Techno Pharm Drug Delivery Devices

Primary packaging and drug delivery devices

Trends in the pharmaceutical market and implications for the supplier industry

Andreas Neumann • Gerresheimer AG, Duesseldorf

Korrespondenz: Andreas Neumann, Gerresheimer AG, Benrather Str. 18-20, 40213 Düsseldorf;
e-mail: A.Neumann@gerresheimer.com

Introduction

According to the World Health Organization (WHO) the worldwide expenditures on health in general grew from US$ 4.4 trillion in 2005[1] to US$ 6.5 trillion in 2012[2], which translates to a compound annual growth rate (CAGR) of 6 %. Respectively, the spending on medicines showed a comparable increase during this period of time. Following data of the IMS Institute for Healthcare Informatics the pharmaceutical market grew even slightly faster at 7 % – 8 % (CAGR from 2005 to 2011).[3] Undoubtedly, historical data are always important and trends can be derived from them. However it is also true what Wayne Gretzky, Canadian ice hockey icon, said: *"I skate to where the puck is going to be, not where it has been."* Thus, consulting latest forecast figures for the global pharmaceutical industry allows for an estimate of 4 – 6 % CAGR – resulting in an overall worldwide spending volume on medicine of US$ 1.2 trillion by 2016[4], or respectively US$ 1.6 trillion by 2020.[5] Other sources indicate worldwide prescription drug sales will grow at around 4 % CAGR between 2012 and 2018.[6] Global megatrends such as population growth and demographic change will result in rising demand for medication and will furthermore make this development relatively immune to economic cycles, like they did in the past.[7] Within these general trends the pharmaceutical market is gaining evermore complexity. Herein we can identify factors, which allow us to derive several implications for industries upstream the pharmaceutical supply chain. Some of the key developments and their direct or indirect impact on the areas of primary packaging and drug delivery devices will be examined in more detail in this article.

Pharmerging Markets

The pharmaceutical market is going through a transformation on a large scale, with quite a decent shift of regional focus. There is a substantial transfer towards the emerging markets observable, as the developed western countries slow down. This growth is mainly driven by the continued positive development in the Pharmerging markets.[8] While growth in developed markets[9] is relatively flat[10] – a solid double digit growth of 13 % – 14 % from 2011 to 2016 can be identified in these comparably young markets. Primarily the BRIC countries (Brazil, Russia, India, China) are driving this development[11]. In 2016 the mature sector will then account for 'only' 57 % of total spending (down from 73 % in 2006), while Pharmerging markets will reach 30 % of global expenditure (cf. Figure 1).[12] According to recently published figures from IMS, Pharmerging countries will all together add US$ 187 billion in annual sales between 2012 and 2017. This is two thirds of global pharma growth and will increase the Pharmerging markets' global share from 23 % in 2012 to 33 % in 2017, with all 4 BRIC countries in the top 10 by sales value (China will account for the bulk of this growth) (Figure 2).[13] In these emerging countries population growth is most evident[14] and accompanied by a prospering level of wealth – expressed by a growing middle class in this sector (cf. Fig-

1) World Health Organization 2005.
2) World Health Organization 2012a.
3) IMS Institute for Healthcare Informatics 2011; IMS Institute for Healthcare Informatics 2012.
4) IMS Institute for Healthcare Informatics 2012.
5) PricewaterhouseCoopers 2012.
6) Evaluate Pharma 2013.
7) Davis/ Philips 2007 and N.N. 2013a.
8) Term coined by IMS: Pharmerging countries are defined as those with >$1Bn absolute spending growth over 2012-16 and which have GDP per capita of less than $25,000 at purchasing power parity (PPP). Tier 1: China; Tier 2: Brazil, India, Russia; Tier 3: Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan and Vietnam, IMS Institute for Healthcare Informatics 2012.
9) Developed markets are defined as the U.S., Japan, Top 5 Europe countries (Germany, France, Italy, Spain, UK), Canada and South Korea, IMS Institute for Healthcare Informatics 2012.
10) PricewaterhouseCoopers 2012.
11) IMS Institute for Healthcare Informatics 2012.
12) IMS Institute for Healthcare Informatics 2012.
13) IMS Health 2013.
14) United Nations 2013.

TechnoPharm 4, Nr. 3, 138–148 (2014)

Figure 1: Spending on medicine by geography.

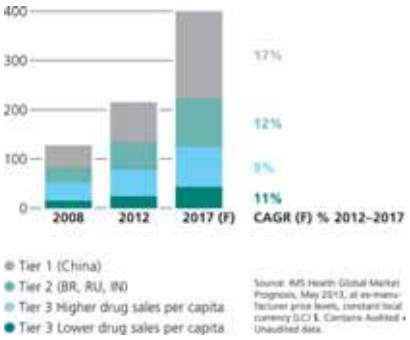

Figure 2: Pharmerging markets sales & growth.

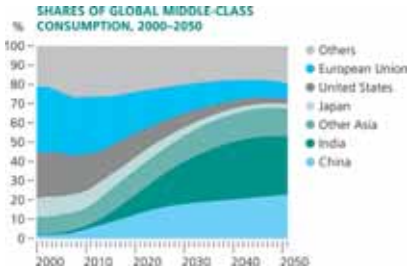

Figure 3: Global middle class.

ure 3).[15] With that millions more people are gaining access to basic medicines. As a result, general growth in medication volumes per se and hence increasing demand for primary packaging and drug delivery device units is foreseeable.[16] In order to serve the industry's needs, suppliers need to be present where pharmaceutical manufacturers are. Therefore, global presence and local proximity are essential for a reliable source of supply, ensuring smooth operations at the filling line. Moreover a robust risk assessment and risk-management capabilities across the extended supply chain have become an essential part of a pharmaceutical company's sourcing strategy.[17] Consequently the existence of several production plants means risk mitigation through back up capacities of upstream products.

