Value-added medicines: how repurposed medicines bring value to patients and pharmacists

Christoph Stoller; Professor Stephan Krähenbühl, MD, PhD; Emilia Minodora Voiculescu, PharmD

The Value Added Medicines Group of Medicines for Europe met at the 2017 European Association of Hospital Pharmacists conference in France to discuss the merits and future of these medicines.

Keywords: Innovation, pharmacy regulation, value-added medicines

Introduction

The Value Added Medicines Group held a satellite symposium entitled 'Value added medicines: what value repurposed medicines might bring to hospital pharmacists' on 22 March 2017 at the 22nd Congress of the European Association of Hospital Pharmacists in Cannes, France.

The Value Added Medicines Group is a sector group of Medicines for Europe. This association was formed 20 years ago as the European Generic medicines Association. While initially aimed at representing the emerging generic drug industry, it later grew to include biosimilar medicines. Most recently, Medicines for Europe has expanded into value-added medicines. Value-added medicines are defined as medicines based on known molecules that address healthcare needs and deliver relevant improvements for patients, healthcare professionals and/or payers [1]. Medicines for Europe joins a host of other associations and companies that are exploring the concept of value-added pharmaceuticals [2].

The need for value-added medicines

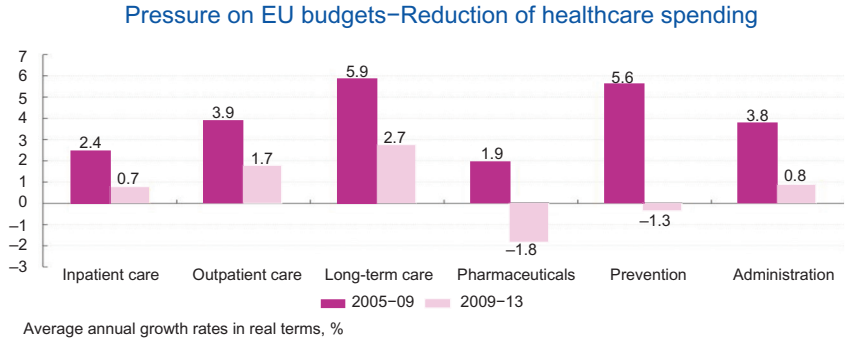
Mr Christoph Stoller (Chair of the Value Added Medicines Sector Group and Senior Vice President Generics and Commercial Operations Europe at Teva Pharmaceuticals) introduced the symposium, highlighting that the Value Added Medicines Group aims to rethink, reinvent and optimize medicines based on known molecules by introducing untapped innovation to improve care delivery [1]. The group's goals are to target patient needs that remain unmet to this day, delivering additional improvements to the healthcare community as a whole. He noted that the Value Added Medicines Group adopts a complimentary perspective to other Medicines for Europe groups (generic and biosimilar medicines) and its membership includes many different companies that are exploring the repurposing of existing medicines.

Mr Stoller highlighted that in recent years healthcare systems in Europe have faced recession and complex issues such as the ageing population, increasing prevalence of chronic diseases and the need for equity of access. Overall, they are being driven to do more with less. This statement was backed up with data from the Organisation for Economic Co-operation and Development (OECD), see Figure 1, which showed that efforts to improve efficiency between 2005–2013 concentrated on cutting healthcare spending costs; particularly pharmaceutical costs. He noted that this threatened European citizens' access to quality care.

Furthermore, Mr Stoller noted that new approaches are needed to preserve universal healthcare coverage and highlighted that in 2014, global spending on new brand-name innovator medicines more than doubled. In terms of healthcare system efficiency, he reported that 20–40% of spending is allocated to unnecessary or non-cost-effective services. These issues lead, amongst others, to patient medication adherence issues, with more than 50% of patients being affected which has great impact on patient well-being and healthcare budgets. He estimated that this costs EU health systems around Euros 125 billion and leads to over 200,000 premature deaths annually. He added that the present suboptimal use of medicines represents an opportunity to rethink and optimize current health delivery systems and reinvent current therapies.

