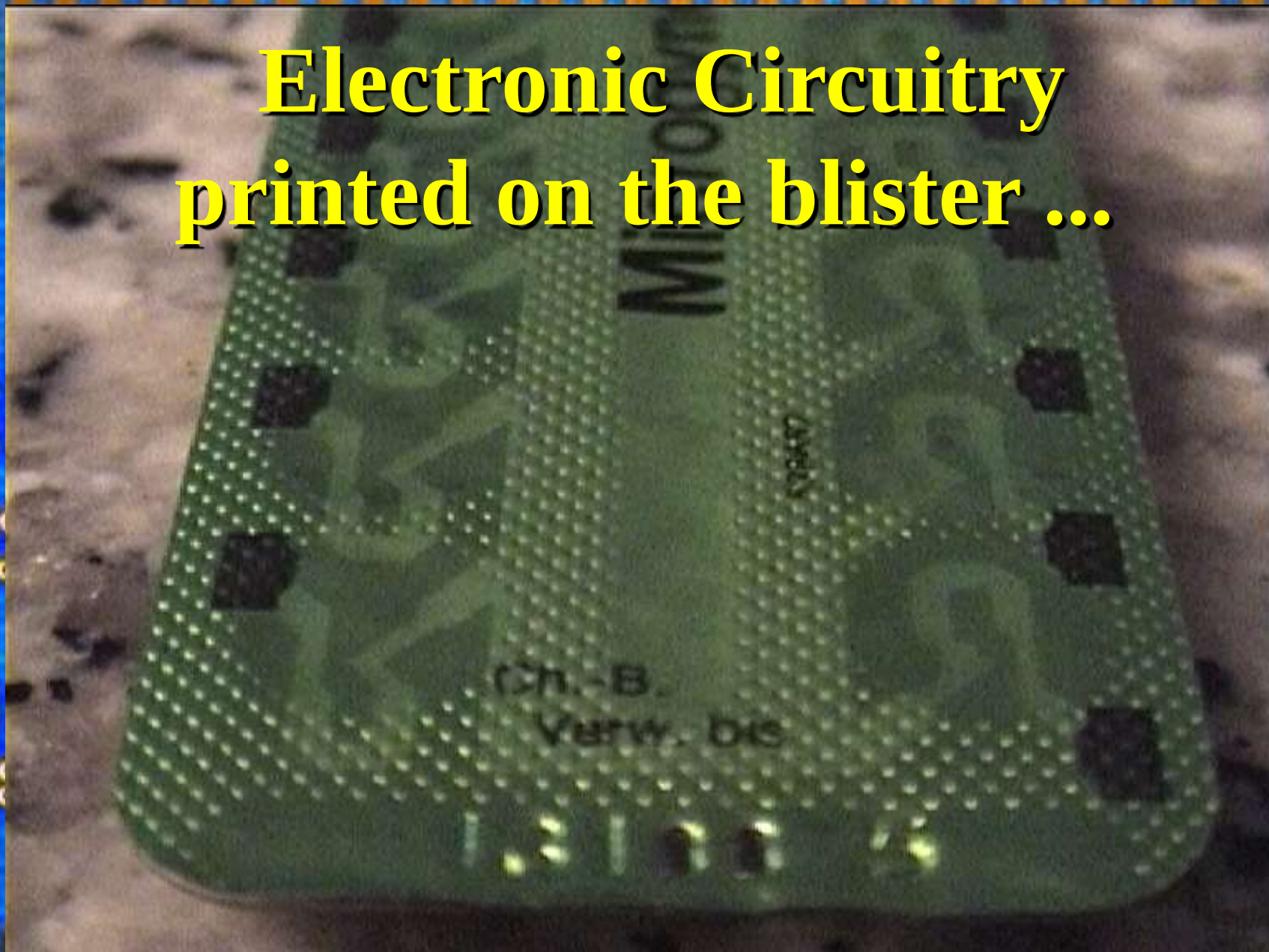
Pilot to enhance compliance

- Netherlands, 20 pharmacies, 200 patients, 1200 Diovan smart blisterpacks
- Normal commercial Diovan blisters
- Measuring compliance vs. lowering of blood pressure
- Duration 6 months
- Contract signed, waiting for regulatory OK
- Average normal compliance is 64%, 2. year only 50%
- Assuming only 20% improvement in compliance, 1000 patients would give additional sales of 99 000 € / year
- Smart blister packs in large series cost 3€ -> 36 000 € / y / 1000 patients

EUREKA!



**Electronic Circuitry
printed on the blister ...**



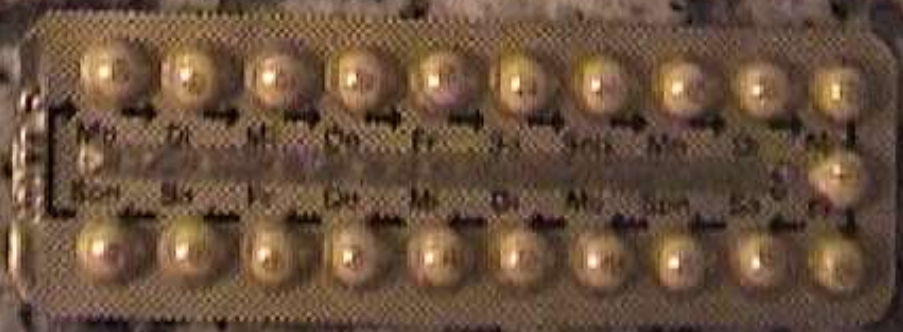
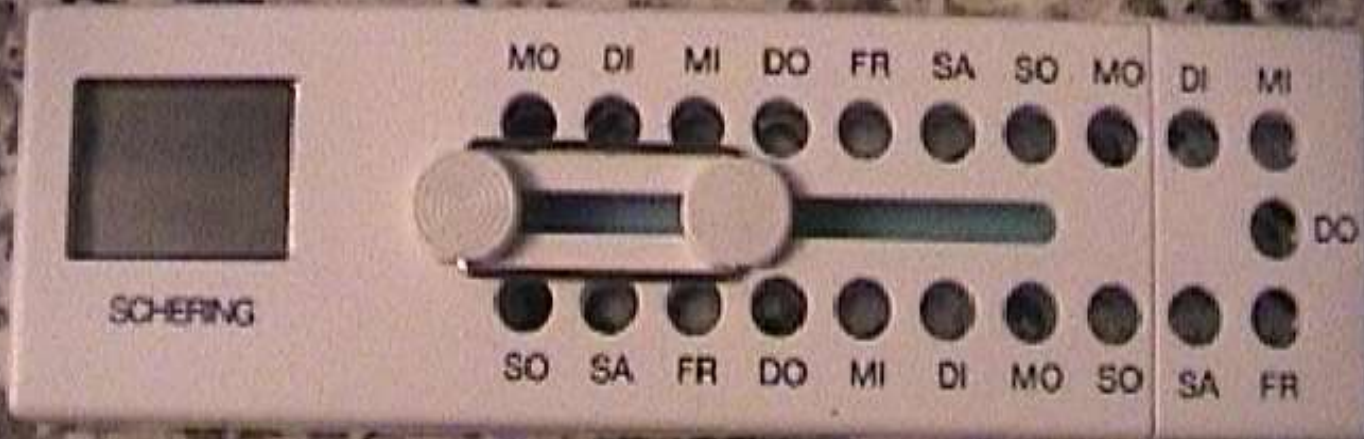
Microgynon 21

