Pharm Med (2014) 28:333–341
DOI 10.1007/s40290-014-0079-x

UPDATE

Forum

1 European Database of Suspected ADRs Open to Public

A European database of suspected adverse drug reaction (ADR) reports (http://www.adrreports.eu/EN/index.html) is now open to the public. The European Medicines Agency (EMA) says the website, which was launched in 2012, now contains suspected ADRs for an additional 1,700 medicines approved in the EU, and its expansion permits public access to information submitted to EudraVigilance.

As well as providing online access to the adverse event data, which can be viewed by outcome as well as age, sex and type of suspected ADR, the website provides information on how to search for ADR reports and how to report adverse events. The EMA has also published a leaflet in all official languages of the EU to encourage patients to report adverse events.

European Medicines Agency. Information on suspected side effects of nationally authorised medicines now available through a single website [online]. 6 Oct 2014. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/10/news_detail_002180.jsp&mid=WC0b01ac058004d5c1. Accessed 12 Nov 2014.

2 NICE Proposes Wider Review for Evaluating New Treatments

The National Institute for Health and Care Excellence (NICE) is calling for a new approach to the way new drugs are evaluated and taken up by the National Health Service (NHS) in the UK.

In addition to changes in its methodology, NICE envisages a wider role for itself. It proposes setting up an office of innovation to assist companies working through stages of development, evaluation and adoption of their products. Additionally, it suggests that an agreement between NICE, the Department of Health and NHS England on the NHS's willingness to pay for new treatments is needed, and that this would take into account special cases, including treatments for ultra-orphan diseases and cancer. Furthermore, NICE says that there should be more productive risk sharing between companies and the NHS—with the aim to progressively reflect the value of new treatments as more becomes known about them.

"We also need to look at other processes, including the model of pharmaceutical research and development, the expectations that companies and patient groups have about how risk and reward is shared between the industry and a publicly funded NHS, and in the arrangements for commissioning expensive new treatments," said Sir Andrew Dillon, chief executive of NICE.

National Institute for Health and Care Excellence. NICE calls for a new approach to managing the entry of drugs into the NHS [media release]. 18 Sep 2014. Available from URL: http://www.nice.org.uk. Accessed 12 Nov 2014.

3 TGA has New Web-Based Report Service

The Australian Therapeutic Goods Administration (TGA) has launched a web-based service for reporting of adverse events by consumers.

There has been limited awareness of available reporting systems for consumers. Each year, over 17,000 suspected adverse events associated with medicines and vaccines are reported to the TGA, but in 2013 only about 3 % of reports were from consumers.

As well as this web-based service to encourage reporting by consumers, the TGA has published a consumer brochure on reporting of adverse events, is implementing awareness activities and messages, and is conducting consumer research to raise awareness.

Therapeutic Goods Administration. New web service helps consumer reporting of 'side effects' [online]. 24 Sep 2014. Available from URL: http://www.tga.gov.au/newsroom/media-2014-consumer-reporting.htm. Accessed 12 Nov 2014.

4 WEB-RADR: New Social Media Project for ADR Monitoring in EU

The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK is leading a consortium of organisations in the EU in a 3-year project called WEB-RADR, which is designed to develop new ways of gathering information on suspected ADRs.

The WEB-RADR project has been set up in response to the rapid adoption of smartphones, apps, and social media for discussing issues regarding medicines and health. This project is to be funded through the Innovative Medicines Initiative, a public–private partnership between the European Commission and European Federation of Pharmaceutical Industries and Associations.

The MHRA will lead the consortium to develop a mobile app for healthcare professionals and the public to report suspected ADRs to national EU regulators. The potential for using publicly available social media data for identifying potential drug safety issues will also be examined. It is possible the new app could also serve as a platform to send accurate, timely, and up-to-date medicines information to patients, clinicians and caregivers.

The WEB-RADR project will also examine the value of these new tools for drug safety monitoring. It will help to develop recommendations for medicines regulators and the pharmaceutical industry internationally on how such new tools should be used alongside existing systems. Mick Foy, Group Manager from the MHRA's Vigilance and Risk Management of Medicines division, has stated that "such data sharing, if properly harnessed, could provide an extremely valuable source of information for monitoring the safety of medicines after they have been licensed."

Medicines and Healthcare products Regulatory Agency. UK regulator leads innovative EU project on the use of smartphones and social media for drug safety information [online]. 05 Sep 2014. Available from URL: http://www.mhra.gov.uk/PrintPreview/PressReleaseSP/CON454333. Accessed 12 Nov 2014.

