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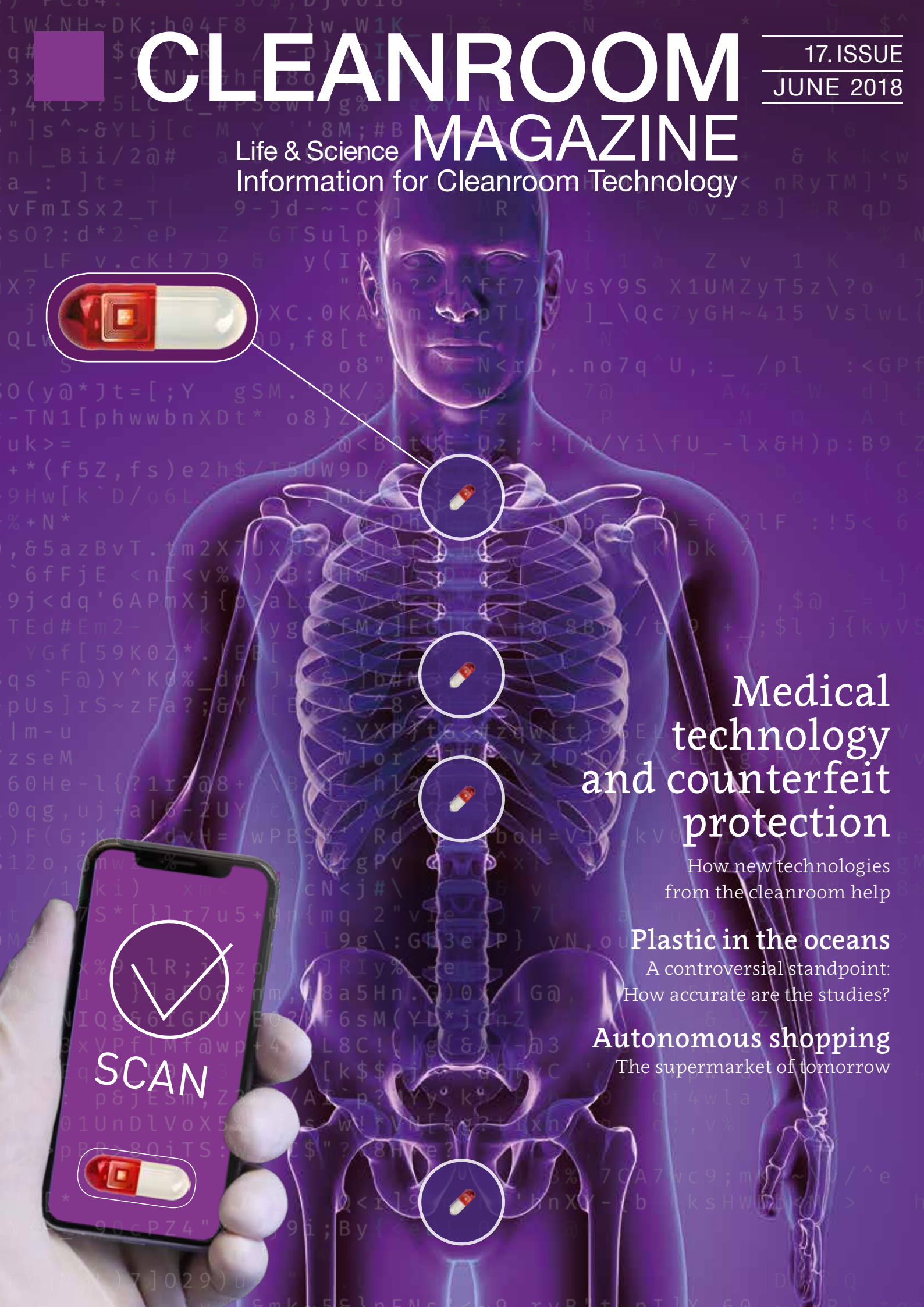

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Medical technology and counterfeit protection

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Which products are most affected by forgery worldwide? Luxury watches? Far from it. Designer jeans? More like it. Electronic parts? You are getting closer. Actually, medicines are leading forgery statistics every year. To change this, track and trace will be introduced to be able to better retrace the delivery routes of pharmaceutical packages from production to pharmacies. But this is only the beginning. Not only packaging, but also medicines themselves will become smart in the future and will merge biotechnology and electronics.

Corpus Delicti in a spectacular case of counterfeit medication in Germany: Omeprazol.