To expand on this, Mr Stoller highlighted that innovation can focus on existing medicinal drug products, particularly those no longer protected by patents. Value-added medicines represent a new form of R & D, merging a pharmacological approach of well-known active substances with more patient and/or healthcare professional insights, and leveraging new technologies to transform existing medicines and address specific needs that could not have been tackled in the past. These medicines can then offer a more tailored experience and deliver better efficacy, safety, tolerability and better administration and ease of use. In addition, it may be that they can be utilized for totally new therapeutic purposes, through drug repositioning (finding new indications), drug reformulation (finding new delivery systems), or complex combinations (new regimens or adding technology), see Figure 2.

Figure 1: Growth rates of health spending for selected functions per capita, OECD average 2005–2013



OECD: Organisation for Economic Co-operation and Development.
Source: OECD Health at Glance, 2015

Submitted: 13 June 2017; Revised: 23 August 2017; Accepted: 25 August 2017; Published online first: 7 September 2017

Overall, value-added medicines can help patients, through better adherence or quality of life; healthcare professionals, by improving safety, efficacy and the number of treatment options; payers, through improved budget efficiency; and researchers, by increasing the opportunities for innovation throughout the medicinal drug product's life cycle.

The Value Added Medicines Group aims to combine new technologies with existing medicinal drug products which requires considerable R & D investment. As such, the group needs to work with all stakeholders (policymakers, patients, healthcare professionals, pharmaceutical companies and payers) to establish a sustainable market model that incentivises R & D and increases access to value-added medicines across Europe.

Continued innovation drives progress for value-added medicines

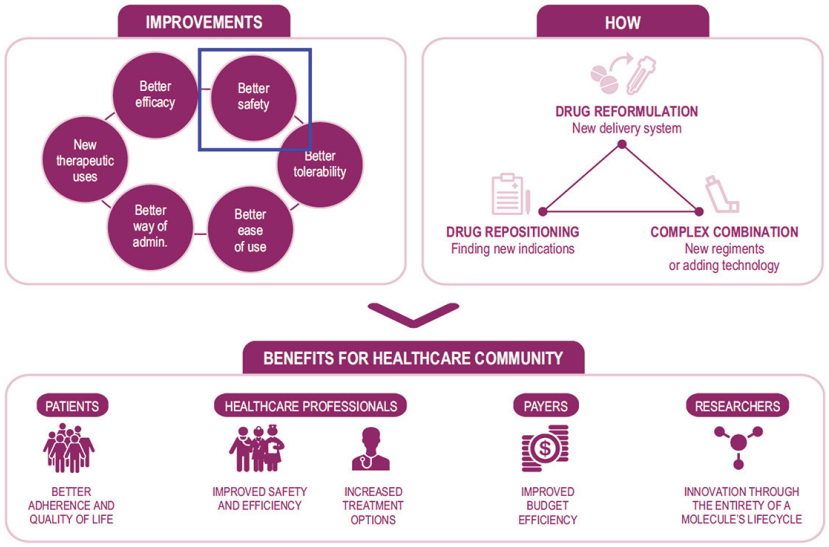
Professor Stephan Krähenbühl's (Professor of Pharmacology and Toxicology, University Hospital, Basel, Switzerland) presentation entitled 'The Importance of continued innovation: perspectives of a healthcare professional', highlighted two key examples of where innovation with existing molecules has led to improved healthcare outcomes. Through their repurposing, these products have facilitated improved safety and an improved administration method.

Better safety: Abacavir

Professor Krähenbühl's first example was the case of Abacavir (ABC), a nucleotide inhibitor used in HIV treatment. After treatment with this medication, approximately 4.5% of patients exhibit a hypersensitivity reaction with severe multi-organ life-threatening effects. He noted that there were indications that this was an allergic reaction to the treatment drug product.