5 Combating Antibiotic Resistance: National Security Priority in USA

The US Federal Government has made combating antibacterial-resistant bacteria a national security priority, and has established the Task Force for Combating Antibiotic-Resistant Bacteria, to be co-chaired by the Secretaries of Defense, Agriculture and Health and Human Services (HHS), said President Barack Obama, in a press release from the White House.

The Federal Government will work within the USA and internationally to detect and prevent antibiotic-resistant infections, implement measures that reduce the emergence and spread of antibiotic-resistant bacteria, and help ensure the availability of effective treatments.

In February 2015, the Task Force is expected to submit a 5-year National Action Plan that outlines actions to be taken to implement the National Strategy for Combating Antibiotic-Resistant Bacteria. The Action Plan will include procedures for creating and integrating surveillance systems and laboratory networks, and will encourage the development of new and next-generation antibacterial drugs, diagnostics, vaccines, and novel therapeutics.

A World Health Organization (WHO) Global Action Plan for Antimicrobial Resistance will also be developed with the assistance of Task Force agencies.

The White House. Executive Order—Combating Antibiotic-Resistant Bacteria [online]. 29 Sep 2014. Available from URL: http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria. Accessed 12 Nov 2014.

6 Vietnam Garners "Impressive Population Health Outcomes"

Vietnam's "impressive population health outcomes" are largely due to the country's focus on making primary healthcare and prevention a priority. This observation was made by Tsung-Mei Cheng, a health policy research analyst at the Woodrow Wilson School of Public and International Affairs at Princeton University, who discussed a wide range of issues related to healthcare and reform in Vietnam with Health Minister Nguyen Thi Kim Tien.

The interview was published in *Health Affairs* and included the following topics: the healthcare workforce and funding; health financing reform and universal coverage; prevention and control of infectious diseases; achieving Millennium Development goals; and the role of government in Vietnam's health system. Of note, Minister Nguyen says that, while Vietnam's health spending is "very small compared to that of most other countries," the offi-

cial WHO figure of $US216 per capita is "too low," and does not reflect "true per capita health spending." However, she continues that the country's spending is still "relatively low," but that 30 % of the total healthcare dollars are allocated to preventive medicine. Minister Nguyen points out that Vietnam has a history of successfully tacking emerging infectious diseases, and was the first country globally to successfully control SARS (severe acute respiratory syndrome). She also highlights the fact that Vietnam has aimed to address the social determinants of health, like education, sanitation facilities, clean drinking water, and improved nutrition to reduce maternal and child undernutrition.

Cheng T-M. Vietnam's health care system emphasizes prevention and pursues universal coverage. Health Affairs 2014; 33(11):2057–63

7 No Further Price Caps on Nonessential Drugs in India

The Government in India has withdrawn the power of the National Pharmaceutical Pricing Authority (NPPA) to cap prices of further nonessential drugs, but price caps that were set for 108 nonessential drugs in July 2014 will remain, according to a Reuters report.

The decision to cap prices of some nonessential drugs in India, in order to make them more affordable to the 1.3 billion people with no health insurance, was challenged in courts. It is likely to affect profit margins of Ranbaxy laboratories and subsidiaries of Sanofi, Merck & Co, Pfizer and Abbott Laboratories.

The NPPA recently added 36 drugs to the list of 348 essential drugs with capped prices.

Kalra A, Siddiqui Z. India withdraws regulator's power to cap non-essential drug prices [online]. 23 Sep 2014. Available from URL: http://in.reuters.com/article/2014/09/23/india-pharmaceuticals-prices-idINKCN0HI0A220140923. Accessed 12 Nov 2014.

8 Swiss Vote Against Move to Public Health System

Sixty-two percent of voters in Switzerland recently opposed the establishment of a single state-run health insurance system, opting instead to retain the current private system, reports the *BMJ*.

The nationwide referendum marks the third time in 10 years that voters have rejected a proposal to move to public health insurance. Such a move is supported by consumer and patient groups, and by the Green Party of Switzerland, which declares that "the profit interests of the powerful insurers have won." They contend that the private system lacks transparency, and that annual increases in health insurance premiums in recent years "have far outpaced consumer price inflation." However, the current government opposes a switch to a public health system, and claims that the latest referendum confirms that most Swiss people are happy with private insurance. Nevertheless, the Swiss interior minister Alain Berset appeared to acknowledge the dissatisfaction of the 38 % who voted for the public system, saying that the vote "helped clarify the situation and paves the way for further reform of the Swiss healthcare system."