Developed Markets

As mentioned above – growth rates in mature markets are comparably flat. However, this does by no means imply that these still very important markets[18] are stagnating. They are rather developing differently and undergo significant alterations themselves. *"It`s not how old you are, it`s how you are old"* (Jules Renard, French Author). First and foremost developed countries suffer most from the often cited demographic change and the resulting aging population (cf. Figure 4).[19]

Additionally epidemiological factors play a key role. Thus "rich people diseases" like obesity and diabetes are major problems for the developed countries. This outlook translates to an increase of chronic diseases diagnosed.[20] Obesity and age are both closely linked to more diseases and, sure enough, epidemics like diabetes, cardiovascular diseases or hypertension are permeating the western hemisphere.[21] According to the worldwide Diabetes Atlas of the International Diabetes Federation one adult in ten will have diabetes by 2030.[22] In the US around 11 % of the adult population are reported diabetics – rising to some 27 % of those aged 65 and older.[23] Accordingly healthcare cost are rising[24] and are condemned to do so further up to an unsustainable level. Following calculations of CEPTON Strategies, cost would reach 30 % of total GDP – if healthcare expenditure continued simply following demographics.[25] This trend reflects growing cost pressure and further need for outpatient and home care that does not require an overnight stay in a hospital. More therapies are being carried out in a patient's private surroundings. A growing number of drug regimens administered at home then again imply new challenges. For one, the need of protecting the youngest generation from accidentally taking the medicine requires more child resistant packaging solutions (cf. Figure 5).

In light of the above described aging population the older generation needs to be provided with senior friendly packaging features, to enable the elder to conveniently access and administer their therapeutics (cf. Figure 6). A combination of child protective and senior friendly packaging is a major challenge to address for the market players.

By all means, within the non-clinical settings at the patient's home, the process of self-administration[26] of drugs is inherent.[27] To support an accurate therapy via self-medication the drug delivery device and its design are therefore – more than ever – playing a major role. Human factors and a patient centric design approach are key to enhance convenience and ensure the necessary precision of dosage. To secure and leverage proven expertise in the field of packaging and delivery device design and industrial scale up (while at the same time being better able to focus on the core business), partnering is clearly a solution for pharmaceutical companies.[28] Longer term relationships and co-devel-

15) The size of the "global middle class" will increase from 1.8 billion in 2009 to 3.2 billion by 2020 and 4.9 billion by 2030. The bulk of this growth will come from Asia: by 2030 Asia will represent 66 % of the global middle-class population, Pezzini 2012.

16) Freedonia 2013.

17) PricewaterhouseCoopers 2011.

18) Canada, France, Germany, Japan, the UK and US still represent 59 % of the industry's total revenues, cf. PricewaterhouseCoopers 2012.

19) United Nations 2013.

20) Wenninger et al. 2011.

21) Bangert 2013.

22) International Diabetes Federation 2012.

23) PricewaterhouseCoopers 2012.

24) Greystone Associates 2013.

25) Müller 2012.

26) This means patients have to administer their medications themselves – without the help or supervision of a healthcare professional.

27) Kelly 2013; Research and Markets 2013.

28) N.N. 2012a.

Development group or major area	Median age (years) 1950	1980	2013	2050	2100
World	23.5	22.6	29.2	36.1	41.2
More developed regions	28.5	31.9	40.5	44.5	46.3
Less developed regions	21.4	20.0	27.2	34.9	40.6
Least developed countries	19.3	17.6	19.7	26.4	35.9
Other less developed countries	21.6	20.3	28.7	37.6	42.8
Africa	19.2	17.6	19.4	24.7	34.9
Asia	22.0	21.0	29.7	39.8	45.4
Europe	28.9	32.7	40.9	45.7	46.8
Latin America and the Caribbean	19.9	19.8	28.3	40.6	48.1
Northern America	29.8	30.0	37.7	40.9	44.6
Oceania	27.9	26.4	32.6	37.0	44.1

Source: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2013). World Population Prospects: The 2012 Revision. New York: United Nations.
Note: Only countries or areas with 90,000 persons or more in 2013 are considered.

Figure 4: Median ages of the world.

opment with partners that are savvy in design, development, tooling and high quality serial production can be identified as one main future stream in the industry. According to a recent study published by Transparency Market Research, the global medical devices outsourcing market is expected to grow at a CAGR of approx. 12 % from US$ 21.1 billion in 2012 to US$ 40.8 billion in 2018. Within this development, the product design segment holds the largest share with 29 %.[29)]

Evaluate MedTech predicts ~4 % CAGR for the drug delivery sector from 2011 – 2018.[30)] The need for a more patient-centric approach in the design of primary packaging and especially of drug delivery devices is also reflected by the general trend towards personalized medicine. Moving away from 'one size fits all' this model of customized healthcare is aiming at meeting more patient-group specific needs (cf. Figure 7).[31)]

By the same token this development promotes a trend in the direction of more individualization in devices. Not least because the delivery device is more often a patient's companion for many years and hence also a lifestyle product that needs to be designed accordingly.

The above stated fact that medications are more and more often taken at home and without the supervision of a healthcare professional presents another challenge – a patients' adherence to pharmaceutical care.[32)] Already today the rate of therapy compliance is low. Patients – for a variety of reasons[33)] – not sticking to their medication plan, cause tremendous costs to a society's healthcare system. A 2013 study of the IMS Institute for Healthcare Economics identifies an US$ 475 billion annual cost saving opportunity from using medicines more responsibly. Following this report non-adherence to medication provides the biggest lever to tackle the situation (cf. Figure 8).[34)] Enhancing adherence involves complementary use of educative, practical and emotionally as well as behaviorally supportive interventions. An increased level of information to improve transparency and to integrate the patient can be understood as one practical approach of advancing compliance. A higher level of information paired with a memory function can be achieved for instance by a dose counter functionality on an inhaler or other mechanical or electronic functions. In these regards the market will likely develop a demand of a smarter generation of primary packaging and drug delivery devices.

Figure 5: Child resistant packaging – closures (Quelle: Gerresheimer AG).

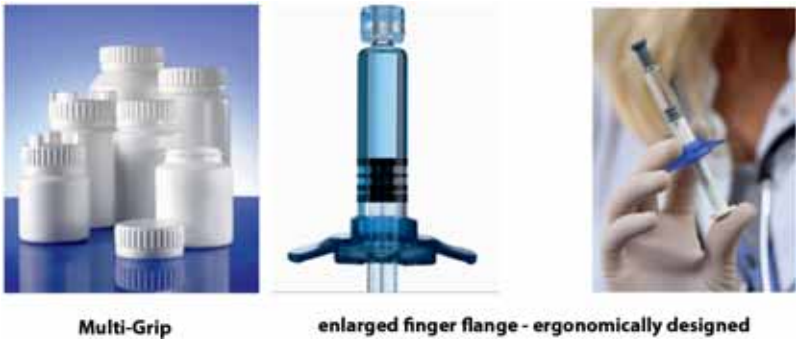

Figure 6: Senior friendly packaging (Quelle: Gerresheimer AG).