SCHERING

Microgynon 21

**Blister circuitry fits
circuitry in Blister monitor ...**

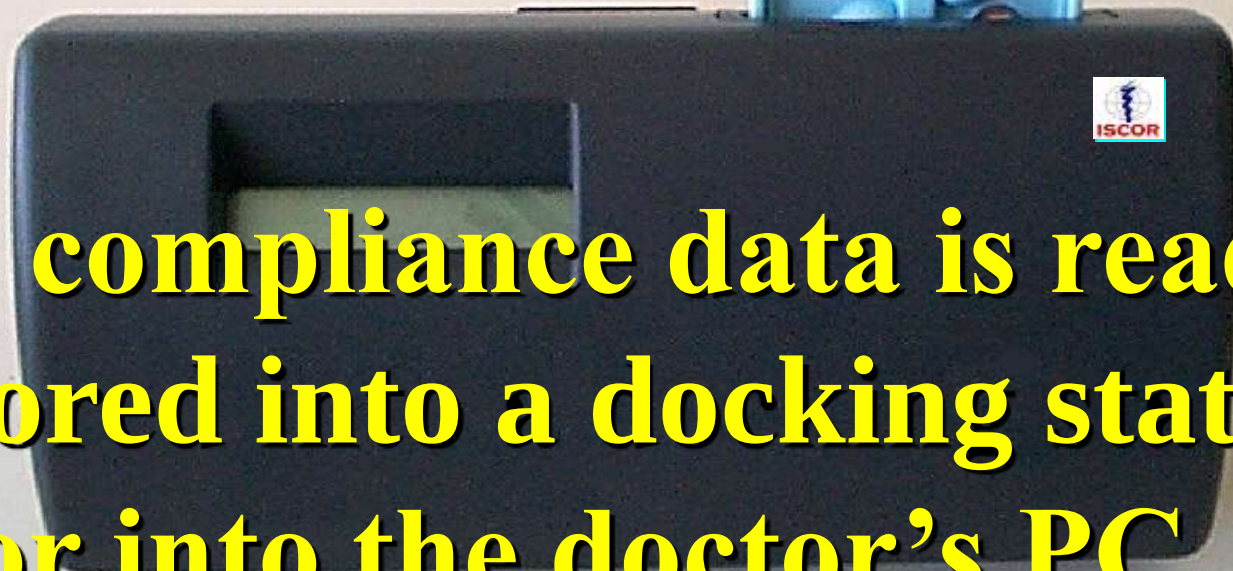




**Blister circuitry fits
circuitry in Blister monitor ...**



**When medication is taken,
blister circuitry will be
disrupted and an electrical
impulse is registered
by the computerchip for
time & date stamp ...**



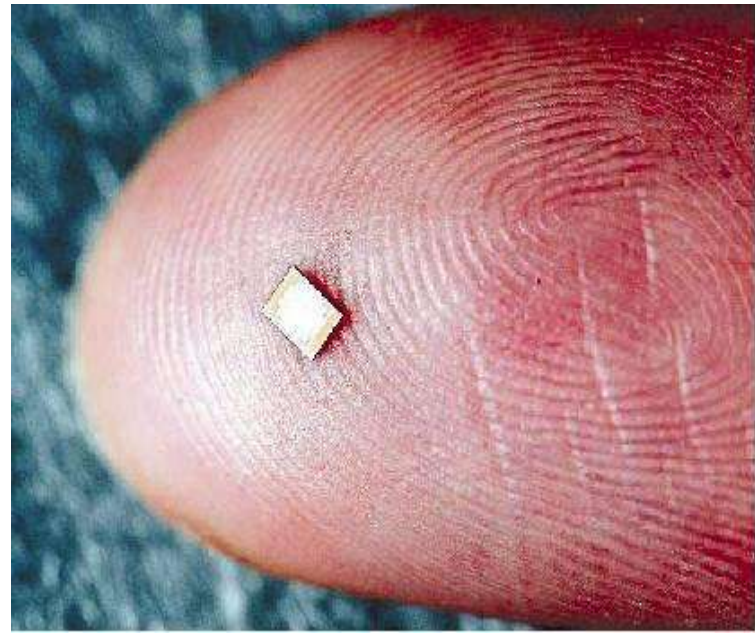
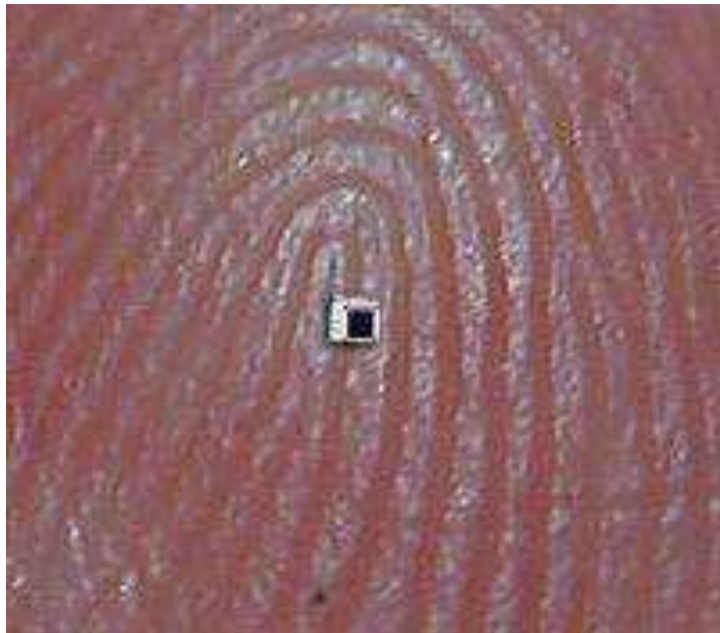
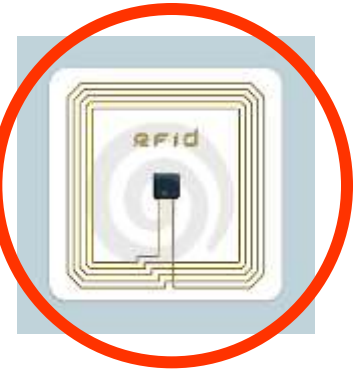
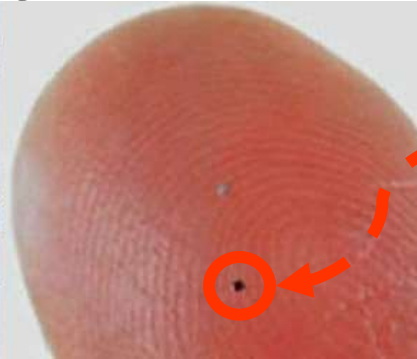
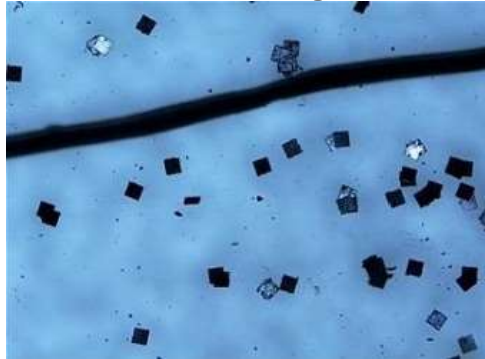
... compliance data is read & stored into a docking station or into the doctor's PC ...