Stafford N. Swiss voters reject plan to switch from private to public health system. BMJ 2014; 349:g5990

9 EU Commission Pharma Policy Change Risky

On 10 September 2014, the new European Commission under President Jean-Claude Juncker announced in a EUROPA press release that it intends to move responsibilities for medicines and medical devices, including the EMA, from the Directorate-General for Health and Consumers (DG SANCO)[1] to the DG Enterprise and Industry (DG-ENTR) [1].

In a EurActiv blog, Jim Murray, a former director of the European Consumers Organisation, said making the DG-ENTR responsible for promoting European pharmaceutical industry as well as policies on medicines and medical devices "is a good day for the pharmaceutical industry, but a bad day for public health" [2]. The task of balancing public health interests with interests of pharma companies should not be managed by one DG, and should not be hidden from public scrutiny, he said.

Health Active International (HAI) Europe also warned that this change may endanger public health [3]. HAI said transferring the EMA to DG-ENTR "will create significant threats to clinical trial data transparency in the European Union … and will most likely jeopardise independent review and, ultimately, patient safety." HAI urged Members of the European Parliament to stand against the decision to move the SANCO units to DG-ENTR.

1. Health Action International. Public health in danger with move of pharmaceutical policy to DG Enterprise and Industry [online]. 12 Sep 2014. Available from URL: http://haieurope.org/wp-content/uploads/2014/09/Statement-PH-in-danger-with-move-of-pharma-policy-to-Enterprise.pdf. Accessed 12 Nov 2014.

2. Murray J. A bad start for the new Commission [online]. 11 Sep 2014. Available from URL: http://www.euractiv.com/sections/health-consumers/bad-start-new-commission-308376. Accessed 12 Nov 2014.

3. EUROPA. The Juncker Commission: A strong and experienced team standing for change [online]. 10 Sep 2014. Available from URL: http://europa.eu/rapid/press-release_IP-14-984_en.htm. Accessed 12 Nov 2014.

10 Pharmacovigilance in China: CADRMS

Ahead of the 2014 International Society of Pharmacovigilance (ISOP) meeting in Tianjin, China, *Drug Safety* has published a leading article exploring the current status of pharmacovigilance in China.

The China Food and Drug Administration (CFDA) has set up the legislative framework for a regulatory system to monitor the development, manufacture, distribution and use of drugs. China has a four-level pharmacovigilance network connected by the China Adverse Drug Reaction Monitoring System (CADRMS), an online reporting system that had received over 6.6 million ADR case reports by 2013. The National Centre for ADR Monitoring (NCADRM) publishes ADR bulletins, National ADR Annual Reports and International Pharmacovigilance Newsletters and provides CADRMS data feedback to manufacturers. The CFDA has implemented risk management by arranging meetings with drug manufacturers, modification of drug package inserts, and by controlling marketing authorisations.

"Seamless information exchange with overseas regulatory authorities and organisations remains an area for improvement. Further development of the China pharmacovigilance system in terms of signal generation, post-marketing pharmacoepidemiology research and education is also needed," said the authors.

Zhang L et al. Pharmacovigilance in China: Current situation, successes and challenges. Drug Saf 2014; 37 (10):765–70

11 Patients to Discuss Benefit–Risk with CHMP

The EMA has launched a pilot project to include patients in discussions of benefits and risks of medicines with the Committee for Medicinal Products for Human Use (CHMP).

Patients will be asked for their views on medicines for which there is an unmet medical need and the CHMP has doubts or concerns. Patients may also be asked for their views when the CHMP is considering whether to recommend that marketing authorisation be withdrawn, suspended or revoked, or that an indication be restricted.

The pilot project is expected to run for 1 year or more to assess the feasibility of involving patients in CHMP deliberations.

European Medicines Agency. Patients to discuss benefit-risk evaluation of medicines with the Committee for Medicinal Products for Human Use [online]. 26 Sep 2014. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/09/news_detail_002172.jsp&mid=WC0b01ac058004d5c1. Accessed 12 Nov 2014.

12 Updated EMA Guidance on Periodic Safety Update Reports

The EMA has updated guidance on submissions of periodic safety update reports (PSURs) for nationally authorised medicines that are subject to EU single assessments, which result in recommendations from the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).

Medicines with data lock points after 1 September 2014 require PSURs to be submitted to all Member States where the medicine is authorised, as well as to the EMA. After assessment by a PRAC member, or Member State appointed by the Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh), one single assessment report will be shared among the marketing-authorisation holders.

From October 2014, PSUR single-assessment procedure numbers will be published in advance in the EU reference dates (EURDs) list, and should be included in submissions by marketing-authorisation holders.

PSURs provide an evaluation of the benefit–risk balance of a medicine and are submitted at defined time points following the medicine's authorisation.