To give an example for an emotional inhibition threshold, preventing a patient from taking its medication one can cite needle phobia. *"Victims of needle phobia possess a high risk of morbidity and mortality as they avoid health care. The etiology of needle phobia lies in an inherited vasovagal reflex of shock, triggered by needle puncture. Individuals who inherit this reflex learn to fear needles through successive exposures to needles."* [35)] To circumvent the puncture by a cannula there are alternative technologies for

29) Transparency Market Research 2012.
30) Evaluate MedTech 2012.
31) Müller 2012.
32) Referring to a patient who does not take a prescribed medication or follow a prescribed course of treatment, cf. Nichols-English/ Poirier 2000.
33) Buston/ Wood 2000; Taddio et al. 2012; Nichols-English/ Poirier 2000.
34) IMS Institute for Healthcare Informatics 2013.
35) Hamilton 1995.

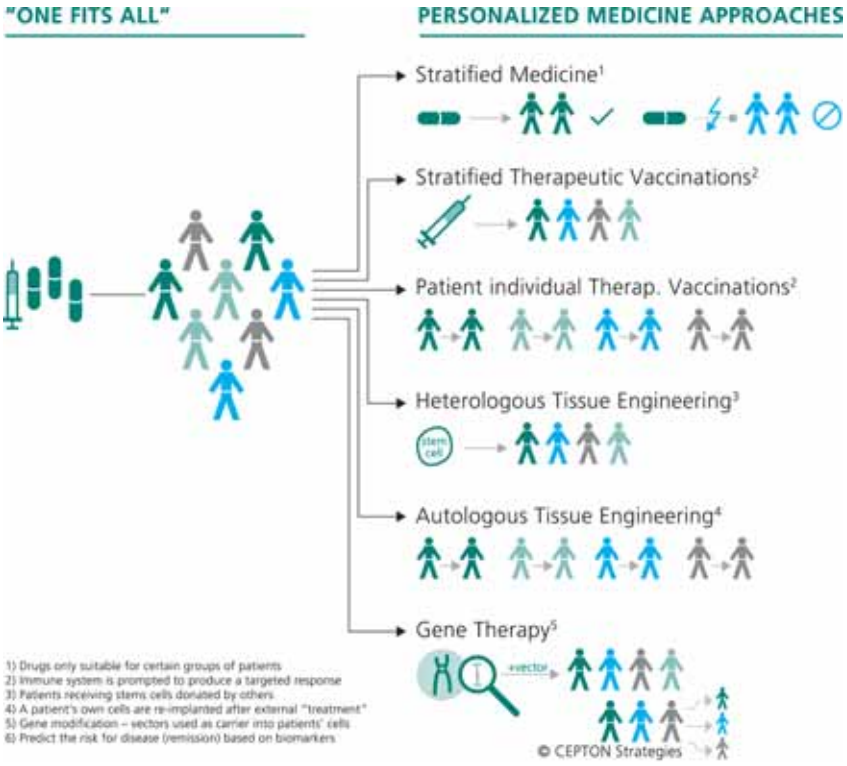

Figure 7: Scope of Personalized Medicine.

Figure 8: Avoidable healthcare cost – non-adherence is the biggest lever.

drug delivery available on the market (cf. Figure 9). A report by Visiongain predicts the global needle-free delivery devices market to be worth almost US$ 5.9 billion by 2022. The market generated sales of US$ 950 million in 2010 (16 % CAGR).[36] However, needle free does not necessarily mean painless[37], and in addition with delivery requirements of certain molecules and larger volume injections[38], this segment is facing its own challenges. Therefore, another alternative for needle phobic patients might lie in the advent of micro-needles to deliver compounds into the highly vascularized dermis. By entering the yet relatively underdeveloped market (according to Dubin, a report from Greystone Associates would put the microneedle drug delivery market at just under US$ 400 million globally by 2012[39]), pharmaceutical companies can differentiate their offering with a patient-friendly, easy-to-apply, low-hazard system.

In an assessment of the developed markets we – at this point – also need to emphasize the general trend towards higher quality standards and increased pressure from the legislative authorities.[40] The pharmaceutical industry is experiencing a period of heightened regulatory scrutiny – originating in the developed countries and effective globally.[41] As a consequence specifications and requirements for the packaging and administration devices of pharmaceuticals become tighter and grow in importance – working with an experienced partner enabling compliant packaging and drug delivery solutions is of paramount importance.

Lasting Patent Cliff & Genericization

One of the most relevant trends for the pharmaceutical industry in general and for 'Big Pharma' in particular, is the *Patent Cliff* [42]. While the first slump hit with some estimated US$ 30 billion branded sales loss in 2012 – which was as steep as never seen before in the industry – the years to come threaten with equally scary sales at risk (cf. Figure 10).[43] [44]

The expiration of a patent on a blockbuster drug can easily impact a pharmaceutical company's bottom line negatively into the billions[45], [46].

"If you're going through hell – keep going"

Figure 9: Needle-free injection system (DosePro® Zogenix) (Quelle: Gerresheimer AG).

– Winston Churchill, English statesman

Being well aware of this trend, the industry is as anxious as ambitious to navigate the patent cliff and invest accordingly. Figure 11[47] illustrates the market launches of European pharmaceutical companies in the

36) Visiongain 2012.
37) Chavan et al. 2013.
38) Tagawa et al. 2012.
39) Dubin N.D.
40) Moore 2013.
41) PricewaterhouseCoopers 2013.
42) a colloquialism to denote the potential sharp decline in revenues upon patent expiry of one or more leading products of a firm, cf. N. N. 2013a.
43) Iskowitz 2013.
44) Evaluate Pharma 2012.
45) Carroll/ Palmer 2012.
46) Stone 2013.
47) Henderson, BoA Merrill Lynch 2013.

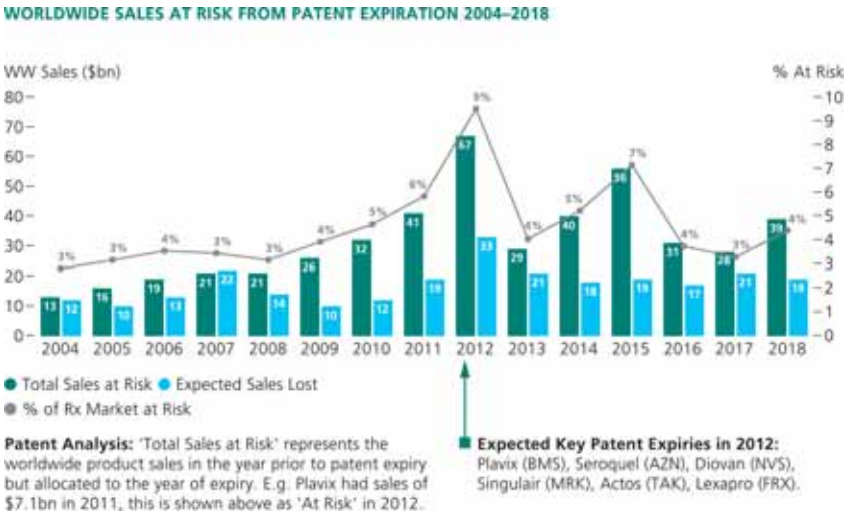

Figure 10: Patent cliff.