EUREKA



RFID

Radio Frequency IDentification

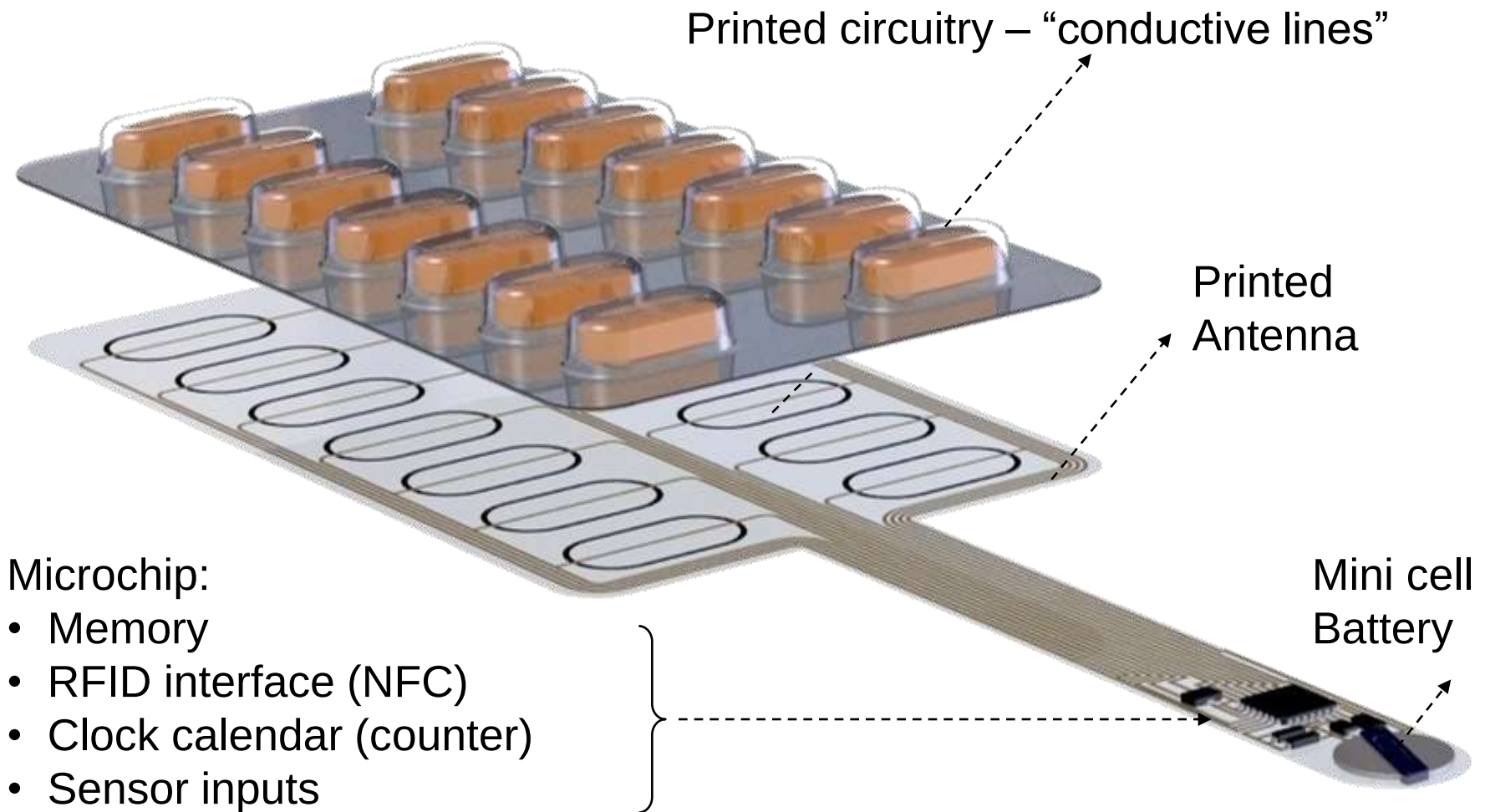


NFC

Near Field Communications



Anatomy of the Technology Principle ...