European Medicines Agency. Regulatory information: European Medicines Agency updates guidance on European Union periodic-safety-update-report single assessment for nationally authorised medicines [online]. 1 Sep 2014. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/08/news_detail_002160.jsp&mid=WC0b01ac058004d5c1. Accessed 12 Nov 2014.

13 New Yellow Card Guidelines for ADRs in Children

The UK MHRA has published new guidelines on reporting ADRs in children and adolescents via the Yellow Card scheme.

The advice on reporting suspected ADRs is now the same in paediatric patients as in adults. A Yellow Card should be completed for all suspected ADRs that are serious, including ADRs that are fatal, life-threatening, disabling/incapacitating, that cause a congenital abnormality or that lead to hospitalisation, and ADRs considered clinically significant. A Yellow Card should also be completed for suspected ADRs associated with new drugs and vaccines.

Medicines and Healthcare products Regulatory Agency. New guidance on reporting suspected adverse drug reactions in children. Drug Safety Update 2014; 8(2):Y1

14 Substandard Drugs Marketed in Africa

Substandard generic drugs that claim to be manufactured in India are being marketed in Africa, according to the

authors of a National Bureau of Economic Research (NBER) working paper.

The investigators conducted a pilot study assessing the quality of 1,470 generic antibacterial and antitubercular drugs (ciprofloxacin, erythromycin, isoniazid and rifampicin) that were labelled "made in India" and marketed in Africa, India and five non-African countries (Brazil, China, Russia, Thailand and Turkey).

Overall, 11 % of these products failed an assessment of active pharmaceutical ingredients (API); most of the drugs that failed were considered substandard because the amount of API was under-dosed. A thin-layer chromatography (TLC) test was passed by 92–94 % of registered drugs in all regions. However, less than 50 % of unregistered drugs in Africa passed the TLC test, and the majority of those that failed were substandard; 68 % of those in India passed the TLC test and 23 % of drugs that failed were substandard; whilst all unregistered drugs in the other countries passed the test. Substandard products appeared to be related to manufacturing rather than improper handling or storage.

"Some Indian manufacturers as labelled in our drug samples do appear to differentially supply poor quality products to African markets where GDP per capita is low and local regulations are weak," said the authors.

Bate R, et al. Poor quality drugs and global trade: A pilot study [online]. Sep 2014. NBER Working Paper No. 20469. Available from URL: http://www.nber.org/papers/w20469. Accessed 12 Nov 2014.

15 Supercomputers Predict Important ADRs for Drug Candidates

Molecular docking performed on high-performance computers (HPCs or supercomputers) may provide "reliable, cost-effective, comprehensive high-throughput screening of a drug candidate for binding across many known on- and off-targets to predict clinically important ADRs," state researchers from the Computational Engineering Division at the Lawrence Livermore National Laboratory (LLNL) in California, USA.

LLNL researchers have discovered a high-tech method of using supercomputers and information from public databases of drug compounds and proteins (such as DrugBank, UniProt and Protein Data Bank) to identify 'off-target' proteins (from DrugBank) with the potential to cause certain ADRs. A software program belonging to LLNL, called VinaLC, was used to determine docking scores for each combination of the 409 off-target proteins identified along with 906 US FDA-approved small-molecule compounds. Logistic regression modelling was used on the resulting docking scores of a subset of 560 FDA-approved drugs to predict 85 adverse effects, which were grouped into ten ADR phenotype groups. The VinaLC off-target models and the DrugBank on-target models yielded comparable median area under the concentration–time curve (AUC) values during tenfold cross-validation (0.60–0.69 and 0.61–0.74, respectively).

LLNL researchers also noted that the VinaLC off-target model outperformed the DrugBank on-target model for predicting two ADR groups: vascular disorders and neoplasms. Furthermore, several associations between neoplasm-related ADRs and known tumour suppressor (Syk) and tumour invasiveness marker proteins were found, and LLNL researchers stated that "many of these associations involve off-target proteins and would not have been found using only the available drug-target data."

LaBute MX, et al. Adverse drug reaction prediction using scores produced by large-scale drug-protein target docking on high-performance computing machines. PLoS One 2014; 9:e106298

16 Brand-name AIs Linked to Discontinuation, Poor Adherence

Breast cancer patients receiving brand-name aromatase inhibitors (AIs) have lower adherence and a higher rate of therapy discontinuation than those receiving generic AIs, say researchers from the USA. As poor adherence and early discontinuation of hormonal therapy are associated with worse survival, public health efforts "should be directed towards reducing out-of-pocket costs for these life-saving medications," they assert.