Figure 11: Filled pipelines.

years past and gives a prognosis of launches in the near future. In the U. S the Food and Drug Administration (FDA) approved 39 new molecular entities (NMEs) in 2012 – the most in 16 years. This trend would suggest that pharmaceutical players are poised for growth after losing billions of dollars in recent years to generic competition.[48] Most drug makers are also better prepared now and it is anything but rare to see them breaking the old 'Blockbuster-mentality' by introducing new business models and thus decreasing their dependency on only few products[49]. This shift towards more diverse portfolios[50] also requires a wider range of diversity regarding packaging.

Despite the fact that 'Big Pharma' is obviously better prepared (the PatentCliff did not come unannounced) it is generally true to say that Generic's growth with solid double digit rates in recent years was more than twice as strong than for the total pharmaceutical industry, hence a general movement towards Generics is evident in the market (cf. Figure 12).[51]

This trend is inevitably leading to increased volumes of Generic units sold. In 2011 already close to 50 % of the pharmaceutical market's volume (as opposed to its value) consisted of Generics – and the trend line is rising (cf. Figure 13).[52]

As a consequence one can read off this trend, there is stronger growth in primary packaging volumes foreseeable. In the course of this "Genericization" packaging plays an increasingly important role. Since generic products are – as a general rule – aiming at providing more cost-effective alternatives to originator brands, the packaging solutions for these drugs are rather standardized, high volume commodity. By the same token however they are providing qualitative protection and delivery of drugs to patients. The surge of copycat drugs also drives interchangeability of products. It is therefore of growing importance to demarcate otherwise similar products from one another. Mee-too products in the biotech area for example may use different drug delivery devices than their reference biologic originator product.[53] Drug delivery devices will be a key part of the biosimilar package required to differentiate from the competition[54] in a market promising significant volume effects (as observed with G-CSF in the UK and Sweden[55]). According to data from IMS this could drive up biosimilars' market growth considerably (cf. Figure 14).[56]

Figure 12: Generic sales and growth vs. total market growth.

Originator Drugs, New Launches & Specialty Therapies

By investigating the geographical origin of new chemical entities (NCEs) launched, we can see below in Figure 15[57] that developed countries – by far – still play the leading role. As a matter of fact, this is

48) Palmer 2013.
49) Bangert 2013.
50) PricewaterhouseCoopers 2011.
51) Lewis 2013.
52) IMS Health 2011b.
53) Taylor 2012.
54) Rotenstein et al. 2012.
55) IMS Health 2011a.
56) IMS Health 2011a; SU = Standard Unit = The number of standard "dose" units sold; G-CSF = Granulocyte colony-stimulating factor = a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream.
57) IMS Health 2013.

mostly due to significant challenges regarding affordability, protection of intellectual property and delays new drugs face in Pharmerging markets.

This trend is also reflected by the product mixes in Pharmerging and developed markets, which have developed very different from one another. Most of the top 20 brands in Pharmerging are older products (a large number of them > 20 years, some even 30+ years), targeting chronic diseases (like hypertension and diabetes). In the top 8 mature markets there is not a single drug among the top 20 that has been launched more than 20 years ago.[58] Venturing an outlook on the global development we will – by tendency – see the highest increase in the area of specialty drugs[59] (cf. Figure 16).[60]

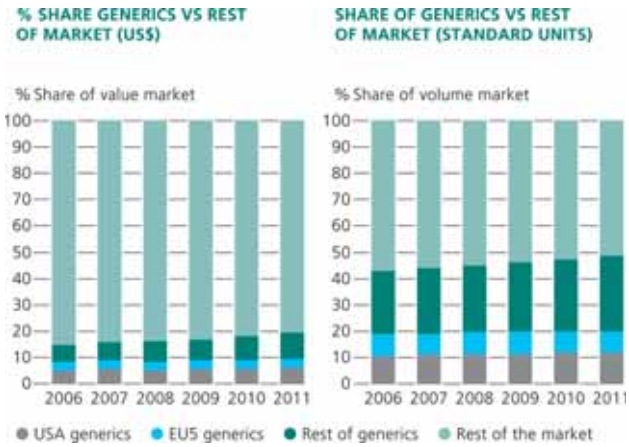

Figure 13: Share of generics: value vs. volume.

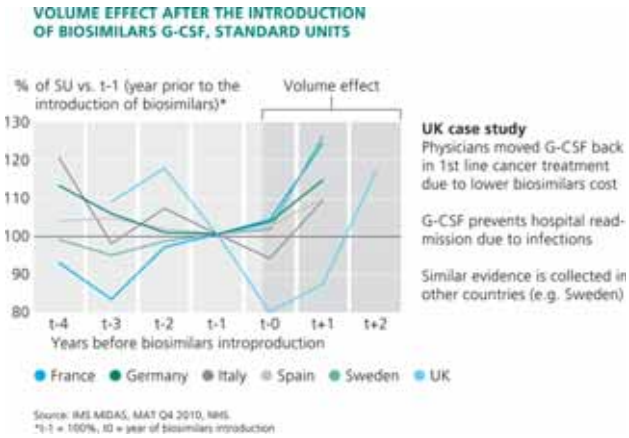

Figure 14: Volume effect after the introduction of biosimilars.

The sustainable growth in the biopharmaceutical sector yields potent drugs with a highly selective action. However these protein and peptide based drugs are complex molecules. Developing, storing and eventually delivering such therapeutics is challenging in many ways – especially regarding stability, pharmacokinetics and bioavailability.[61] Due to their specific properties biotech drugs require sophisticated drug delivery and primary packaging systems.