A skin patch test can often be used to test for such allergic reactions in patients. Other methods include the isolation of lymphocytes from patients and the detection of a reaction in these cells when exposed to the drug. In this case, positive CD8 cell proliferation, activated by Abacavir *in vitro,* was found to be associated with patients that exhibit an HLA-B*5701 phenotype, which can be identified through genetic drug screening. Following this discovery, scientists in Australia [3] carried out a prospective randomized double-blind multicentre study of 1,956 patients with HIV type 1, who had not previously been treated with Abacavir. Half of these patients were screened for the HLA-B*5701 phenotype. Those with this phenotype were not treated with Abacavir, but all other patients did receive Abacavir treatment. The other half of patients were not screened and all patients were treated with the drug. Results showed that in the screened group, patients did not experience any allergic reaction, whereas in the unscreened, 3% exhibited hypersensitivity. This suggests that, HLA-B*5701 genotyping of patients reduces clinically diagnosed hypersensitivity reactions and might be able to eliminate immunologically confirmed hypersensitivity reactions.

Figure 2: What are value-added medicines



VALUE ADDED MEDICINES are medicines based on known molecules that address healthcare needs and deliver relevant improvemens for patients, healthcare professionals and/or payers

Source: www.medicinesforeurope.com

Figure 3: Patient phenotype screening

HLA-B*5701 screening for ABC HSP Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	p Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	p < 0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	p < 0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	p < 0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	p < 0.001

HLA-B*5701 genotyping reduces clinically diagnosed hypersensitivity reactions
HLA-B*5701 genotyping eliminates immunologically confirmed (patch clamping) hypersensitivity reactions (NPV 100)

N Engl J Med. 2008;358:568-79.

Without this screening method, Professor Krähenbühl noted that this drug is likely to have been removed from the market due to safety concerns associated with the severe hypersensitivity reaction. Now, all patients are screened prior to its administration and its use is now safer, see Figure 3.

Better administration method: nasal application

Midazolam, a drug typically used for anaesthesia and sedation, has traditionally been administered orally or intravenously. However, due to metabolism occurring in the intestines and liver, its bioavailability to patients following administration via these methods becomes significantly

reduced (30%). Due to this, together with some additional factors, its nasal application was investigated by hospital pharmacists and clinical pharmacologists at the University Hospital of Basel, Switzerland [4].

The nasal application of drugs has advantages brought about by the high vascularization in this region. The respiratory region is 130 cm², with high vascularization and permeability, and the olfactory region is 15 cm² with high vascularization and direct access to the central nervous system (CNS). In addition, nasal application:

- is non-invasive and easy to apply
- circumvents intestinal and hepatic presystemic metabolism
- is rapid for a non-invasive application
- does not require the preparation to be sterile.

On the other side, disadvantages [5] include:

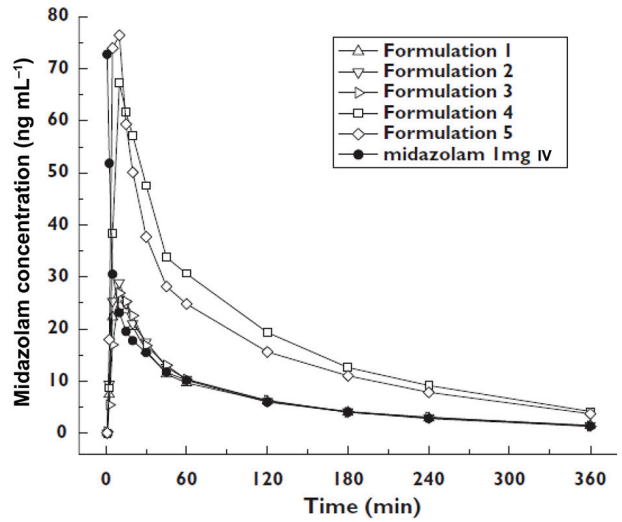
- low dosage volume (100–150 µL)
- nasal irritation can occur/system toxicity if adjuvants are used
- absorption is altered in patients with nasal diseases.

In the midazolam study, the pharmaceutical drug products' pH dependent solubility was investigated. More midazolam was solubilized at lower pH, however, the solutions were kept above pH4 to prevent nasal irritation. Solubility agents in the form of cyclodextrin derivatives were also added to increase solubility. The pharmacokinetics after nasal and intravenous (IV) application were compared and showed 80–90% bioavailability of midazolam following nasal application, see Figure 4.