Pharmacy and claims data for the period January 2007–December 2012 were derived for 5,511 women (mean age 61 years) with early breast cancer receiving brand-name AIs ($n = 2,815$) or generic AIs (1,411); the remainder switched from brand-name to generic AIs once generic products were introduced in 2010.

The median 30-day co-payment was higher for brand-name than generic AIs ($US33.3 vs. 0.04). A total of 32.6 % of patients receiving brand-name AIs discontinued therapy compared with 16.2 % of those receiving generic AIs. In a multivariable Cox-proportional hazard analysis, therapy discontinuation was linearly associated with higher monthly copayments of $15–30 and >$30. A multivariate logistic regression analysis showed that patients receiving generic AIs were more likely to be adherent to therapy than those receiving brand-name AIs. Adherence was also positively associated with a high annual household income of >$100,000 per year, and inversely associated with co-payment amount.

Hershman DL, et al. The change from brand-name to generic aromatase inhibitors and hormone therapy adherence for early-stage breast cancer. J Natl Cancer Inst 2014; 106(11):dju319

17 NICE Encouraged to be More Favourable to Industry

UK NICE committees are being encouraged to be more favourable to pharmaceutical and medical device industries.

Concerns regarding pressure to permit doctors to prescribe drugs not yet appraised by NICE, and to be more lenient in assessing evidence, have been raised since George Freeman was appointed to a new ministerial post to accelerate innovation in life sciences. Professor James Raftery, from the University of Southampton, said that, with the new minister being responsible for the Department for Business, Innovation and Skills as well as the Department of Health, there is a risk that greater weight will be given to industrial policy, which may impose costs on the NHS.

George Freeman is also responsible for the MHRA, the Cancer Drugs Fund, and a new scheme for the uptake of new drugs and medical technology, which includes adaptive licensing and early access. He said he is committed to accelerating assessment and approval of new promising drugs, and that "the rapid development of breakthroughs in genomics, informatics, and new diagnostics means that NICE's processes will have to adapt."

"This recent change in ministerial accountability leaves NICE's functions unchanged but provides a greater opportunity for us to engage with and influence the development of a more productive relationship between the life sciences industries and the NHS," said Andrew Dillon, the chief executive of NICE. NICE is seeking to employ a non-executive director from the life sciences industry.

Cohen D. Insiders say NICE is being encouraged to be more favourable to industry. BMJ 2014; 349:g6387

18 Time for the USA to Adopt HTAs for Cancer Drugs?

The adoption of some form of health technology assessment (HTA) into US healthcare policy "should be encouraged," as it will "contribute to better decision making and long-term sustainability," contend George Dranitsaris from Canada and George Papadopoulos from Australia.

Dranitsaris and Papadopoulos outline the current rigorous HTA programmes in Australia, Canada and the UK that consider clinical efficacy and safety, price and overall value before a recommendation for reimbursement is made for a new cancer drug. They note that the USA is "unique among developed countries," in that risk sharing, price negotiations and HTA "do not have a role in drug-funding decisions" made by US Medicare. However, they suggest that with the advent of the Affordable Care Act (ACA), "this may change," as reducing costs and improving efficiency "are important components of the ACA." As such, Dranitsaris and Papadopoulos say that HTA and cost-effectiveness assessments may have a "greater role to play" in the reformed US healthcare system. HTA programmes similar to those used in the UK or Australia are unlikely to be implemented in the USA, they say, for "political and historical reasons." Therefore, any HTA programme "must be custom made to fit the unique structure of the US health care system," they conclude.

Dranitsaris G, et al. Health technology assessment of cancer drugs in Canada, the United Kingdom and Australia: Should the United States take notice? Appl Health Econ Health Pol 2014 Oct 2. [Epub ahead of print]

19 Record Seizure of Experimental 'Smart Drugs' in UK

The biggest ever single seizure in the UK of 'smart drugs', also known as cognitive enhancers or nootropics, has been announced by the MHRA.

The seizure came after receiving intelligence from the Norwegian Medicines Agency after a number of packages were detained by Norwegian customs. A full investigation was initiated after a UK source was identified and found to be selling the unlicensed Russian drug, phenylpiracetam [fonturacetam]. Over 20,000 units of 13 different types of cognitive enhancement medicines were seized, representing an approximate value of £200,000. Drugs seized included aniracetam, centrophenoxine (meclofenoxate), citicoline, nefiracetam, oxiracetam, phenibut, pramiracetam, sulbutiamine, sunifiram, vinpocetine, Noopept (GVS-111), phenylpiracetam and picamilon (nicotinoyl-GABA).