▶ For almost five years, they had deceived pharmaceutical distributors with counterfeit medication. Until the end, they had produced more than 600,000 packages of the stomachic Omeprazole. They had made revenues of almost 15 million Euros. Then, the first patient became suspicious. The information provided on the packaging and on the package insert were contradictive. This mistake blew their cover in February 2013. And then the group of German forgers from a town near Hamburg were busted. Their group, which included a trained pharmacist, executed their coup absolutely professionally. They had the medicines produced by a company in Spain that is also officially producing medication for the pharmaceutical industry. The brothers had packaged them in a warehouse into copied boxes of renowned manufacturers and had supplemented them with package inserts. Under the disguise of different company names, they had channelled the medicines through distributors.

Forgery is an international problem

According to Dr Reinhard Hoferichter from securPharm, "the proportion of counterfeit medication that enter legal distribution channels and thus get into pharmacies is very small. However, every forgery is one forgery too much." The forgers from Northern Germany had used the original API (active pharmaceutical ingredient). But this is rather an exception than the norm. "Counterfeit medication sometimes are of an unbelievably bad quality. In many cases, they are produced under hair-raising hygienic conditions. APIs are blended or replaced, in the worst case by harmful substances, in the second worst case with ineffective ones."

On a global scale, pharmaceuticals are the products most affected by forgery. Netnames, a company that have committed themselves to brand protection,

Dr. Reinhard Hoferichter, securPharm.

estimate the worldwide damage for the pharmaceutical industry in the amount of 150 to 200 billion Dollars per year. This has a particularly high impact on developing countries. World Health Organization (WHO) hypothesize that 10 to 30 percent of medicines are forged, for some pharmaceuticals, the proportion could be as high as 60 percent. "The damage dealt to the pharmaceutical industry is considerable, of course. However, the involved health risks are and will be more important", says Hoferichter. "And as forgery is not a national, but an international problem, the European Union stipulated the so-called Falsified Medicines Directive in 2011, which calls for a consistent forgery protection for the whole of Europe." According to this directive, all medicines subject to medical prescription that are traded in the EU have to be equipped with safety features.

Once per year, Interpol and customs authorities in more than 100 countries initiate a concentrated campaign against the illegal trade of pharmaceutical products.

European initiative ensures unambiguous coding of medicines as of 2019

The initiative securPharm is charged with implementing the directive in Germany. Leading associations of pharmacists, pharmaceutical manufacturers and wholesalers belong to this initiative. Hoferichter summarizes that "the smallest packaging units of all prescription medicines have to equipped with two safety features in the future: an unambiguous serial number and a tamper-evident safety seal." The serial number is included in a Data Matrix Code and will be sent to both national databases as well as to the EU hub. When a pharmacy scans the packaging, the system matches the serial number with the database. If it is either not listed in the data base or locked, the system triggers the alarm. When scrutinizing the tamper-evident safety seal, pharmacists furthermore determine whether the packaging has been opened before. In case this is applicable, they will take the product off the market, as the original medicine could have been replaced by counterfeit medicine.

Joerg Willburger is product and project manager for the field of pharmaceutical packaging at Bosch Packaging Technology.

"After implementing the new system, it will be much more an effort to introduce counterfeit medicines into legal distribution channels", says Hoferichter. However, the effort for players in the pharmaceutical industry should also not be underestimated. "To enable the matching of data when authenticating pharmaceutical products in pharmacies in every EU member state,

it was not only necessary to establish appropriate databases, but also to coordinate the IT infrastructure and to involve all stakeholders." On the other hand, manufacturers have to modify their packaging processes. The first step is the design of the folding boxes which have to provide enough space for the matrix code, followed by an upgrade of the packaging lines and finally the implementation of the new IT structure into the merchandise management system and other internal processes.

"To meet the new safety requirements, a solid interaction between pharmaceutical manufacturers and plant manufacturers is key", says Joerg Willburger from Bosch Packaging Technology. As product and project manager in the field of pharmaceutical packaging, he speaks from experience. "Serialisation requires pharmaceutical manufacturers not only to purchase packaging machines, but also the involved necessary IT services. In doing so, they are bound to certain distributors on a long-term basis. This is why not only their offer, but also the chemistry between them have to be right."