Professor Krähenbühl highlighted that this study resulted from a collaboration between clinical pharmacologists and hospital pharmacists, without any intervention from pharmaceutical companies. Further collaborative efforts ensued, with neuroscientists being involved to determine if there was any difference in effects on the brain brought about by the different administrative methods.

In his concluding remarks, Professor Krähenbühl noted that many drugs currently on market could be further developed in different ways. He added that at present, investigation of drugs for repurposing is common, especially in the case of anticancer medicines where more indications are often found as time goes on. He also noted that new galenical formulations are particularly common in paediatrics (off-label and off-licence due to a lack of studies). Professor Krähenbühl stressed that hospital pharmacists can play an important role in development through initiating studies, particularly those related to administration of therapies.

Figure 4: Midazolam – pharmacokinetics of nasal preparations



Br J Clin Pharmacol. 2010;69:607-16.

Overcoming the barriers that prevent value-added medicines reaching patients

Ms Emilia Minodora Voiculescu's (Medical Advisor, Fresenius Kabi Deutschland GmbH, Germany) presentation entitled 'Why are value-added medicines relevant for hospital pharmacists: challenges and opportunities', highlighted the key issues encountered when bringing value-added medicines to market.

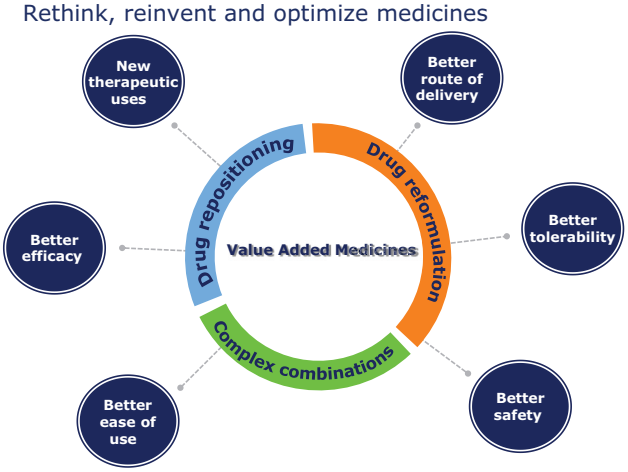
Initially, Ms Voiculescu introduced Fresenius Kabi as a company with a large portfolio of IV drugs, infusion therapies, clinical nutrition, medical devices and transfusion technologies. The company provides high quality and affordable products for the therapy and care of critically and chronically ill patients in hospital and outpatient care. Value-added medicines play an important role in the company as they foster innovation and help achieve better patient outcomes.

To get the most from value-added medicines through innovation, the points introduced by Mr Stoller were reinforced, see Figure 5:

- Drug repositioning can lead to better efficacy and new therapeutic uses
- Drug reformulation can lead to better route of delivery, better tolerability and better safety
- Complex combinations can lead to better ease of use

However, for a pharmaceutical company to bring a value-added medicine to the market for a new indication, there are a number of hurdles to overcome. Ms Voiculescu gave detailed examples of how regulatory

Figure 5: Improvements by value-added medicines



approval, pricing and reimbursement and healthcare organization decision-makers, see Figure 6, create barriers to market entry for this type of product.

Regulatory issues for value-added medicines

Regulators are aware that incremental innovation is possible for patented pharmaceutical products, hence a different regulatory framework is in place for registration of such medicines. However, under Article 10(3) of Directive 2001/83/EC (hybrid applications: changes in the active substance(s), therapeutic indications or strength, pharmaceutical form or route of administration, are made to the reference product) that most value-added medicines refer to for registration, preclinical tests and clinical trials may be required for repurposing approval. These additional studies have an associated price tag and thus create a financial burden for the pharmaceutical company driving the innovation. This creates barriers to the market and means that potentially useful products may not be developed.