Drug delivery devices

Since the route of delivery of specialty therapies is almost exclusively via parenteral injection[62], drug delivery devices are being taken more into consideration and already at an early stage in the development of innovative medication. Following the above stated trend of individualization in healthcare, there will prospectively be smaller patient target-groups. This means more specific devices will evolve, leading to a greater diversity in form and design (cf. Figure 17). We will see further ergonomic shapes and functions, addressing human factors and permitting individual, accurate dosage for patients that may have an impaired motor function and self-administer their drugs in a non-clinical setting. Furthermore this innovative market environment – along with the industry leaving the blockbuster path and focusing on tighter disorder patterns like orphan diseases – will result in shorter product lifecycles.

Moreover, branded originator products face a rising need of differentiation and lifecycle management because of the generic and biosimilar competition (as outlined above).[63] As an instance of managing a product's lifecycle the switch of an injectable therapy's primary packaging container towards more sophisticated system (e.g. from a vial to a prefilled syringe), is still instrumental to optimize lifecycles. Although the drug is normally still understood as the main product differentiator, the drug delivery device is becoming increasingly important as another means of differentiation in more competitive markets.[64] Protecting a treatment as combination product[65] (by competition law) can provide a major competitive edge to the pharmaceutical company and also enhance a drug's economic lifecycle.

Primary packaging

Already for decades Type I Borosilicate Glass[66] provides several benefits to manufacturers of parenterals. It is of transparent clarity and therefore allows for visual inspection of the drug; it is inert against most sub-

58) IMS Health 2013.

59) Specialty therapies are products which are often injectables, high-cost, biologic or requiring cold-chain distribution, cf. IMS Institute for Healthcare Informatics 2012.

60) IMS Institute for Healthcare Informatics 2012.

61) Sacha et al. 2010.

62) IMS Institute for Healthcare Informatics 2012.

63) Dubey/ Dubey 2009.

64) Simpson 2012.

65) Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products. FDA expects to receive large numbers of combination products for review, cf. FDA 2013c.

66) Borosilicate glass is characterized by highest hydrologic resistance and lowest alkali leakage. It is regulated by three international paharmaceopoeias (USP, EP and JP) as well as the international standards ISO 719/720 and ISO 4802-1, cf. Petersen 2012.

Figure 15: Global launch sales.

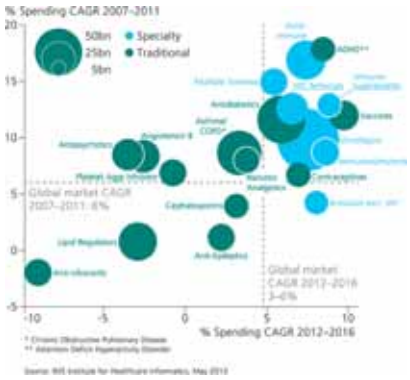

Figure 16: Spending and growth in leading therapy areas.

stances and stable almost infinitely, which translates to best conditions for storing and a long shelf-life. Its impermeability to water vapor and gases is adding to the expediency for injectable solutions. Together with the comparably long history of Active Pharmaceutical Ingredient (API) on the market with this material, the relatively favorable price proves that it is an excellent and lasting packaging solution.[67] However, there are also shortcomings which become even more important with regards to highly potent and sensitive modern drugs. Glass is comparably fragile and can break on the impact of mechanical stress.[68] Also the surface properties of a glass container are of utmost importance, particularly on the inner side in contact with the product. Extractable metal ions may leach depending on the pH value. Aqueous parenteral solutions with a pH value > 7 attack the glass surface. Under such circumstances the glass structure releases metal ions with potential adverse effects on the stability of sensitive biotech drugs.[69] In this context there is a need to debate the topic of delamination, where glass flakes may elute from the glass matrix' surface and thus contaminate the drug.[70]

Specialty drugs like biologics are mostly very expensive. One vial can easily cost several hundreds or even thousands of dollars on the market.[71] Hence breaking glass during processing (filling – especially also in light of process containment for production of cytotoxics), or adulteration of the compound (through extractables and leachables) or contaminated solutions (by delamination) could come dearly expensive to the industry.[72] Advancements in therapeutics and diagnostics yielding highly potent drugs should be responded to by innovations in the area of primary packaging and delivery systems. Therefore innovative materials like cyclo olefin polymers/ copolymers (COP/ COC)[73] are explored and promise to be a valid packaging alternative. Differently to glass, COP's break resistance is higher, the range of pH-value tolerance is wider and there is no peril of potentially leaking metal ions. The appeal of the polymer packaging solution lies also in its excellent drainability properties, which is particularly important for expensive biotech drugs.[74] At the present time COP is primarily used for the manufacture of vials and syringes. Looking at the latter we can state further benefits of the polymer over glass. Whereas for production and later application of prefillable glass syringes the use of glue, tungsten and silicon is necessary, there is no need for tungsten and glue in the fabrication of COP syringes. Additionally less siliconization (which is used to ensure full functionality of glass syringes, but could also cause aggregation of proteins) is needed.[75]

However advantageous polymers may be, there are also considerable downsides to COP containments. On the one hand they are more scratch-prone than glass, and on the other hand they are significantly more permeable to gas and water vapor. Over a products shelf life oxygen permeability may infringe sensitive proteins and water vapor may have undesired effects on hydrophilic substances like lyophilized compounds.[76] To overcome these deficits containers with a multi layer structure have been developed to address the current market needs. Figure 18 shows the combination of a COP and a polyamide (PA) layer. The advantages of this design are the enhanced break resist-

Figure 17: Diversity of medical Devices – providing differentiation opportunities (Quelle: Gerresheimer AG).

67) Petersen 2012.
68) Sacha et al. 2010.
69) Dirk 2011.
70) Petersen 2012.
71) N.N. 2012b.
72) Dirk 2011.
73) Cyclo olefin polymers are thermoplastic hydrocarbon polymers with a cycloaliphatic structure in the main chain, cf. Petersen 2012.
74) Dirk 2011.
75) Jones et al. 2005.
76) Petersen 2012.

Figure 18: Mulitlayer parenteral vial (MultiShell®) (Quelle: Gerresheimer AG).

ance (Multilayer vials demonstrate up to 10 times higher impact resistance compared to glass vials), the significantly better barrier properties than 'single layer' plastic vials (ensured by the PA layer), and at the same time glass-like transparency without metal ion release.[77] Two further major arguments pleading for polymer usage for high value drugs are its low adsorption of protein-like molecules and its excellent drainability. It has been scrutinized that – depending on the surface of the material in contact with the drug – adsorption of molecules can happen. Representative studies show an exemplary loss of nine per cent of a model molecule due to adsorption onto a glass surface.[78] Less molecule loss and a higher drainability require considerably less overfill (which is normally performed to ensure therapy efficiency). This in turn translates to significant cost reduction for the biopharmaceutical company which should easily compensate the higher price of multilayer plastic vials.