The MHRA has stated that the seizure of such a large range of cognitive enhancers illustrates the burgeoning demand and variety of new active substances entering the marketplace. In addition, it highlights concerns around increasing experimentation among users of these substances. One of the products seized, sunifiram, has never been tested or undergone clinical trials in humans.

While it is not illegal to possess any of the seized medicines, sale and supply of a prescription-only or unlicensed medicine is an offence in the UK. MHRA Head of Enforcement, Mr Alastair Jeffrey, has stated that "the idea that people are willing to put their overall health at risk in order to attempt to get an intellectual edge over others is deeply troubling." In addition, Ms Barbara Sahakian from the University of Cambridge School of Clinical Medicine warns that "there are also no long-term safety studies of the effects of these cognitive enhancing drugs in healthy

people," and that purchasers may not be aware of what the drug actually contains or whether it is contraindicated for them specifically.

Medicines and Healthcare products Regulatory Agency. Medicines watchdog makes record seizure of experimental smart drugs [online]. 29 Oct 2014. Available from URL: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON468298. Accessed 12 Nov 2014.

20 Inclusive Shared Savings "a Step in the Right Direction"

While "not a panacea to control cost," a strategy of inclusive shared savings "offers a step in the right direction," contend Drs. Harold Schmidt and Ezekiel J. Emanuel from the University of Pennsylvania, USA.

Drs. Schmidt and Emanuel suggest that the strategy of inclusive shared savings, which aims to lower medical costs through savings shared by patients and physicians, may be "particularly attractive" in situations where treatments have similar clinical effectiveness and moderate differences in convenience, but "substantially differ in cost." They contend that an inclusive shared savings strategy would retain physicians' incentives for providing lower-cost but "otherwise equivalent" interventions, but would extend the shared savings to patients. Such a strategy would fully align patients' out-of-pocket costs with the value of health services, thus financially rewarding patients for choosing less costly but equally effective treatments.

Drs. Schmidt and Emanuel also note that an inclusive shared savings strategy "may encourage shared decision making," as physicians would be required to inform patients about the clinical comparability and costs of their therapeutic options. In addition, patients would be protected from selecting "cheaper but inferior" interventions, assert Drs. Schmidt and Emanuel, as the available options would be based on expert opinion and evidence-based guidelines. They conclude that the inclusive shared savings approach "should be evaluated in a rigorous trial or demonstration project."

Schmidt H, Emanuel EJ. Lowering medical costs through the sharing of savings by physicians and patients: inclusive shared savings. JAMA Intern Med. Published online 20 October 2014. doi:10.1001/jamainternmed.2014.5367

21 Biosimilars Escalating, Expected to Deliver Big Savings

With 700 biosimilars moving through drug pipelines or already approved, they are expected to account for a quarter of sales from off-patent biologics by 2020, according to a *Thomson Reuters* report. Biosimilars have the potential to offer the benefits of reference biologics at prices that are affordable in developing countries.

A study complied by *Thomson Reuters BioWorld* provides information for companies and regions interested in the emerging biosimilars market. South Korea is the current leader in this market, and India expects that biosimilars will become the primary drugs in its biopharma industry.

According to the study, biosimilars offer cost savings of 20–30 % compared with innovator biologics, and are expected to provide cost savings of $11–33 billion in the EU by 2020. Small start-up companies manufacturing biosimilars could dominate large pharma companies in emerging regions. Although the market uptake of biosimilars in the EU is slow, the USA will permit interchange ability, which is expected to increase the speed of uptake and lower prices. It is expected that lower-priced biosimilars will permit accessible treatment with biologicals for the first time in African, Asian, Eastern European and Latin American markets.

Thomson Reuters. Getting ahead in the emerging biosimilars market [online]. 29 Sep 2014. Available from URL: http://thomsonreuters.com/articles/2014/getting-ahead-in-the-emerging-biosimilars-market. Accessed 12 Nov 2014.

22 3-D Printers Could Provide Low-Cost Personalised Drugs

Researchers at the University of Central Lancashire in England have developed a technique that enables 3-D printers to create customised drugs.

The technology, which is undergoing a patent application, can be used to replicate existing tablets and to create drugs tailored according to a patient's needs. It has the potential to reduce the cost of manufacturing personalised tablets for individuals, which was estimated to cost the NHS more than £11 million for the month of March in 2011.

The researchers developed a drug-polymer filament, to replace the standard filament in a 3-D printer, that can be used to print tablets with improved appearance while maintaining accurate weight and dose. The technique is expected to be used by pharmaceutical companies and hospitals within 5 years and could be used by the public within 10 years.