To overcome potential market barriers, a European Commission (EC) group, Safe and Timely Access to Medicines for Patients (STAMP), is currently investigating the issue of repurposing established medicines. Within the European regulatory framework, some incentives already exist:

- 1-year data exclusivity - for new therapeutic indications for a well-established substance
- 8 (+2)-year data and market protection – for already authorized products developed for paediatric populations (PUMA – paediatric-use marketing authorization)
- 10-year market exclusivity – for repurposed medicines granted and orphan drug designation

Pricing and reimbursement issues for value-added medicines

The current EC incentives for repurposing established medicines do not circumvent all barriers to the market and have not been successful in allowing many value-added medicines to market. In fact, there are signs that these incentives are being underutilized by the pharmaceutical industry. One reason for this apparent lack of interest in these incentives by the industry may be related to the different pricing and reimbursement issues across Europe.

A handful of countries in Europe operate a free pricing of pharmaceutical products policy (Denmark, Germany, The Netherlands and the UK. All others have pricing regulations in place which may be external reference pricing (comparison to average price outside the country), or internal reference pricing regulations (comparison to price of the originator). Both methods of pricing regulation can generate a negative knock-on effect that means healthcare requirements are not met. Even with price regulation in place, the final approved price paid can be affected by volatile currency exchange rates and proxy prices (derived from calculations) that are used for comparison. In addition, the tendering process in a given country might erode the approved prices of medicines even further.

In 2014, the Public Procurement Directive (Directive 2014/24/EU) introduced the Most Economically Advantageous Tender (MEAT) criterion. This aimed to switch the emphasis of public procurement from price alone, to quality and other social and environmental criteria, see Figure 7. Despite this, the lowest price criterion is still applied in many countries across Europe, meaning that value-added medicines have few opportunities to enter markets.

In addition, Ms Voiculescu described a 'holistic view on tenders', to show how the best value for money for patients and healthcare systems could be achieved. This would:

- foster competition and long-term sustainability of medicine supply
- award innovation going beyond price and recognizing the added value that innovative products bring to patients and health systems
- ensure optimal price–quality ratio rewarding valuable innovation.

Ms Voiculescu summarized pricing policies that lead to reduced access to value-added medicine access:

- *Pushing prices down*
  This can occur due to: systematic positioning as a generic medicine and inclusion in internal reference pricing groups based on active substance; external reference pricing, especially when value-added medicines are considered differently from a pricing and reimbursement perspective in different countries; and tenders/procurement policies with award criteria based exclusively on economic criteria for the active substance (lowest price).

Figure 6: Pathway to market for value-added medicines

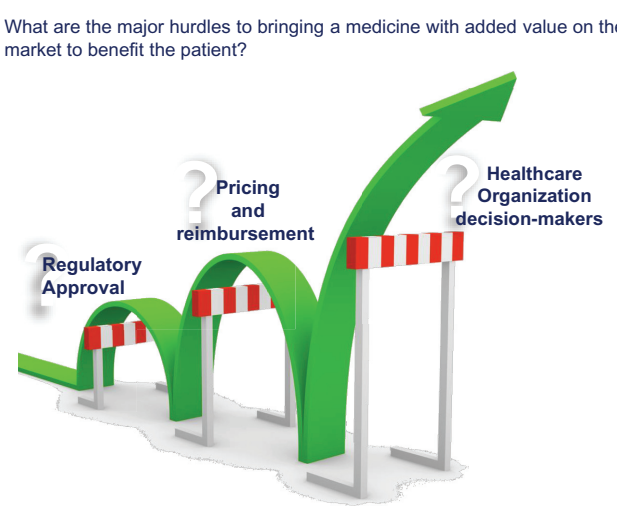


Figure 7: The M.E.A.T. criterion

Source: Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement

- *A single pricing rule across all indications* Instead, indications of a drug should be distinguished with different prices per indication.

Such policies can cause pharmaceutical companies not to invest in, or launch, and even withdraw value-added medicines from certain countries. This can lead to inequities in patient access to medicines across countries.

Health technology assessment: (HTA)

The health technology assessment (HTA) is used in some European countries. Here, new treatments/medications added to market are compared, based on clinical scientific criteria, with products already available. Thus, it gives evidence-based guidance to pricing and reimbursement. However, Ms Voiculescu noted that the current HTA systems do not adequately accommodate value-added medicines. HTA requirements are configured for innovative medicines, rather than pre-existing medications. The HTA decision-making framework should be adapted to account for the distinct characteristics of value-added medicines that are not currently captured, e.g. patients' and healthcare providers' preferences, more weight of quality of life and health economic benefit.