Modern packaging machinery equips pharmaceutical packages with Data Matrix Codes and tamper-evident safety seals.

feature an unambiguous serial number that effectively serves as a container for the codes of the single packages. "And also the pallets with the boxes are serialised. This means that the data base knows which package from which box, from which pallet is being scanned in a pharmacy." This is one possible and the only legal way how medicines are channelled from manufacturers to patients. However, there is another, covert way which leads across the globe via dubious email offers and shady internet pages

> »In the future, these processes have to be relocated from gray rooms into cleanrooms.«
>
> Kai Dürfeld, science journalist

Coding equipment is placed in gray rooms

The devices that add the data matrix code and the tamper-evident safety seals to the packaging are placed in gray rooms. This is because the medicines have already been packed into blisters or filled into vials at this stage. As single folding boxes are rarely sent off, they are bundled as larger package units. These larger boxes also

In the struggle against the illegal trade of medicines, there is an annual week of action that is called Pangea, just like the primeval supercontinent that connected the whole world. This action coordinated by Interpol involves customs and policy authorities form more than 100 states. More than 12 million vials, pills and capsules fell into their clutches in 2016. Their combined value: almost 47 million Euros. The proportion that was withdrawn from the market by German authorities amounted to 50,915 packages of illegal medicines. One year later, they seized about 67,900 packages of pills, capsules and vials. These are being offered on the internet. They are mostly shipped from India, China or Thailand, but also from Poland or Russia.

The El Dorado for counterfeiters of medicines: the internet

The trade in medicines outside state-approved, regulated and controlled channels is illegal. Therefore, customs authorities check all shipments on a random basis. If a shipment is intercepted, the recipient is caught in the crosshairs of the customs officers and becomes the focus of an investigation. A large proportion of illegally traded medicines contain little or no API at all. Often, the added substances present health risks or the conditions during their production do not meet any medical standards. But in spite of the sanitary and financial risks, internet trade is flourishing. Potency pills, hair restorers and slimming products, whose prescription is associated with a great sense of shame or hormones such as anabolic steroids which find use

beyond medical indication and whose prescription is therefore controlled scrupulously are particularly popular. In development countries, there is an additional high demand, mainly for antibiotics and malaria medications. According to estimates, approximately 450,000 people die of malaria every year because they take counterfeit medicines without sufficient medical effect.

According to Hoferichter, "the proportion of counterfeit medicines that enter distribution channels is very high." This is why additional measures for forgery protection would be sensible for pharmaceutical manufacturers, whose products are particularly affected by illegal trade. For example measures that do not target the folding boxes, but the very medicinal product inside them.

As stated by Willburger from Bosch Packaging Technology, "a whole range of these measures are currently investigated regarding their feasibility. This involves research of luminescent markers or artificial DNA, for example." During the latter mentioned procedure, the four bases, of which the molecule of life consists, can be assembled in any desired combination and added to the medicinal product. The analysis of the DNA and authentication of the code are nowadays not a problem anymore. "At the moment, it is not possible to assess which approach will gain acceptance. But it is certain that all processes in which tracers are mixed into the medical product have to be relocated from gray rooms into cleanrooms."

Another concept integrates a second typical cleanroom user into the process of counterfeit protection apart from pharmaceutics: microelectronics. Researchers are considering to equip medicinal products with razor-thin microchips. These chips are designed to carry information about the medicines. It would be not much of an effort to read the chips and confirm the authenticity of the goods. In contrast, it would be costly to forge them and therefore the expense would not be profitable for forgers any more.