The area of high price specialty drugs is increasingly becoming subject to criminal business practices. Counterfeit medicines[79] of high value originator products provide a profitable opportunity to forgers and are being detected more and more frequently.

"Fake is as old as the Eden tree." – Orson Welles

In the cause of 2012 the FDA issued a series of alerting letters concerning bogus oncology drugs.[80] Authorities like Interpol or the WHO state that the prevalence of fake drugs is growing in general.[81] In this context anti-counterfeiting packaging is playing an increasingly important role to ensure drug integrity. Hence there are several features for different packaging types readily available for the industry. On item level we can observe the widening use of stand-alone tamper-evident closures for drug containers themselves (cf. Figure 19).

Additionally there are solutions rising in the marketplace that are systemic and involve the whole pharmaceutical supply chain. These track and trace approaches are not stand-alone, but need an accompanying database to verify a drug's origin and authenticity. The primary packaging can be tagged with a data carrier such as a 2D data matrix containing relevant information and linking the product to the above mentioned database. The 2D code can either be printed on or burned in with high-end laser coding technology (cf. Figure 20). As an alternative medium also Radio Frequency Identification (RFID) tags represent powerful data carrier solutions. According to recently passed legislation anyway, the topic track and trace is irrevocably gaining ground in the pharmaceutical industry.[82]

Figure 19: Tamper evident packaging solutions (Quelle: Gerresheimer AG).

In order to establish a successful anti-counterfeiting strategy it is recommendable to implement different countermeasures in combination. As a basic rule we can say: The more layers of security features that can be implied, the more difficult they are to copy and to overcome, hence the more promising the anti-counterfeiting strategy.

Conclusion and Outlook

"You must look within for value, but must look beyond for perspective." – Denis Waitley. The above outlined trends provide both, a challenging surrounding as well as promising opportunities for the pharmaceutical packaging industry in general and for the most innovative and reliable players in particular. The substantial shift towards the emerging markets together with global population growth and improved access to medication will increase overall demand of packaging volumes. Local proximity of globally active suppliers is of key importance to participate in and benefit from these growth dynamics.

At the same time it is paramount not to neglect the developed markets. However mature they seem, their patterns of reaching maturity – characterized by demographic change, the rise of chronic diseases,

77) Dirk 2011.

78) Dirk 2011.

79) Counterfeit medicine is fake medicine. It may be contaminated or contain the wrong or no active ingredient. They could have the right active ingredient but at the wrong dose. Counterfeit drugs are illegal and may be harmful to your health, cf. FDA 2013a.

80) FDA 2013b.

81) Interpol 2013; World Health Organization 2012b.

82) Helfand 2013; Vaczek 2013; Carrera 2013.

TechnoPharm 4, Nr. 3, 138–148 (2014)

prevailing pressure on healthcare cost leading to more home- and self-medication – provide major opportunities for the manufacturer of primary packaging and drug delivery devices. Human factors and a patient centric design – coping with increasingly heterogeneous patients' needs – are main principles of the future (not least also to improve patients' therapy adherence). As indicated we will likely see more electronics in devices, culminating in further features allowing for online connectivity and in turns enabling physicians to monitor and treat their patients remotely. Moreover the ongoing increase in regulatory scrutiny will further demand highest quality at all stages of the pharmaceutical supply chain – especially also for packaging and drug delivery solutions.

The prevailing patent cliff and the corresponding change of business models away from the 'one-size-fits-all' blockbuster strategy towards more specific therapies and patient groups will presumably continue to drive a more diverse portfolio of packaging and drug delivery solutions. The closely related trend of Genericization which will firstly and by nature increase the demand of packaging unit volumes will likewise contribute to more differentiated products.

The progressing advent of specialty biotech drugs – which gain ground first and foremost in the developed markets – require sophisticated primary packaging and drug delivery systems. Advancements in pharmacology and biotechnology creating highly potent drugs need to be embraced by appropriate solutions of an equally innovative supplying industry. Within the rise of specialty therapies – that are mostly injectables – drug delivery devices like autoinjectors will be taken into consideration at an earlier stage of the drug development and will also very likely get a greater deal of attention while registered as combination (drug-device) product. Furthermore the decision of the primary packaging material is set to become more focused on. Above stated advantages and disadvantages of several different subject matters justify the expectation of a coexistence of proven and reliable glass containers and innovative mono- or multilayer polymer solutions.

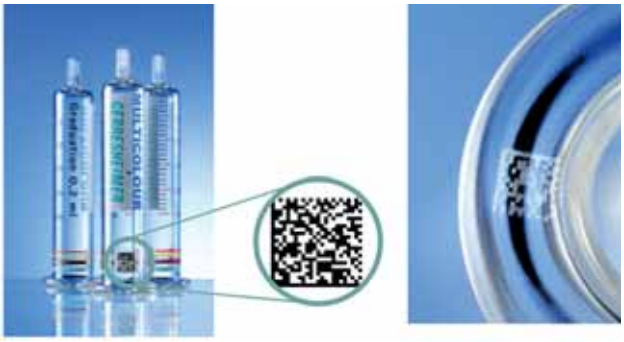

Figure 20: 2D datamatrix application for track and trace (Quelle: Gerresheimer AG).

Due to increasing environmental pressures also sustainable processes and eco-friendly materials need to be taken into account. In light of the ongoing distribution of fake medicine and the closely related legislation in these regards, we saw that developments in anti-counterfeiting- and smarter packaging solutions will gain momentum. On item level one can predict more features ensuring temper evident or such characteristics providing for a drug's track and traceability.

In conclusion, the overall balance of trends seems to allow for the statement that – although challenging – packaging is playing an essential part in the future of drugs.

References

Bangert, H. (2013), Pharma-Unternehmen – Das Leben danach, FOCUS-MONEY Magazin, No.31, July 2013.

Buston, K., Wood, S.F. (2000), Non-compliance amongst adolescents with asthma: listening to what they tell us about self-management, in: Family Practice, 17 (2).

Carrera, A. (2013), Falsified Medicines Directive goes into effect in the UK, *http://www.pharmaceutical-technology.com/news/newsfalsified-medicines-directive-goes-into-effect-in-the-uk?WT.mc_id=DN_News*, accessed 09/03/2013.

Carroll, J., Palmer, E. (2012), Top 15 drug patent losses for 2013 – Cymbalta *http://www.fiercepharma.com/special-reports/cymbalta-1,* accessed 08/13/2013.