FANTASTIC PLASTIC

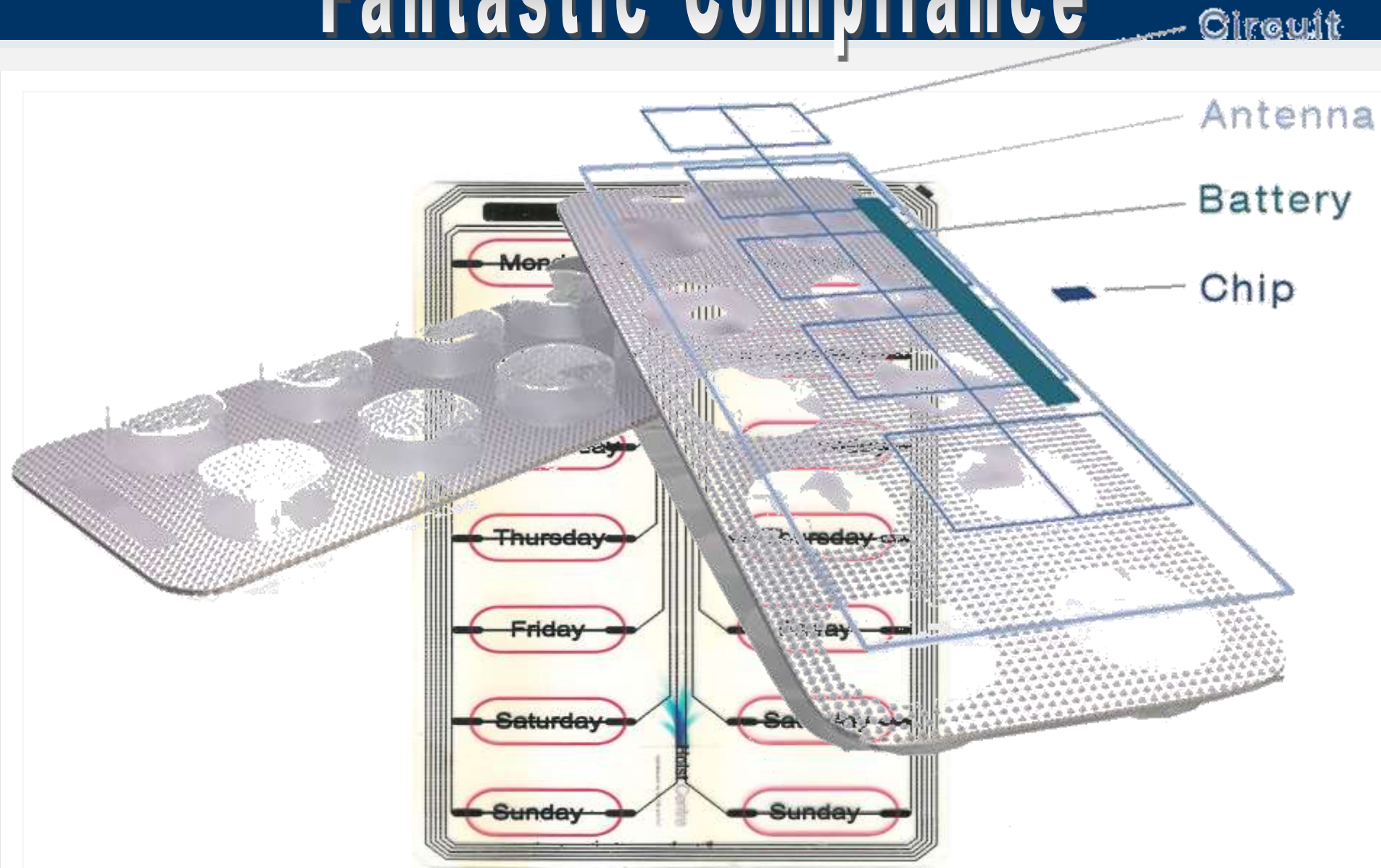
AN INVITATION TO PARTICIPATION

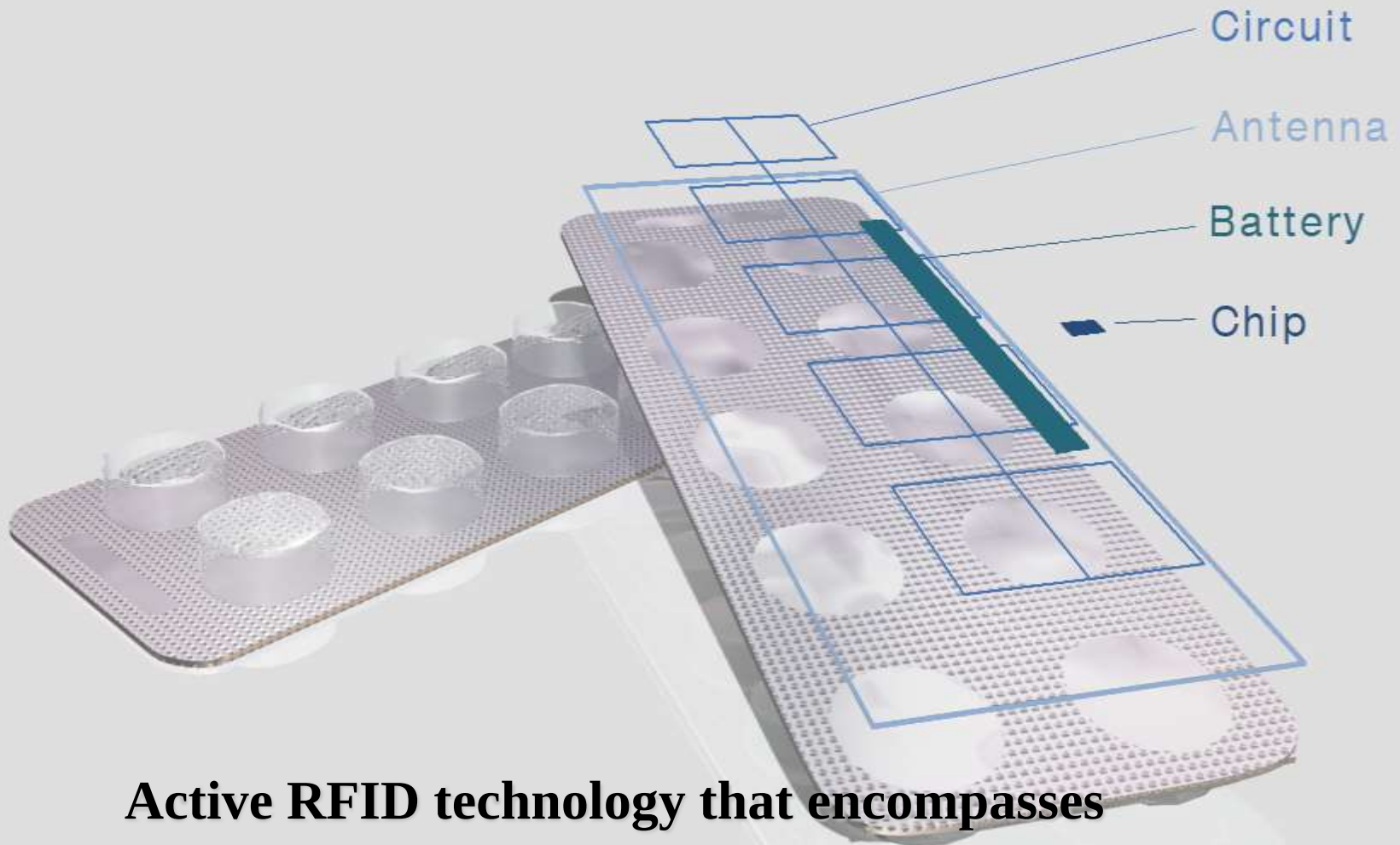


*But i always say, **one** is a company, **two** is a crowd and **three** is a party*