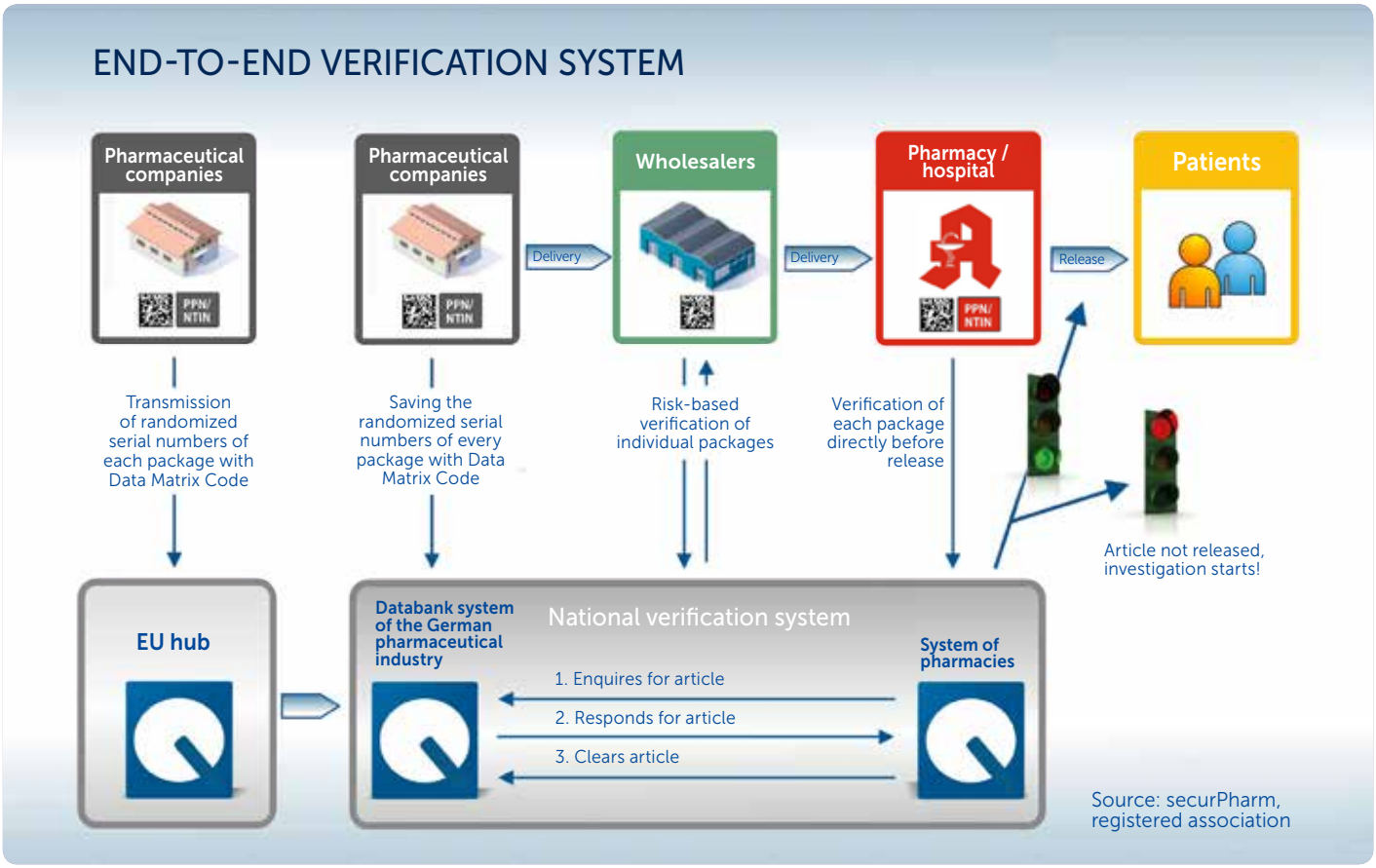
The first "smart pill" is approved in the US since the end of 2017

While microelectronics as counterfeit protection in medicinal products is still only a notion, there has been considerably more progress in another field. In November 2017, the US Food and Drug Administration (FDA) approved the first "smart pill". The American company Proteus Digital Health has developed the microchip for oral administration. It is applied in a medicinal product developed by the Japanese pharmaceutical manufacturer Otsaka, which is administered for the treatment of schizophrenia and other severe depression. Electronics have a simple task in this treatment: controlling the regular intake of the medication. To facilitate this, the pills send a signal as soon as they get in contact with gastric acid, which is received and evaluated outside of the body. This could proof vital for patient survival. Physicians could analyse treatment success in more detail. And it could also have a relieving effect for healthcare systems, as every medication that is not taken causes costs. A study showed that these costs amount to approximately 13 billion Euros per year in Germany. More companies have long since jumped on the bandwagon. For example, the miniature sensor called IDTag, which is produced by the American company etectRx, will be embedded in hard gelatine – or hydroxypropyl methylcellulose (HPMC) – capsules. It also provides information on the recent intake in the patient's stomach and is egested naturally after successful completion of its task. At the end of 2017, the system was chosen for a large scale study that investigates the medication discipline in HIV risk groups.

> »To control the intake of medication with smart pills is just the beginning though.«

However, controlling the intake of medication with smart pills is just the beginning. In the future, they will help to directly detect diseases in the body or transport medication. Google X, the research subsidiary of the Alphabet Corporation, for example count on magnetic nanoparticles, which dock on to disease-specific biomarkers in the organism and transmit their concentrations to a diagnosis module in the form of a bracelet. Rani Therapeutics, a start-up from the US, develop a "robot pill" filled with medicine. This pill transports its valuable cargo safely through the aggressive environment in the stomach. As soon as it arrives in the small intestine, it directly injects the medication into the intestinal wall.