Chavan, B., Doshi, A., Malode, Y., Misal, B. (2013), Review on needle free drug delivery systems, in: International journal of pharma research & review, Sept. 2013, 2(9).

Davis, J., Philips, C. (2007), Abstract: Defensive Equity Investing – Appealing Theory, Disappointing Reality.

Dirk, W. (2011), A Question of Use, in: Pharmaceutical Manufacturing and Packing Sources, *http://www.samedanltd.com/magazine/15/issue/157/article/3018*, accessed 08/28/2013.

Dubey, R., Dubey, J. (2009), Pharmaceutical Product Differentiation: A Strategy for Strengthening Product Pipeline and Life Cycle Management, in: Journal of Medical Marketing: Device, Diagnostic and Pharmaceutical Marketing April 2009 vol. 9 no. 2.

Dubin, C. (N.D.), Macro Opportunities For Microneedles, *http://www.lifescienceleader.com/magazine/past-issues3/item/3580-macro-opportunities-for-microneedles?list=n,* accessed: 09/05/2013.

Evaluate MedTech (2012), World Preview 2018 – A Consensus View of the Medical Device and Diagnostic Industry.

Evaluate Pharma (2012), World Preview 2018 – Embracing the patent cliff.

Evaluate Pharma (2013), World Preview 2013, Outlook to 2018 – Returning to Growth.

FDA (2013a), Counterfeit Medicine, *http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/default.htm*, accessed 09/03/2013.

FDA (2013b), Health Care Provider Alert: Another Counterfeit Cancer Medicine Found in U.S., *http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/ucm338283.htm*, accessed 09/03/2013.

FDA (2013c), Combination Product Definition, *http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm*, accessed 09/04/2013.

Freedonia (2013), World Pharmaceutical Packaging, Study# 3025, May 2013.

Greystone Associates (2013), Drug Self-Administration Markets to 2018, Study Code: DSA429F, March 2013.

Hamilton, J. (1995), Needle phobia: A neglected diagnosis, in: The Journal of Family Practice, Vol 41 (2), Aug 1995.

Helfand C. (2013), Track-and-trace taking shape in U.S., *http://www.fiercepharmamanufacturing.com/story/track-and-trace-taking-shape-us/2013-06-04*, accessed 09/03/2013.

Henderson Global Investor, BoA Merrill Lynch (2013),

http://www.focus.de/finanzen/boerse/pharma-unternehmen-das-leben-danach_aid_1052045.html, accessed 08/14/2013.

IMS Institute for Healthcare Informatics (2011), The Global Use of Medicines: Outlook Through 2015.

IMS Institute for Healthcare Informatics (2012), The Global Use of Medicines: Outlook Through 2016.

IMS Institute for Healthcare Informatics (2013), Advancing the responsible use of medicines *http://www.responsibleuseofmedicines.org/*, accessed 08/22/2013.

IMS Health (2011a), Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape.

IMS Health (2011b), The Global Generics Market, CPhI Pre-Conference, Frankfurt October 24th 2011.

IMS Health (2013), Pharmerging Markets – Picking a pathway to success.

International Diabetes Federation (2012), Diabetes Atlas – Fifth edition, Update 2012,*http://www.idf.org/diabetesatlas/5e/diabetes,* accessed 08/21/2013.

Interpol (2013), Pharmaceutical crime – A major threat to public health, *http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Pharmaceutical-crime*, accessed 09/03/2013.

Iskowitz, M. (2013), 2013 Pharma Report: Don't Look Back!, in: Medical Marketing & Media (May 02, 2013).

Jones, L., Kaufmann, A., Middaugh, R. (2005), Silicone Oil Induced Aggregation of Proteins, in: Journal of pharmaceutical sciences, Vol. 94, No. 4.

Kelly, L. (2013), Self-Administration: Power to the Patient, Savings to Healthcare, *http://social.eyeforpharma.com/patients/self-administration-power-patient-savings-healthcare*, accessed 08/21/2013.

Lewis, G. (2013), DCAT Week, NY: Prospects for Pharma in a changing world, Source: IMS Health, MIDAS, MAT Sept 2012, Rx only. Market Segmentation + LIC countries, data on file.

Moore, C. (2013), A Regulatory Perspective on the Current and Future State of Pharmaceutical Quality, at: International Conference on Drug Development, Austin, TX, Feb 26, 2013, *http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM359267.pdf*, accessed 09/20/2013.

Müller, M. (2012), Pharma on the edge – challenges beyond 2020, *http://www.pharma-jahrestagung.de/wp-content/uploads/2012/09/11_m-c-mueller.pdf*, accessed 08/22/2013.

N.N. (2012a), The role of partnership in building value, in: Manufacturing Chemist, March 2012.

N.N. (2012b), The 11 Most Expensive Medicines in America, *http://www.medicalbillingandcoding.org/blog/the-11-most-expensive-medicines-in-america/*, accessed: 08/29/2013.

N.N. (2013a), Definition of ‚Patent Cliff', *http://www.investopedia.com/terms/p/patent-cliff.asp*, accessed: 08/14/2013.

N.N. (2013b), Which 4 sectors are beating the S&P 500? *http://money.msn.com/top-stocks/post.aspx?post=9241bb36-22b2-4fd6-9840-cdbb78d0d02b,* accessed: 08/20/2013.

Nichols-English, G., Poirier, S. (2000), Optimizing Adherence to Pharmaceutical Care Plans, in: Journal of the American Pharmacists Association 2000;40(4).

Palmer, E. (2013), FDA Approvals of 2012, *http://www.fiercebiotech.com/slideshows/fda-approvals-2012,* accessed 08/14/2013.

Petersen, C. (2012), Containers Made of Cyclic Olefins as a New Option for the Primary Packaging of Parenterals, in: Pharm. Ind. 74, Nr. 1 2012.

Pezzini, M. (2012), An emerging middle class, in: OECD Yearbook 2012.

PricewaterhouseCoopers (2011), Pharma 2020: Supplying the future – Which path will you take?

PricewaterhouseCoopers (2012), From vision to decision – Pharma 2020.

PricewaterhouseCoopers (2013), Managing Regulatory Compliance, *http://www.pwc.com/il/en/pharmaceuticals/managing-regulatory-compliance.jhtml*, accessed 09/20/2013.

Research and Markets (2013), Drug Delivery Technologies Market (Metered Dose Inhalers, Needle-Free Injectors, Auto-Injectors, Nasal Sprays, Transdermal Patches, Nebulizers, Infusion Pumps, Drug Eluting Stents, Sustained Release, Ocular Implants) – Global Forecasts To 2017, April 2013.