Andy Warhol

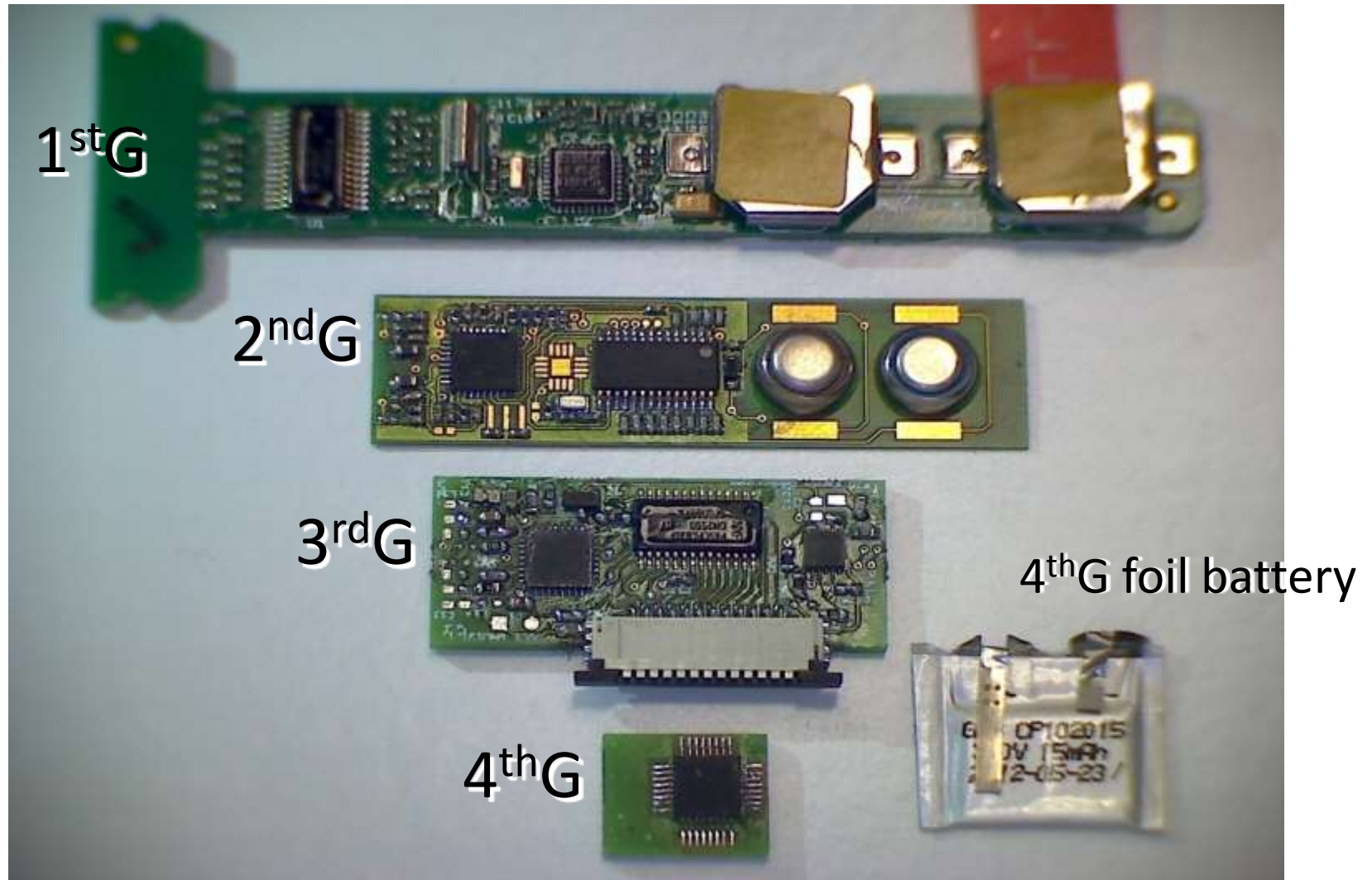
Fantastic Compliance



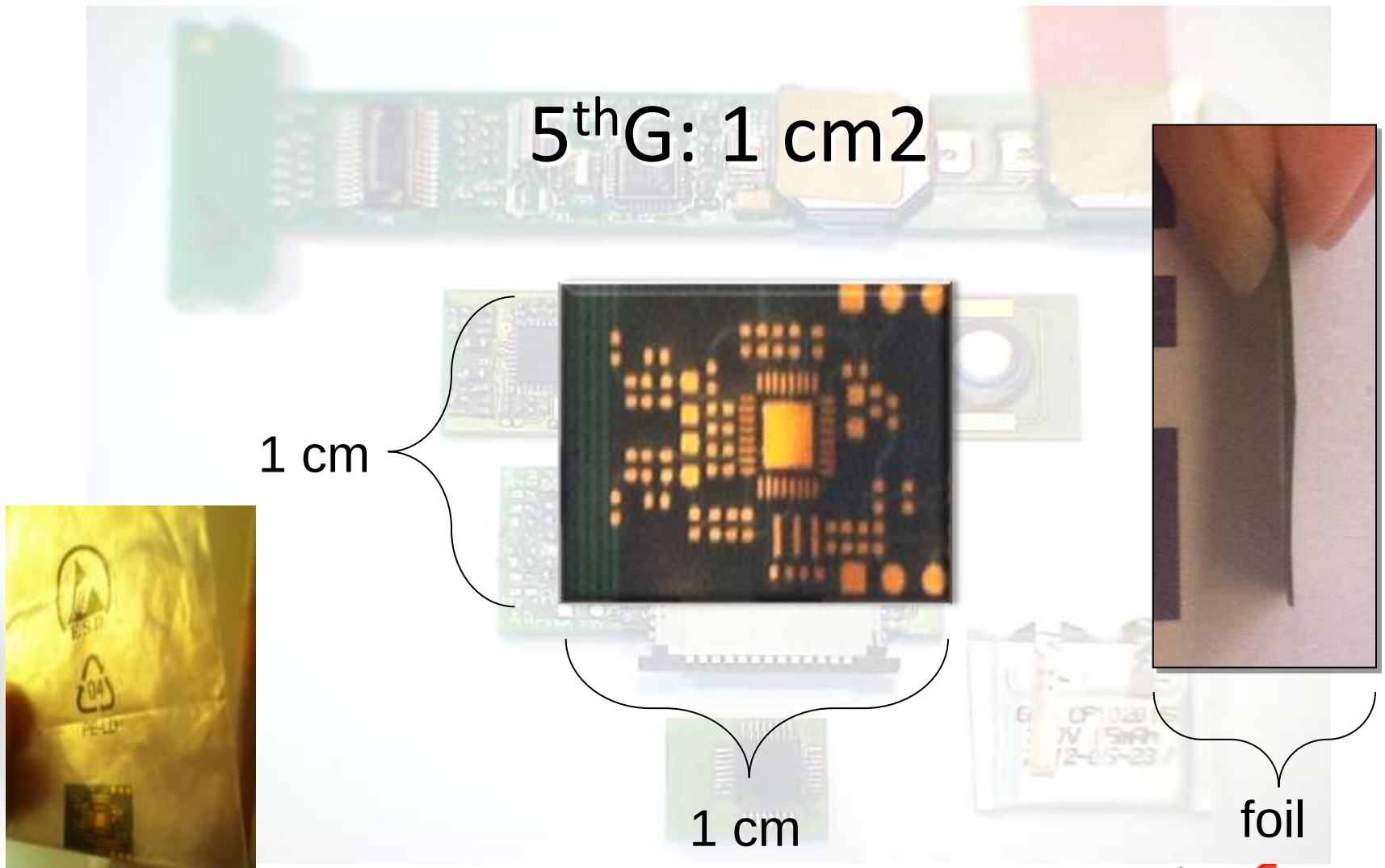


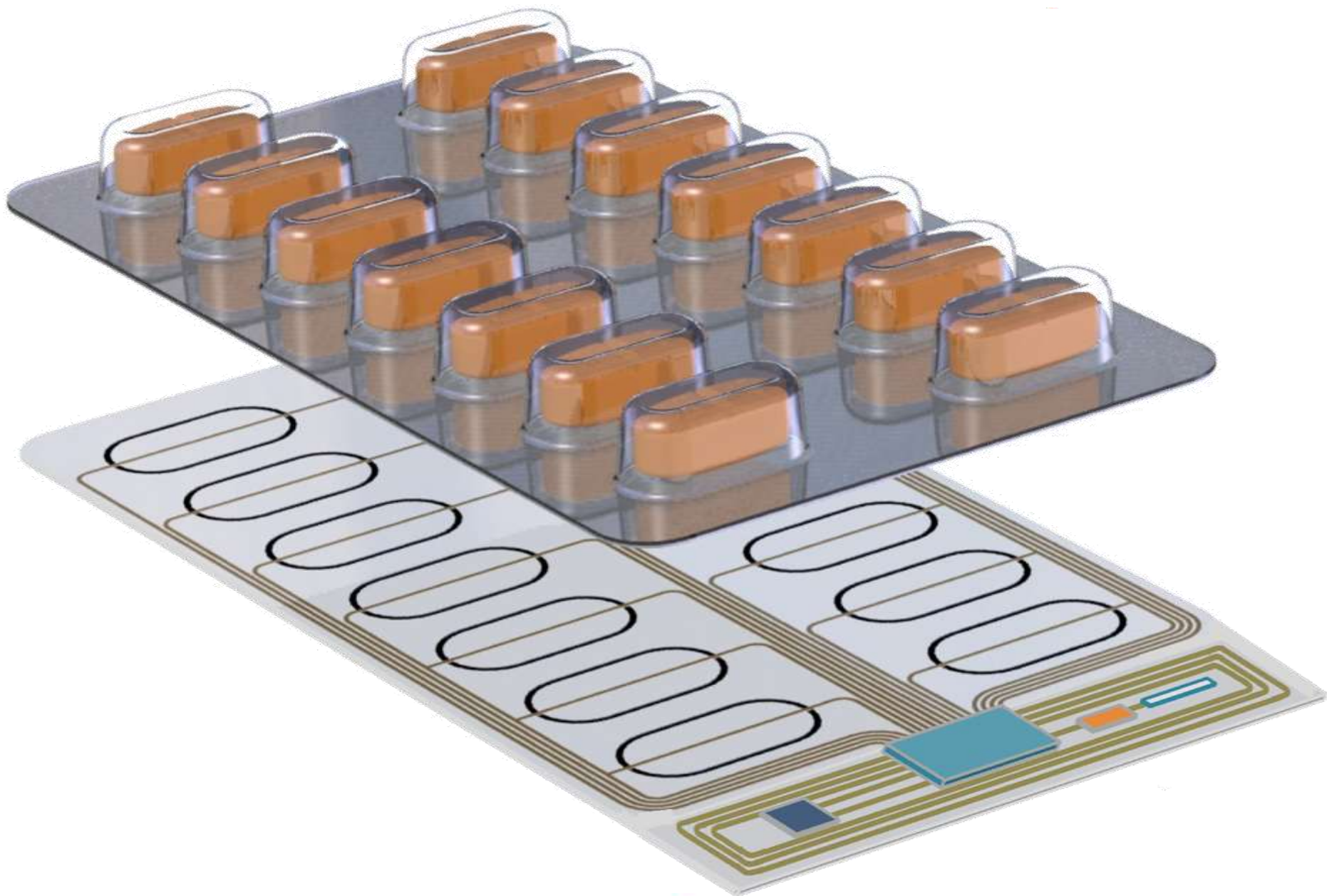
Active RFID technology that encompasses the standard, existing process of medication blister-packaging to fully benefit from therapy compliance measurement & monitoring right out of an existing, standard medication blister package.

Technology Generations: 4thG ...

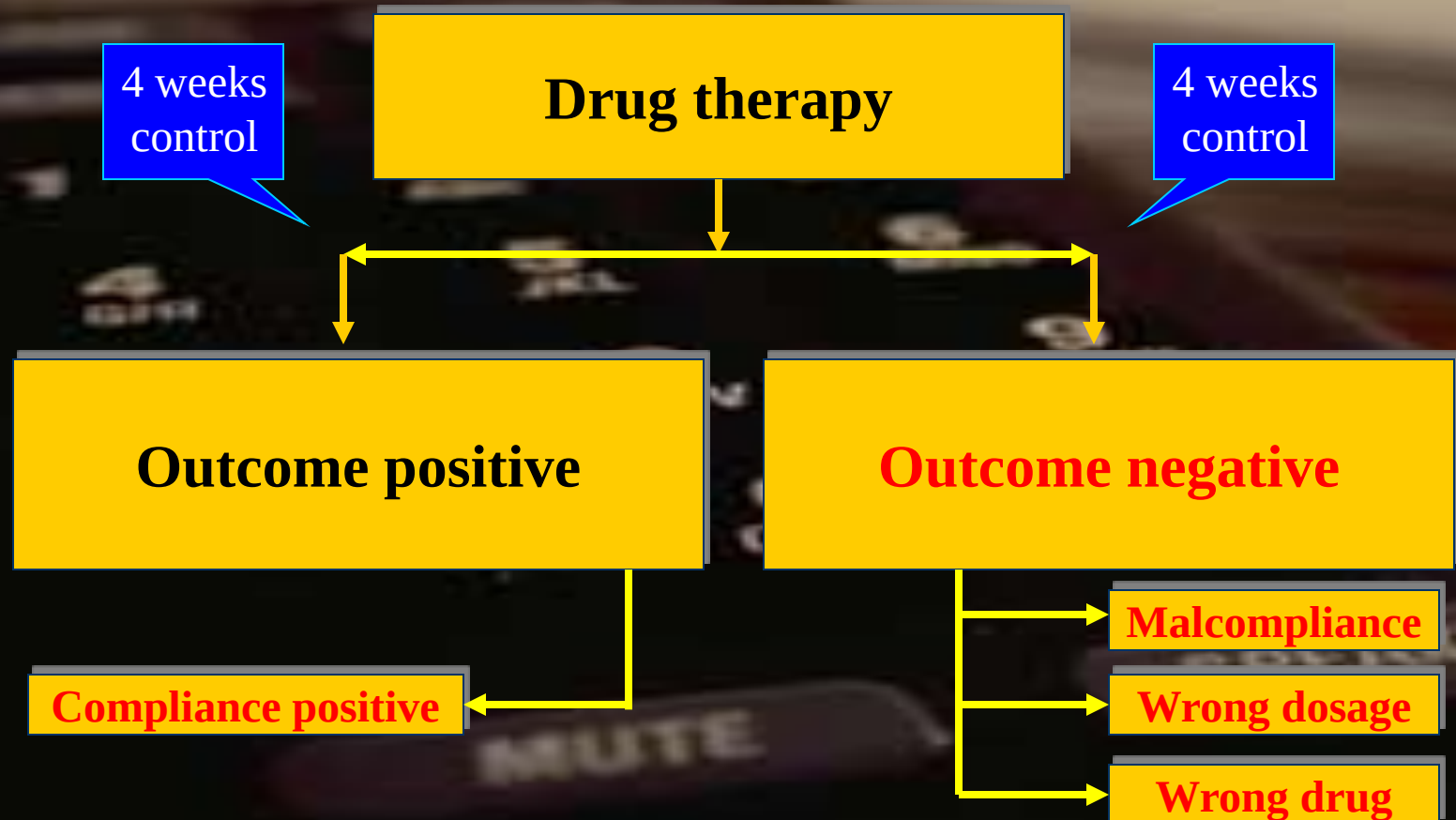


Technology Generations: 5thG todote ...