Smart pills are still in the early stages of their development. But high investments, above all made by tech giants like the Google parent company Alphabet, already suggest their high potential for the medical market of the future.



A verification system is necessary for a check of all prescription drugs regarding their authenticity. In Germany, this system is set up by securPharm.

Interview: Can you connect carbon with silicon, Mr. Offenhäusser?

In biology, carbon-based cells have been studied; in microelectronics, there has been a focus on computer chips made from silicon. In bioelectronics, they have set out to connect both systems. Professor Andreas Offenhäusser at the Institute of Complex Systems (ICS) at Jülich Research Centre (FZJ) explains the involved challenges.

To merge biologic systems with computer chips sounds a little bit like science fiction. Professor Offenhäusser, since when is bioelectronics a scientific field of research?

First efforts in the field of bio-sensor technology were made as early as in the 1960s. These sensors combine electronic elements with biologic components and enable them to recognize certain substances. After this, there was a considerable development boost in the 1980s.

We at the institute specialise in neuroelectronics, which is the research of connections of electronics to the neural system. Furthermore, we are investigating biosensors, which work outside of the human body. A recognition reaction on the sensor indicates the concentration of certain biomarkers in blood. This is suitable to detect diseases such as heart attacks or malaria.

Does this mean that chips in your body will soon be as normal as a smartphone in your trouser pockets?

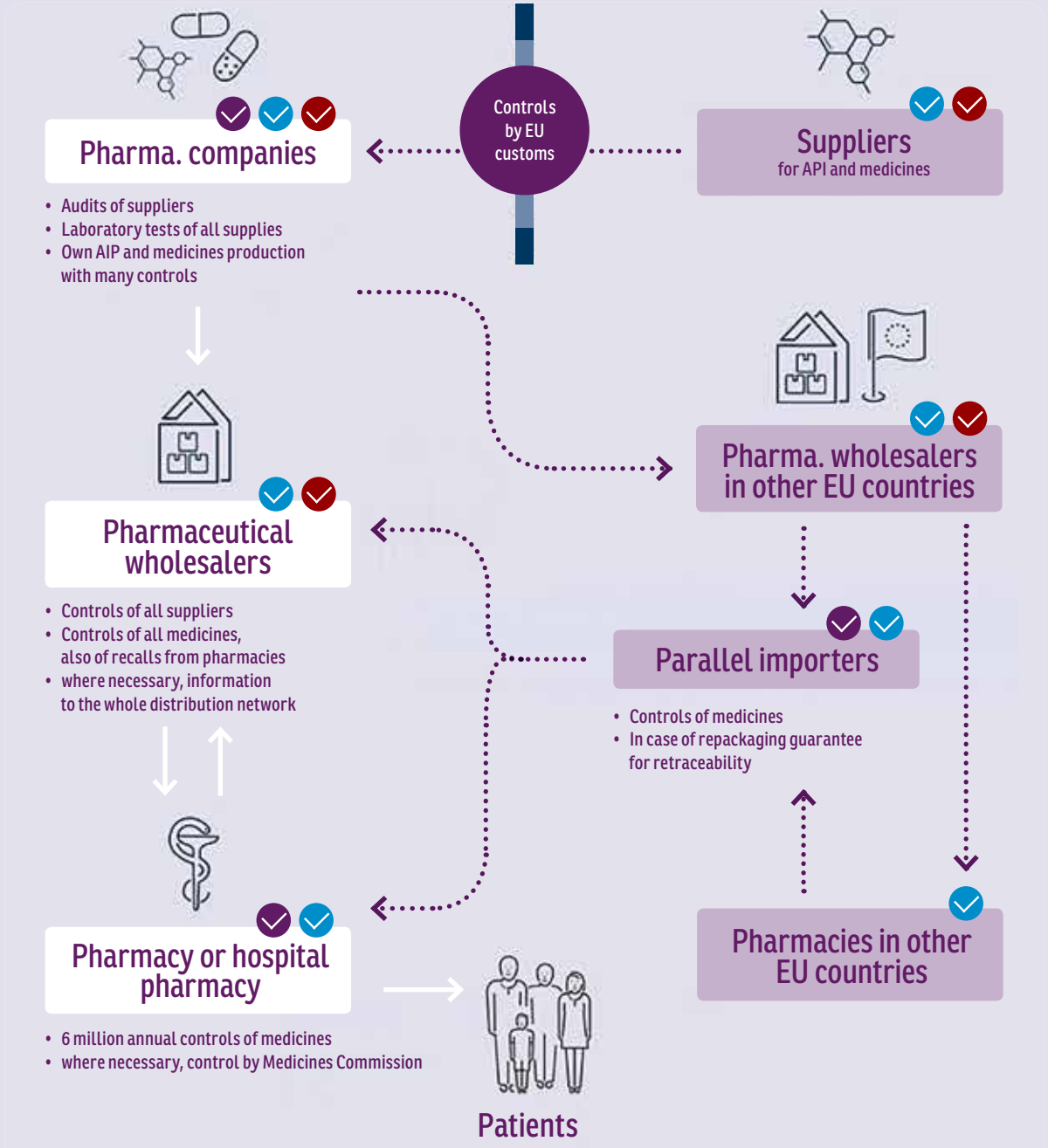
This will probably still take some time. Let's take the example of a glucose sensor. It is typically based on an electrochemical cell and stems from developments in the 1950s and 1960s. Although these sensors were introduced to the market quite early, they are nowadays still applied ex vivo, and therefore outside of the body in the majority of cases. There are first systems that are implanted into the skin and can be read out with smartphones. However, these are still exceptions.