Ms Voiculescu stressed that all value-added medicines stakeholders should be involved in early dialogue relating to adaptation of the HTA. They should contribute scientific advice in parallel to determine the data needed for value-added medicines to be successfully brought to market. In addition, legislative barriers should be removed for value-added medicines to go through the HTA process successfully.

Case studies: Sweden and Romania

Ms Voiculescu used Sweden and Romania as case studies to emphasize how regulation, pricing policy and healthcare systems, can either facilitate or impede the availability of value-added medicines.

Sweden

For value-added medicines, the pricing and reimbursement landscape in Sweden facilitates market access. Here, a societal perspective has been adopted, assessing both costs and benefits of therapies. There is a free pricing policy whereby the government does not impose the price of drugs. Reimbursement is based on three main criteria: the human value principle, the need and solidarity principle and the cost-effectiveness principle that considers the cost and benefit to patients. In addition, Sweden has a tendering system in place that compares products and awards points for several criteria, including manageability, labelling and packaging or design of the product, see Figure 8.

Romania

In contrast, value-added medicines struggle to reach the market in Romania. Here, the cost of medicines is set at the lowest price within a basket of 12 EU countries, the first generic drug launched cannot exceed 65% of the innovative product price, there is a claw-back tax, and contracting authorities often use the lowest-price criterion in tenders. Due to these policies, low-cost medicines are reportedly produced at a loss once claw-back taxes are accounted for. In the last four years, 2,000 generic drug products have disappeared from the market in Romania, with 850 being discontinued in 2015. Consequently, issues faced by the Romanian healthcare system have included more out-of-pocket expenses for patients, a lack of appropriate and timely treatment options in hospitals, and patients have faced a shortage of essential drugs. Within this context, it is clear that value-added medicines have a restrictive market access pathway, see Figure 9.

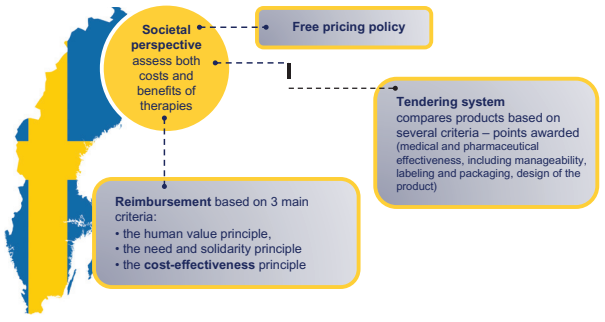
Hospital pharmacists can facilitate access to the most appropriate level of care for patients, therefore improving their outcomes and consequently increasing efficiency, effectiveness and productivity of healthcare organizations. Ms Voiculescu concluded her presentation by calling for the proactive involvement of hospital pharmacists. These individuals can bring about changes in the system and facilitate innovation to add value for the patient.

Discussion: audience Q&A

Following the main presentations, the three speakers answered questions from the audience. They outlined some of the differences between drug regulation and pricing in Europe and the US. Ms Voiculescu noted that the environment in Europe is very heterogeneous compared to the US, and that prices in the US are not regulated, but negotiated. Professor Krähenbühl mentioned that in Switzerland, the health authority decides if a drug should be available on the market and the independent regulators and price setters then determined its price.

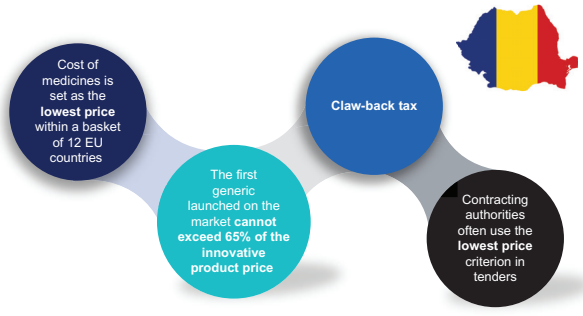
Professor Krähenbühl highlighted the important role that hospital pharmacists can play in innovation related to value-added medicines. He stated that the nasal application of drugs occurred as a result of pharmacists' observation of patient requirements and that physicians had not previously considered this method for administration of midazolam. Collaboration between pharmacists and physicians can lead to further successful clinical