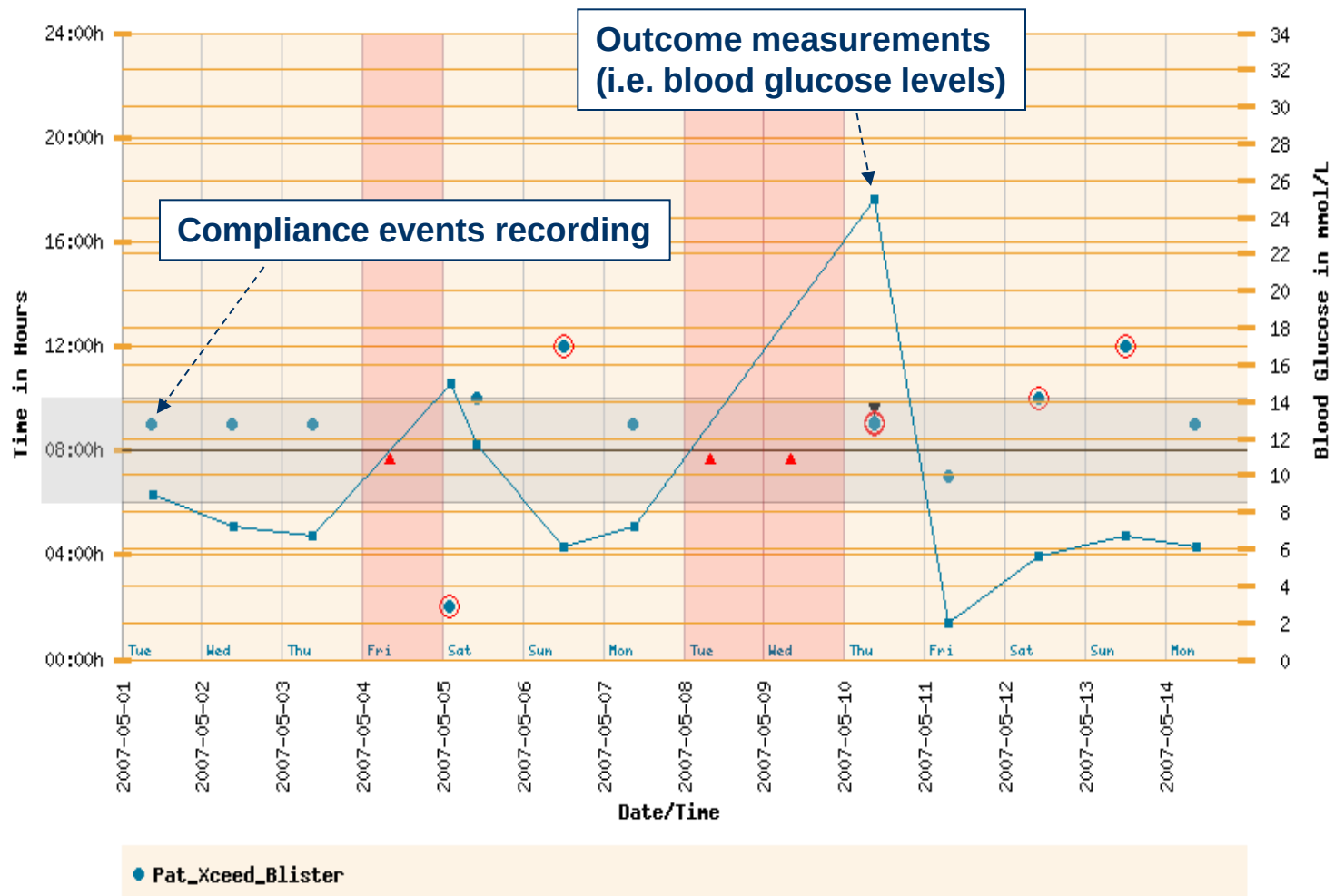




Compliance Monitoring: Correlating Compliance and Outcome



Example: Non-Adherence of Medication Taking in Diabetes³⁹



Live (clinical) trials: 2005-2006, the onset ...

Evidence of Functionality ...



OBJECTIVE THERAPY COMPLIANCE MEASUREMENT WITH AN ELECTRONIC BLISTER: A FEASIBILITY STUDY

Hein AW van Onzenoort¹, Cees Neef², Willem J Verberk³, Peter W de Leeuw⁴, Paul-Hugo M van der Kuy⁵



¹Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ²Department of Clinical Pharmacy and Toxicology, University Hospital Maastricht, Maastricht, The Netherlands; ³Microlife Corporation, Taipei, Taiwan; ⁴Cardiovascular Research Institute Maastricht (CARIM), Maastricht University and, Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands; ⁵Department of Clinical Pharmacy, Orbis Medical Centre, Sittard, The Netherlands

1st In-Package Therapy Adherence Monitoring: DIOVAN160, 2005, Novartis, NL



MEDICCONE
Compliance Controlled



> PAK VAN MIJN HART

> PAK VAN MIJN HART

> PAK VAN MIJN HART

> PAK VAN MIJN HART

Diovan
introduceert de
eerste verpakking
die kan **denken**.



THERAPIETROUW >



SMARTSTRIP >



STANDAARD SCANNER >



SCANNERSCREEN >

Er zijn veel initiatieven voor het verbeteren van therapietrouw
gevoeren - met uitstekend succes - maar het project **Pak van mijn
Hart** van **ePro Clinics** en **Diovan** lijkt toch wel heel kansrijk te zijn.
Het probleem bij (de controle van) compliance is natuurlijk dat er
zich zoveel buiten het gezichtsveld van de arts en de apotheker
afspelt. Namelijk bij de patiënt thuis. U kunt er nooit zeker van zijn
of de patiënt zich aan de **voorgeschreven situatie** houdt.

Daar komt nu verandering in. Diovan heeft samen met ePro
een 'slimme verpakking' ontwikkeld die **registreert** wanneer er een
tablet uit de blister wordt gedrukt. In de verpakking zit een kleine
chip die alles vastlegt. Zo kan
precies worden gevolgd hoe
trouw de patiënt zich aan de
voorgeschreven therapie houdt.

Hoe krijgt u de gegevens uit de verpakking?

De arts en apotheker zijn samen van **downloading**
belang voor Pak van mijn Hart. Immers, elke maand zal de patiënt
een **lege** verpakking gaan inwisselen bij de apothek voor een
volle. Dit is het cruciale moment waarop de gegevens worden 'uit-
gelezen'. Dit gebeurt met een **scanner (stand alone)** die in de

apothek staat. Als de bestandsverdracht correct is verlopen, dan
krijgt de patiënt een **nieuwe** verpakking. Dit lijkt misschien
omslachtig, maar in de praktijk werkt het erg **veelzijdig**: het enige
dat de apotheker hoeft te doen is de cor-
recte patiëntcode intypen en daarna de
verpakking op de scanner te leggen. Vanaf
dat moment gaat alles 'automatisch' en