"The invented system can provide medical institutions with a new option and maintain dosage form properties while accurately adjusting the dose with simple software order, something that was considered before to be costly and required experienced staff and dedicated facilities," said Dr. Mohamed Albed Alhnan from the School of Pharmacy and Biomedical Sciences.

Boardman L. 3D printers could create customised medicines on demand, says the University of Central Lancashire [online]. 22 Oct 2014. Available from URL: http://www.uclan.ac.uk/news. Accessed 12 Nov 2014.

23 Increasing Patient Engagement Pays Off Around the Globe

Increased patient engagement "at all levels" may lead to decreased costs and avoid costs wasted on "well-intentioned but poorly designed initiatives that are destined to fail because they do not address the needs of patients and families," contends a multinational team of researchers.

The research team selected four case studies from around the globe to illustrate "how the opportunities for engagement set out in the global health partnership framework are being pursued." The first of these case studies is the 'Big White Wall', on online mental health community set up in 2007 in the UK where members can gain support in managing their care from family members, clinicians and other sufferers. An economic review of the Big White Wall indicated that it is producing savings of £370 per member per year, through reducing demands on the UK NHS, while "achieving high levels of satisfaction and improved outcomes." The second case study concerns the United Arab Emirates (UAE) genetic screening initiative, started a decade ago. Mandatory premarital screening was subsequently introduced. As part of the initiative, student ambassadors were recruited to educate their peers about the importance of genetic screening.

The third case study involves the development of the WHO 7-day mother and baby postnatal checklist, delivered via the mCheck system. The aim of the checklist is to assist new mothers in playing a more active role in their baby's medical care, and to increase their "engagement, commitment, and power in managing her family's health." Results from a pilot study using the checklist in India are awaited. The final case study concerns an initiative introduced in 2009 at the Beth Israel Deaconess Medical Centre in Boston, USA, which sought to increase the involvement of patients and their families in improving care. Allowing patients access to their clinical records resulted in 77–87 % of patients reporting feeling more in control of their healthcare, and led to increased medication adherence.

The researchers conclude that the "encouraging message" from these case studies is that "patient, family, and community involvement may improve the effectiveness of existing programmes of health care as well as extending their reach."

Laurance J, et al. Patient engagement: four case studies that highlight the potential for improved health outcomes and reduced costs. Health Affairs 2014; 33(9):1627–34

24 Less Toxicity with Targeted Therapies Spells Lower Costs

Newly approved anticancer drugs are associated with an increased risk of serious adverse events, except for agents directed against specific molecular targets on cancer cells, according to a multinational group of investigators [1]. Their results "provide exciting news," say Terhi Hermanson from Helsinki University Central Hospital, Helsinki, Finland, and colleagues, in an accompanying editorial [2]. While targeted therapies are costlier than traditional chemotherapy, the higher costs "are offset by less costly toxicity management," Hermanson and colleagues add.

For their meta-analysis, the investigators identified 19 experimental anticancer drugs approved by the US FDA during the period 2000–2011, and assessed grade 3–4 toxicities occurring among patients participating in the pivotal trials supporting their approval [1]. They also determined costs (2013 $US) associated with acquisition of the drugs and with managing toxicity.

Grade 3–4 adverse events occurred among 3,793 patients in experimental arms and 2,145 patients in control arms. The most commonly reported adverse event was treatment-related fatigue, followed by diarrhoea, nausea and vomiting, febrile neutropenia and rash. Compared with controls, the pooled relative risk of any grade 3–4 toxicity was 0.67 (95 % confidence interval [CI] 0.36–1.27) for targeted therapies, 1.73 (95 % CI 1.25–2.40) for new chemotherapy, and 3.39 (95 % CI 2.23–5.15; $p < 0.001$) for less-specific targeted therapies. The median monthly cost associated with drug treatment was $6000, with less-specific targeting therapies costing the most. Costs associated with managing grade 3–4 adverse events were estimated at an average of $50 per patient for those receiving targeted therapies compared with $275 and $140 per patient for those receiving less-specifically targeted therapies and chemotherapy, respectively.

Hermanson and colleagues point out that some beneficial targeted therapies, such as rituximab and trastuzumab, were registered before the period studied by the investigators [2]. They contend that, if these drugs had been included, the finding of less toxicity in the targeted therapy arms "might have been even more pronounced."