Figure 8: Sweden – integrating societal perspective in pricing and reimbursement decisions



Source: The Swedish Pharmaceutical Reimbursement System: A brief overview, Pharmaceutical Benefits Board

Figure 9: Romania – short-term approach focussed on cost-containment



outcomes in the future and pharmacists' input can be of help in clinical trials.

When it comes to collaboration between pharmacists, physicians and industry, Ms Voiculescu pointed out that a patient-centric approach should always be adopted and that all stakeholders should have this in mind when developing medicines. Professor Krähenbühl noted that researchers want to improve our scientific knowledge, but sometimes this can clash with financial or patent issues of concern to pharmaceutical industry. He stressed that, for successful partnerships and increased innovation, collaborations need to be established early in the R & D process.

The speakers also addressed concerns related to the cost-effectiveness analysis of an expensive medicine with an easy delivery method, when compared to a less-costly medicine with labour-intensive set up and monitoring. Both Ms Voiculescu and Professor Krähenbühl agreed that this differs greatly between countries and health organizations. It is often the case that the budgets for these delivery methods will be separate (drug versus healthcare time) adding additional complications when assessing cost-effectiveness.

Conclusion

During the symposium organized by the Value Added Medicines Group of Medicines for Europe entitled 'Value added medicines: what value repurposed medicines might bring to hospital pharmacists', speakers Mr Christoph Stoller, Professor Stefan Krähenbühl and Ms Emilia Minodora Voiculescu, discussed how these medicines can improve patient outcomes and identified the specific hurdles for their market entry. These discussions follow on from those presented in a previous Medicines for Europe report [2] and paper published in *GaBI Journal* [6].

Mr Stoller introduced the symposium and the Value Added Medicines Group. He highlighted that value-added medicines are established medicines that can be used for totally new therapeutic uses, through drug repositioning, drug reformulation, or complex combinations. Their introduction can help patients, healthcare professionals, payers and researchers, but a sustainable market model is needed to incentivize R & D and increase access to value-added medicines.

Professor Krähenbühl's presentation highlighted two key examples where innovation on existing medicines have improved healthcare outcomes, showing that continued innovation drives development. The examples were immunogenicity screening of Abacavir treatment for HIV patients that led to improved product safety, and how nasal application of a drug was developed as an improved administration method by hospital pharmacists to increase drug bioavailability. He concluded by stating that pharmacists can play an important role in development through initiating studies even where clinicians have not noticed a demand.

Ms Voiculescu highlighted key issues encountered when bringing value-added medicines to market. These included regulatory approval, pricing and reimbursement, and communication with healthcare organization decision-makers. She used Sweden and Romania as case studies to emphasize how systems can either facilitate or impede the availability of value-added medicines. She called for the path to innovation to be cleared of barriers to make more medicines available to patients.

The overall emphasis made by the speakers was on research and innovation. They used specific examples to highlight how this can lead to advances and availability of better treatment options in the form of value-added medicines. However, they also made it clear that further steps need to be taken to increase collaboration and innovation and remove barriers to the market.

Acknowledgement

The authors wish to thank Alice Rolandini Jensen, MSci, *GaBI Journal* Editor, in preparing this meeting report.

Disclosure of financial and competing interests: The satellite symposium was organized by the Biosimilar Medicines Group, a sector group of Medicines for Europe. Fees were paid to the organization for the conference slot, however, none of the speakers received direct payments from Medicines for Europe. Ms Emilia Minodora Voiculescu is an employee of Fresenius Kabi. Mr Christoph Stoller is an employee of Teva Pharmaceuticals.

Professor Stephan Krähenbühl declares that there is no conflict of interest to report.

Provenance and peer review: Not commissioned; internally peer reviewed.

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DOI: 10.5639/gabij.2017.0603.027

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