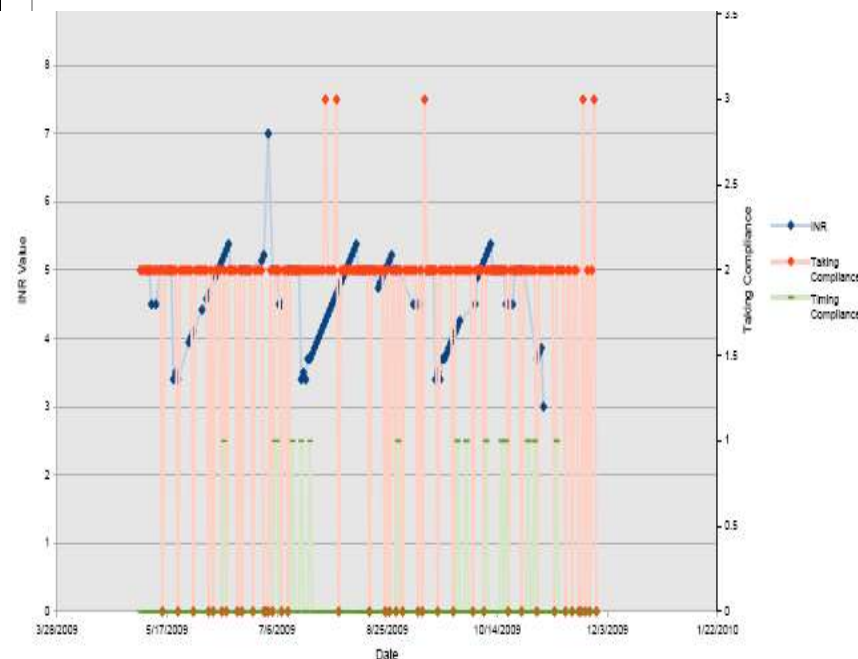


NOVARTIS

Live (clinical) trials: 2007-2010, 2 theses (Jekle, Zeiter) Evidence of Functionality ...



Prof. Dr. Irene Krämer,
University of Mainz
Pharmacy Department
Johannes Gutenberg-University
Hospital
Mainz, Germany



Conclusion:

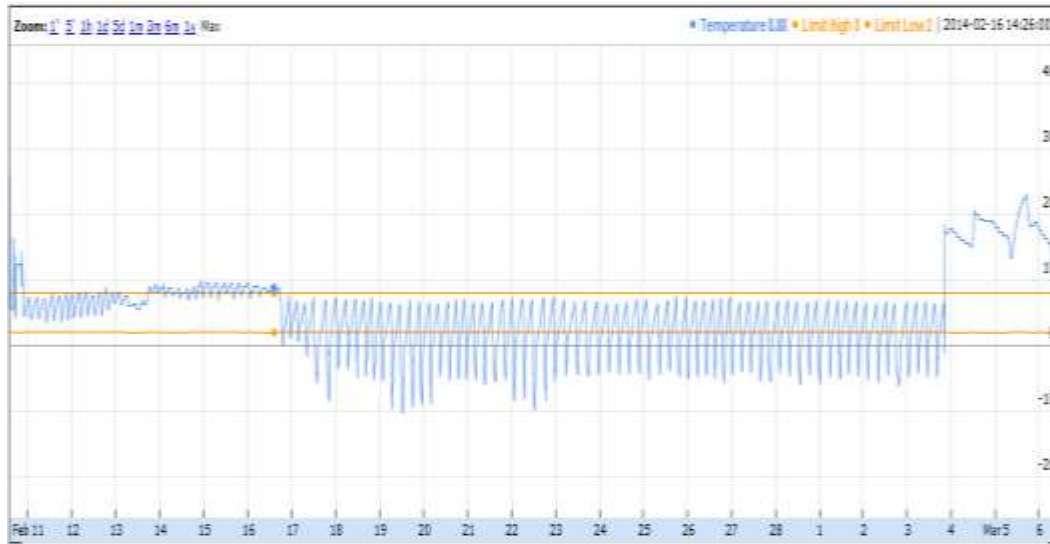
Effective therapy adherence leads to regular, tied INR values in chronic patients. MEDICCINE enhances the status required.

Assembly of the Technology onto Blisters ...



Smart blister (Phenprogamma study, UniMainz, 2008-2010, Prof.Dr. Irene Krämer et al.)

Pilot “Efficiency & Wastage of Returned Medication”, Evidence of Functionality re: T⁰-Monitoring ...



*Prof. Dr. Toine Egberts,
Prof. Dr. Marcel Bouvy,
University of Utrecht,
Department of Pharmaceutical
Sciences, Pharmacotherapy,
Utrecht UMCU, Netherlands*



Dr. Bart van den Bemt, Principal Investigator

“TTR” – Time in Therapeutic Range ...

“Time in Therapeutic Range” will be a innovative parameter for the Qualification Rate of Therapy Adherence, researched in concertation with LUMC’s Famacology Dept. and LUMC’s GMP Medication Packaging capabilities.



Prof.Dr. H.-J. Guchelaar, Dr. D.J. Moes

LEIDEN UNIVERSITY MEDICAL CENTER

Live (clinical) trials: 2008- ongoing (theses a.o. Walter, Boeni) Evidence of Functionality ...



Polymedication Electronic Monitoring System (POEMS):
Introducing a new technology as gold standard for therapy adherence measurement.



Philipp Walter
eidg. dipl. pharm

Fabienne Boeni
eidg. dipl. pharm

Markus Messerli
eidg. dipl. pharm

Dr. Markus Lampert

**Prof. Dr. med
Rudolf Bruppacher**

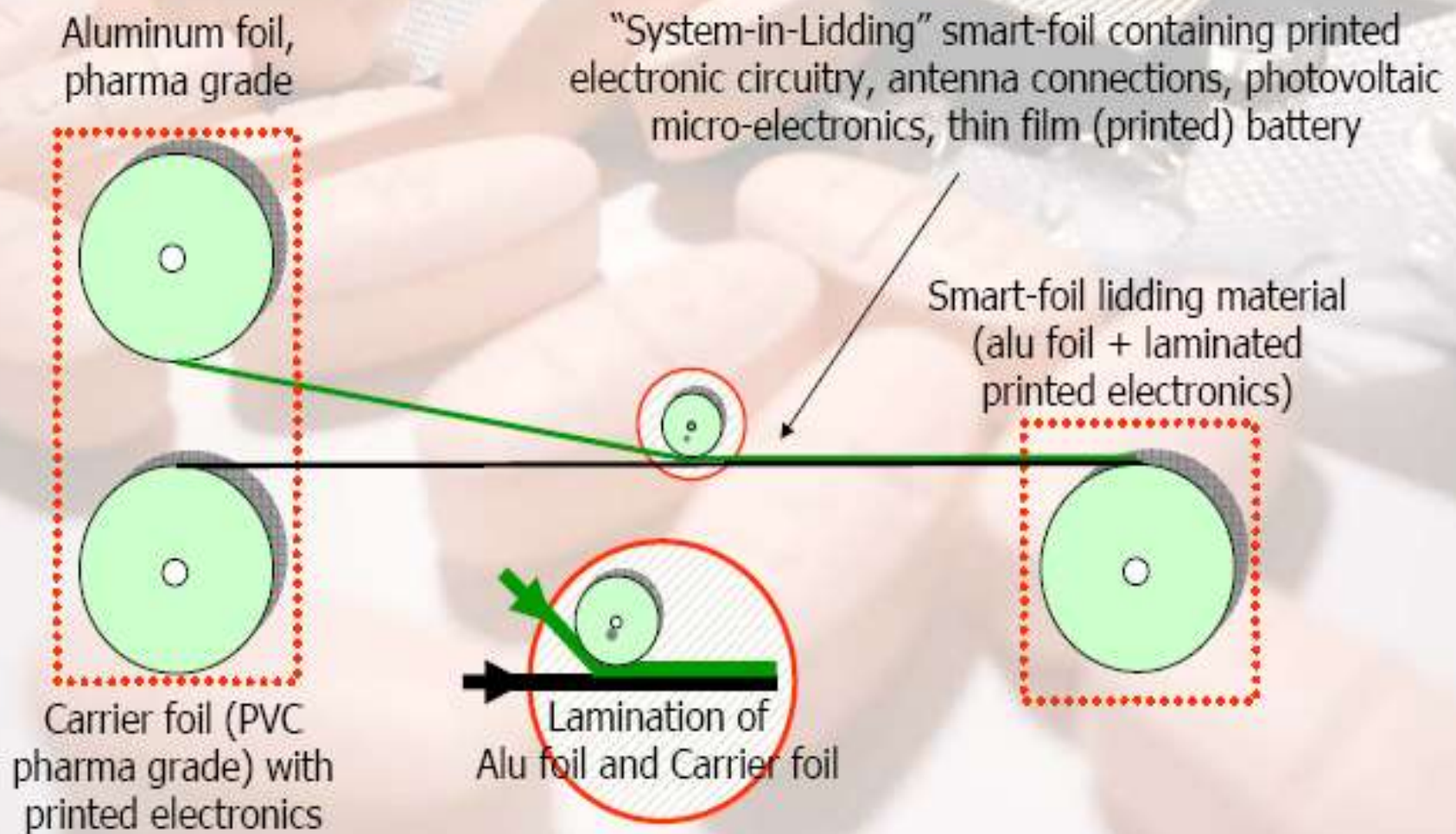


**Pharmaceutical Care
Research Group**

Promising Perspectives ...