The safe way of medication to patients

Controls by pharmaceutical companies

Controls by pharmaceutical wholesalers

Controls by drug authorities (EMA, BfArm, Paul Ehrlich Institute, local supervisory authorities)



Numerous measures within the supply chain protect the **legal distribution of medicines** against the introduction of counterfeits.

Since 2019, an IT system additionally protects the supply chain. The German part is set up by the organisation **securPharm**, which includes members of the pharmaceutical industry, wholesalers and pharmacies.

vfa. Die forschenden Pharma-Unternehmen

Where are the hurdles for bioelectric implants?
The greatest challenge still is to slip the body an implant without it even noticing it. It does not matter by the way whether this implant is artificial bone replacement material or a microelectronic component. When you introduce a foreign system into the body, it answers with a defence reaction. In most cases, the implant will be covered with according cells and will sooner or later fail to fulfil its function.

Let's take the example of the field of neural implants, in which we specialise at the institute. Currently, there are only a few that are approved by the FDA. And even these are only allowed to remain inside the patient's body for a few weeks. The problem here also is the defence reaction. With a neural implant, we introduce a material hard as steel into our body's softest area, which is our brain. Of course, the metal is moving and this in turn leads to a permanent irritation. It is comparable to poking around in a gummy bear with a fork, as I usually tell my students. This leads to micro-injuries in the brain. They trigger a defence reaction, the implant is encapsulated and after only a short time fails to work as it should.

What do you think are the most exciting developments in bioelectronics?
Particularly in neuroelectronics, I have high expectations regarding the developments of the next few years. The cochlea implant is working quite well already. Deep brain stimulation for Parkinson's patients represents a really successful system. And retinal implants are also on the market already, even though we still have to struggle with difficulties in this field. However, I think that the most exciting developments are new materials for bioelectronics. There are promising concepts in this field. On the one hand, these include very thin materials, on other hand very soft ones that are based on polymers. Probably hardness of electronic elements is a decisive factor for the defence reaction, as hard foreign bodies seem to present mechanic errors to the organism.


Prof. Dr. Andreas Offenhäusser.

Will not only our household appliances, but also our implants communicate in the future?
When I think of the Internet of Things, this is to be feared. [laughs] When all conceivable appliances in our households, at the office or in cars communicate with each other, why should this not also be the case for implants in the body? I think this will certainly happen.

And where do you perceive the greatest chances for bioelectronics?
On the one hand, I perceive them in personalized medicine, when a chip sends a signal like: the body lacks this and that. Please provide supply. Or: now, this medication is advisable and later another one. On the other hand, I perceive a great potential in bioelectronics when we consider the replacement of malfunctioning systems in the body. For example, when an eye fails to work, it is replaced by a CCD chip. Who knows, maybe the spare parts for aging bodies are produced in chip factories in the future? ■

Save the date!

Save the Date: Cleanzone 2018 with the main focus on "Safety in cleanrooms"

High health risks for patients, great economic damages to pharmaceutical companies: counterfeit protection and digital access controls are more and more important for the cleanroom industry. This is why Cleanzone 2018 puts the main focus on the topic safety in cleanrooms. Personalized medicine and its requirements for cleanrooms is another focus that has been set for the trade fair that will take place in Frankfurt from 23 to 24 October 2018. This is a field that is gaining more and more importance due to the implementation of bio and gene technology in daily healthcare practice and the resulting possibilities of individual diagnoses and therapies.