1. Niraula S, et al. Risk of incremental toxicities and associated costs of new anticancer drugs: a meta-analysis. JCO 2014; 32(32):3634–42
2. Hermanson T, et al. Toxicity and costs of toxicity associated with new cancer drugs: International implications. JCO 2014; 32(32): 3591–92

25 Reports of Muscle Rupture with Statins in Netherlands

The Netherlands Pharmacovigilance Centre Lareb has received 11 reports of muscle rupture associated with the use of statins in the period from 22 February 2006 until 12 January 2014.

Statins are indicated for the treatment of hypercholesterolaemia, and among the most important and well-known ADRs of statins are the musculoskeletal ADRs (e.g. myalgia, muscle cramp, myopathy, myositis and rhabdomyolysis).

Across the 11 case reports of muscle rupture associated with statin use, the drugs of interest included simvastatin, rosuvastatin, atorvastatin, pravastatin and fluvastatin.

Lareb noted that the association between statin use and muscle rupture showed "strong significant disproportionality" in its own database and those of the WHO (107 reports) and Eudravigilance (118 reports). While this association has not been described in the literature, "it is plausible that statin-induced myotoxicity can predispose muscles to tear," according to Lareb. The agency concludes that its data suggest that "statin-induced muscle rupture can occur without intense muscle contraction and without the presence of myalgia" and that this association "is a new signal" that requires further investigation by the marketing authorisation holder and other national centres.

Netherlands Pharmacovigilance Centre Lareb. Statins and muscle rupture [online]. Oct 2014. Available from URL: http://databankws.lareb.nl/Downloads/KWB_2014_3_statin2.pdf. Accessed 12 Nov 2014.

26 Immunoglobulin Products: Risk of Blood Clots

Following a safety review, prescribing information for all immunoglobulin products in Canada (including Gamastan S/D, Gammagard liquid, Gammagard S/D, Gamunex, Hizentra, IGIVnex, Immune Serum Globulin [Human], Octagam and Privigen) has been updated to strengthen warnings on the rare but serious risk of blood clots that may result in myocardial infarction or stroke, says Health Canada.

Blood clots are a known risk with immunoglobulins injected intravenously, but evidence suggests that the risk also exists with other routes of administration, including intramuscular and subcutaneous injections. Blood clots have been reported in patients with and without risk factors, and irrespective of immunoglobulin dosage or route of administration.

A notice has been sent to healthcare professionals to inform them of the updated warnings and risk factors associated with blood clots.

Health Canada. Information Update: Safety information on the risk of blood clots with immunoglobulin products [media release]. 9 Oct 2014. Available from URL: http://www.hc-sc.gc.ca. Accessed 12 Nov 2014.

27 Dopamine Receptor Agonists: Risk of Impulse Control Disorders

Dopamine receptor agonists are associated with a risk of impulse control disorders, according to the findings of a retrospective study published in *JAMA Internal Medicine* [1].

The investigators identified 1,580 cases of impulse control disorders reported to the US FDA Adverse Event Reporting System; 710 cases were in patients receiving dopamine receptor agonists and 870 cases were in patients receiving other drugs.

Dopamine receptor agonists were strongly associated with impulse control disorders (proportional reporting ratio [PPR] 277.6; $p < 0.001$). The association was strongest for pramipexole (PPR 455.9; $p < 0.001$) and ropinirole (PPR 152.5; $p < 0.001$), but a signal was also observed for aripiprazole (PPR 8.6; $p < 0.001$).

"At present, none of the dopamine receptor agonist drugs approved by the FDA have boxed warnings as part of their prescribing information," the investigators noted. They said data from this study, as well as previous studies, demonstrate that more prominent warnings are required.

In a commentary in *JAMA Internal Medicine* [2], Dr. Joshua Gagne, from Brigham and Women's Hospital and Harvard Medical School, questioned whether the association found in the study was "a true causal connection and not merely a pattern among random data." He concluded that "the likelihood of a causal connection is high."

"Physicians have overestimated the benefit and underestimated the risks associated with the use of dopamine receptor agonist drugs in patients with Parkinson disease. In our view, these medications should be used less frequently and with great caution, paying close attention to possible untoward effects on behavior and impulse control," said Dr Howard Weiss and Dr Gergory Ponone, from Johns Hopkins University, in another commentary in *JAMA Internal Medicine* [3].

1. Moore TJ, et al. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Intern Med. Published online 20 October 2014. doi:10.1001/jamainternmed.2014.5262

2. Gagne JJ. Finding meaningful patterns in adverse drug event reports. JAMA Intern Med. Published online 20 October 2014. doi:10.1001/jamainternmed.2014.3270

3. Weiss HD and Pontone GM. Dopamine receptor agonist drugs and impulse control disorders. JAMA Intern Med. Published online 20 October 2014. doi:10.1001/jamainternmed.2014.4097