Rotenstein, L., Ran, N., Shivers, J., Yarchoan, M., Close, K. (2012), Opportunities and Challenges for Biosimilars: What's on the Horizon in the Global Insulin Market?, in: Clinical Diabetes October 2012 vol. 30 no. 4.

Sacha, G., Saffell-Clemmer, W., Abram, K., Akers, M. (2010), Practical fundamentals of glass, rubber, and plastic sterile packaging systems, in: Pharmaceutical Development and Technology, January-February 2010, Vol. 15, No. 1.

Simpson, I. (2012), The Role Of Drug Delivery Devices In The Pharmaceutical Industry, *http://proddownloads.vertmarkets.com.s3.amazonaws.com/download/255e6398/255e6398-5aa0-4897-8252-a06300a6c2ab/original/simpson_col1_052012_final.pdf*, accessed 08/27/2013.

Stone, K. (2013), Which Popular Drugs Are Going Off-Patent in 2013-2016?, *http://pharma.about.com/od/BigPharma/a/Which-Popular-Drugs-Are-Going-Off-Patent-In-2013-2016.htm*, accessed 08/13/2013.

Taddio, A., Ipp, M., Thivakaran, S., Jamal, A., Parikh, C., Smart, S., Sovran, J., Stephens, D., Katz, J. (2012), Survey of the prevalence of immunization non-compliance due to needle fears in children and adults, in: Vaccine, Vol. 30, Issue 32, 6 July 2012.

Tagawa, Y., Oudalov, N., El Ghalbzouri, A., Sun, C., Lohse, D., (2012), Needle-free injection into skin and soft matter with highly focused microjects, in: LAB CHIP 2013, 13.

Taylor, N. (2012), FDA biosimilar guidance permits alternative drug delivery devices, *http://www.biopharma-reporter.com/Bio-Developments/FDA-biosimilar-guidance-permits-alternative-drug-delivery-devices*, accessed 08/26/2013.

Transparency Market Research (2012), Medical Devices Outsourcing Market – Global Industry Size, Market Share, Trends, Analysis, and Forecast, 2012 – 2018, *http://www.sbwire.com/press-releases/medical-devices-outsourcing-market-global-industry-size-market-share-trends-analysis-and-forecast-2012-2018-195036.htm*, accessed 08/22/2013.

United Nations (2013), World Population Prospects – The 2012 Revision – Volume I: Comprehensive Tables.

Vaczek, D. (2013), Drug Companies Face Year of Reckoning for Serializing Products, *http://www.pmpnews.com/news/drug-companies-face-year-reckoning-serializing-products,* accessed: 09/03/2013.

Visiongain (2012), Needle-Free Delivery: Technology and Market 2012-2022, *http://www.visiongain.com/Press_Release/141/The-total-needle-free-delivery-market-is-expected-to-grow-rapidly-as-more-opportunities-arise-from-new-technology-and-emerging-economies*, accessed: 09/05/2013.

Wenninger, I., Weser, F., Wiedemann, C., Müller, M. (2011), Pharma on the edge – From globalization to personalized medicine – it's time for change, CEPTON Strategies.

World Health Organization (2005), Fact sheet 2005: Spending on health – A global overview,

http://www.who.int/nha/use/Highlight_5_Aug2008.pdf, accessed: 08/20/2013.

World Health Organization (2012a), Spending on health: A global overview, Fact sheet N°319

April 2012, *http://www.who.int/mediacentre/factsheets/fs319/en/index.html*, accessed: 08/20/2013.

World Health Organization (2012b), Medicines: spurious/falsely-labelled/ falsified/counterfeit (SFFC) medicines, Fact sheet N°275, May 2012, *http://www.who.int/mediacentre/factsheets/fs275/en/*,

TechnoPharm 4, Nr. 3, 138–148 (2014)

ecv

Pharmaceutical Dictionary
English, German, French, Spanish

J. Brawley, A. Maas

978-3-87193-386-8 (Buch)
- € 89,00
- 5. überarbeitete und ergänzte Auflage 2010
- 1.175 Seiten, 12,5 x 21 cm, flexibler Einband

978-3-87193-391-2 (CD)
- € 85,00
- 5. überarbeitete und ergänzte Auflage 2010
- mit MS-WORD Wörterbuchfunktion

978-3-87193-392-9 (Buch + CD)
- € 156,00

Online-Version (sechssprachig)
- www.pharmaceutical-dictionary.eu

Das viersprachige Wörterbuch mit den wichtigsten Fachbegriffen für die Pharmatechnologie

Das Wörterbuch umfasst eine Sammlung von mehr als 7.000 Wörtern in jeder Sprache.
Die Begriffe kommen aus der pharmazeutischen Technologie wie z.B. Produktion, Qualitätskontrolle und -sicherung, aus der Zulassung und beziehen darüberhinaus auch Grundlagenwissen aus der Pharmazie mit ein. So weit wie möglich werden die Terminologie der europäischen Pharmakopöen sowie z.B. die GMP-Guidelines mit den Empfehlungen von EU, EMA und ICH berücksichtigt.

Zielgruppen
- Pharmazeutische Industrie
- Zulieferindustrie
- Auftragshersteller
- Maschinen- und Anlagenbauer
- Planungs- und Beratungsunternehmen
- Universitäten und Fachhochschulen
- Behörden

Online Version mit Chinesisch und Russisch!

Bestellung:
Tel. +49 (0)8191-97000 358,
Fax +49 (0)8191-97000 293,
eMail: vertrieb-ecv@de.rhenus.com
Onlineshop, Leseproben und Inhaltsverzeichnisse – www.ecv.de

ECV · Editio Cantor Verlag

15 JAHRE

Maas & Peither
GMP VERLAG

GMP-Risikoanalysen

Standardvorlagen für Räume und Ausrüstung im pharmazeutischen Umfeld

Profitieren Sie von
- der verdichteten Erfahrung von Praktikern
- einer optimierten Methode
- der Identifizierung möglicher Fehler und deren Ursachen.

Grundwerk mit 3 Standardvorlagen zu technischen Systemen
- im Ringordner
- als Dateien zur direkten Bearbeitung

Kostenlose SOP „Technische GMP-Risikoanalysen" und Bestellung unter
www.gmp-risiko.de

Neueinführung Juni 2014
360,- € zzgl. MwSt. und Versand*

*Angebot gültig bis 31.07.2014