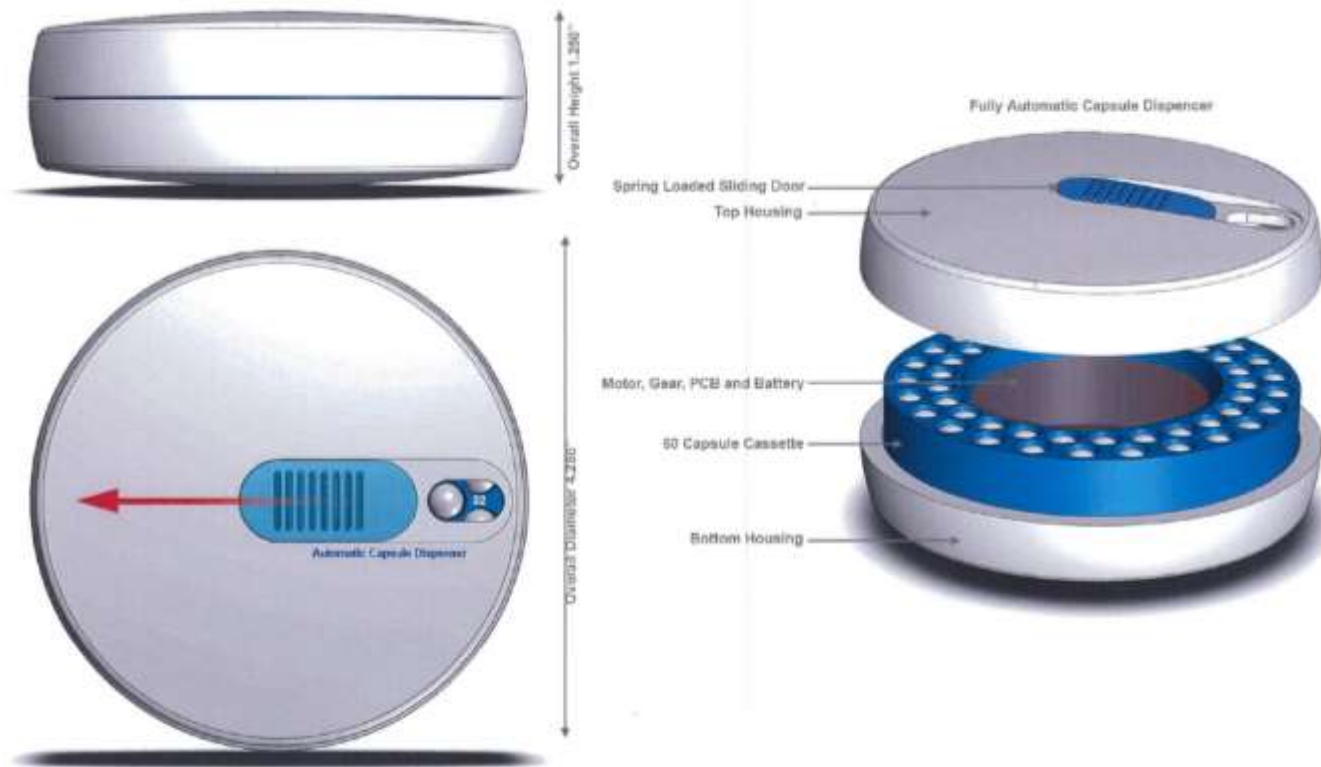
Medicicine™ Smart-foil Production (Lamination) process in appropriate Plant ...





Capsule dispenser: OMG!

50



Single unit capsule dispenser:

- Cap furnished with standard (blister) OtCM™ electronics,
- Cap fits standard capsule sizes, i.e. 00, 0E, 0, 1, 2, 3, 4,

Tablet /Capsule/Pill Dispenser: OMG!

51



Single unit dose dispenser:

- Cap furnished with standard (blister) OtCM™ electronics,
- Cap fits standard US medication bottle with standard neck finish, (GPI/SPI, Glass Packaging Institute/Society of the Plastics Industry)



Live Demo, Cell Phone via Chromecast ...



Right in front of us!

- *Most of the time a good solution is right in front of our nose ...*
 - *De facto, it is the “science” of Serendipity: finding a solution through opportune research ...*

“One Fine Day in the Good Old Jungle ...”

Right in front of us!



“One Fine Day in the Good Old Jungle ...”



Hippocrates

A phonecall a day, keeps the doctor away.

Plus or minus 2300 years past, Hippocrates, the Godfather of Medicine, gave early warnings of medication non-adherence to his students and peers: Rx-infidelity*.

Non-adherence is a problem that disrupts the healthcare system in many ways. If medication is not taken as prescribed, odds are that full benefit of a treatment is not derived.



As of now a new technology has arrived that dramatically increases the adherence rates for patients. The name is MEDICCINETM, smart medication packaging, to objectively measure therapy adherence, using the most recent RFID/NFC microchip technology (NXP Semiconductors) and taken up by pharma companies for mass volume commercial medication packaging.

A commercially available medication blister of any Rx-drug is furnished with a microchip label that provides the intelligence to identify when a tablet, pill or capsule is taken. This "time & date stamp" is stored and can be "scanned" with the MEDICCINAPP™ that runs on any Smartphone, whilst it is sent to MEDICCINETM, the expert database on mobile Internet.

At last, 2300 years after Hippocrates, patients and their doctors have a practical solution to avoid therapy non-adherence. Moreover, health risks can be prevented and medicines work more efficaciously. And, not in the least, colossal healthcare costs are saved!

*On Regimen of Acute Diseases, by Hippocrates of Cos

Finally, there is a remedy against infidelity

CONFRÈRE CLINIQUE
observance médicamenteuse de thérapie **TRANSNATIONAL**

De Run 4312-C 5503 LN Veldhoven (Eindhoven) The Netherlands

Phone: +31 (0)40 3524764 Cell Jos Geboers: +31 (0)6 53265347 Cell Willem Kort: +31 (0)6 43014695

www.confrerie-clinique.com



Hippocrates

Finally a prescription that cures infidelity.

Plus or minus 2300 years past, Hippocrates, the Godfather of Medicine, gave early warnings of medication non-adherence to his students and peers: Rx-infidelity*.

Non-adherence is a problem that disrupts the healthcare system in many ways. If medication is not taken as prescribed, odds are that full benefit of a treatment is not derived.



As of now a new technology has arrived that dramatically increases the adherence rates for patients. The name is MEDICCINETM, smart medication packaging, to objectively measure therapy adherence, using the most recent RFID/NFC microchip technology (NXP Semiconductors) and taken up by pharma companies for mass volume commercial medication packaging.

A commercially available medication blister of any Rx-drug is furnished with a microchip label that provides the intelligence to identify when a tablet, pill or capsule is taken. This "time & date stamp" is stored and can be "scanned" with the MEDICCINAPP™ that runs on any Smartphone, whilst it is sent to MEDICCINETM, the expert database on mobile Internet.

At last, 2300 years after Hippocrates, patients and their doctors have a practical solution to avoid therapy non-adherence. Moreover, health risks can be prevented and medicines work more efficaciously. And, not in the least, colossal healthcare costs are saved!

*On Regimen of Acute Diseases, by Hippocrates of Cos

A phonecall a day, keeps the doctor away.

CONFRÈRE CLINIQUE
observance médicamenteuse de thérapie **TRANSNATIONAL**

De Run 4312-C 5503 LN Veldhoven (Eindhoven) The Netherlands

Phone: +31 (0)40 3524764 Cell Jos Geboers: +31 (0)6 53265347 Cell Willem Kort: +31 (0)6 43014695

www.confrerie-clinique.com

Thank you ..!



The Achilles Heel of Healthcare ...
Overcome!