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UPDATE

Forum

1 EMA Acknowledges Outcome of Recent UK Referendum

The European Medicines Agency (EMA) has acknowledged the result of the recent UK referendum for the nation to leave the European Union (EU), but emphasised that its operations will continue as usual in the meantime.

On 23 June this year, a majority voted against continued membership of the UK within the EU and "it is now up to the UK government to decide how to act upon the outcome of the referendum", stated the EMA. The agency highlighted that "no Member State has ever decided to leave the EU, so there is no precedent for this situation".

The EMA also acknowledged and welcomed the expressions of interest from some EU Member States to host the agency in the future (given the EMA's headquarters are currently in London, UK). However, the agency noted that the decision on the future location of the EMA following the exit of the UK from the EU will be decided by the common agreement among the remaining Member States.

"We are confident that the Member States will take the most appropriate decision on [the] EMA's location and arrangements in due course, taking also into account the complex political and legal environment generated by the outcome of the UK referendum", concluded the EMA.

European Medicines Agency. Statement on the outcome of the UK referendum. 2016 Jul 6. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002566.jsp&mid=WC0b01ac058004d5c1. Accessed 8 Aug 2016.

2 First-In-Human Clinical Trial Guidelines Under Review in EU

A EU-wide review is underway into first-in-human clinical trials and the data needed to enable appropriate design and trial initiation, according to the EMA.

This review—which will focus on best practices and guidance—is being conducted in conjunction with the European Commission and all EU Member States. The review will also identify areas that may need revising following the death of a volunteer (and hospitalisation of five others) during a phase I first-in-human clinical trial of BIA 102474 in Rennes, France in January this year. Furthermore, the EMA's review will consider the findings from two in-depth investigations conducted by the Temporary Specialist Scientific Committee set up by the French regulatory agency, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), and the Inspectorate for Social Affairs in France. Last week, the ANSM determined that approval of the first-in-human trial of BIA 102474 was justified, despite the resulting death and neurological adverse effects experienced by the trial participants.

Two groups of experts have already initiated preparatory work. One group is looking at preclinical aspects and the data required from laboratory tests and animal studies to safely initiate first-in-human clinical trials. The second group is evaluating clinical aspects of the design of first-in-human clinical trials, and how these could be improved to ensure the safety of volunteers involved in these trials. Information from these two groups will be used to agree upon a concept paper by July this year, which will identify areas for change and proposals to further minimise the risk

of similar accidents. Subsequently, this concept paper will form the basis of an EU-wide expert group discussion on the revision of guidelines, which will include targeted discussions with stakeholders and public consultation on the proposed changes later this year.

European Medicines Agency. Improving safety of first-in-human clinical trials. 2016 May 27. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/05/news_detail_002538.jsp&mid=WC0b01ac058004d5c1. Accessed 8 Aug 2016.

3 Canadian Guidelines for Labelling, Packaging of Drugs

New practice guidelines are available in Canada that are designed to provide safe and clear labelling and packaging for prescription drugs, non-prescription drugs and natural health products.

Health Canada has highlighted that "the label and package are the first points of interaction between a health product and a consumer or healthcare professional" and also that "they communicate key information about the safe and proper use of health products". The agency also noted that the "Plain Language Labelling Initiative" has been introduced in an effort to make the label and packaging of any given product easier to read and understand. The information presented in these guidelines is intended to provide direction to pharmaceutical companies (sponsors), manufacturers and license holders, and ultimately to support the design and development of labels and packages (both inner and outer) "that are clear, effective, and minimize the risk of errors causing harm", stated Health Canada.

The first guideline—entitled the "Good Label and Package Practices Guide for Prescription Drugs"—is focussed on prescription pharmaceuticals, biologics and radiopharmaceuticals, and drugs that are permitted to be sold without a prescription but that are obtained or administered under the guidance of a healthcare professional (e.g. insulin, injectable epinephrine, exempted codeine preparations) [1].

The second guideline—entitled the "Good Label and Package Practices Guide for Non-prescription Drugs and Natural Health Products"—is focussed on both of these categories as well as contact lens disinfectants [2].

Aspects of product labelling that are not covered in either of the guidelines include the naming of health products, user-applied labels, product monographs, package inserts, and Patient Medication Information.

1. Health Canada. Good label and package practices guide for prescription drugs. 2016 Jun 30. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2016-label-package-practices-pratiques-etiquetage-emballage-rx/index-eng.php. Accessed 8 Aug 2016.
2. Health Canada. Good label and package practices guide for non-prescription drugs and natural health products. 2016 Jun 30. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2016-label-package-practices-pratiques-etiquetage-emballage-non/index-eng.php. Accessed 8 Aug 2016.

4 PHARMAC to Change the Way it Makes Decisions

In its most significant change in 23 years, New Zealand's Pharmaceutical Management Agency, PHARMAC, has announced it will now take into consideration the impact of a funding decision on a person, their extended family and on wider society.

The change came about after extensive, nationwide consultation with a range of stakeholders—including patients, clinicians, care-givers and consumers.

PHARMAC will consider these impacts in terms of need, health benefits, costs and savings, and suitability.

"This change has been collaborative, and reflects the considerable input of the public to our consultation…PHARMAC have always taken into account a wide range of factors when we make decisions, but this improvement means we are more explicit about them. This greater clarity will have benefits for our decision-making and for public understanding of how PHARMAC goes about its work", said PHARMAC Chief Executive Steffan Crausaz.

PHARMAC. New Zealand public help improve PHARMAC decision making. 2016 Jul 6. Available from URL: https://www.pharmac.govt.nz/news/media-2016-07-06-factors. Accessed 8 Aug 2016.

5 Switzerland to Resume Drug Pricing Controls

Switzerland will resume drug pricing controls in 2017, which could save the country CHF180 million over three years, according to Switzerland's Health Minister, Alain Berset.

Between 2012 and 2014, the price checking policy of comparing the cost of drugs in Switzerland with that of other countries saved Switzerland CHF600 million (equivalent to $US618 million). However, after the Swiss Federal Court ruled last year partially in favour of a pharmaceutical company complaint that price controls were unfair, amendments have been made to include requirements for the Federal Health Office to include consideration of the comparative clinical effectiveness of different medications for the same condition, as well as comparing costs.

Additionally, Berset announced that he will focus on the high price of generic drugs, which are estimated to cost

50 % more in Switzerland compared with other European countries. Generic prices will be linked to the volume of sales of the original brand-name drug, with a higher number of sales corresponding to a greater price difference between the generic and original drug. This method of pricing generic drugs is expected to result in an additional saving of CHF80 million over the 3-year post-implementation period. However, the generic price reference system is not expected to be in place before 2019 due to law revisions being required.

Swissinfo. Government to resume drug pricing controls. 2016 Jul 6. Available from URL: http://www.swissinfo.ch/eng/health-check_government-to-resume-drug-pricing-controls/42277762. Accessed 8 Aug 2016.

6 PMDA's Safety Information Email Service Now More User-Friendly

Improved, user-friendly versions of a Japanese safety information email alert service (PMDA Medi-navi) and its additional feature (called "My Drug List for Safety Updates") are now available.

Implemented in March 2016, the PMDA Medi-navi service sends email alerts (only available in Japanese language) to registered institutions when important safety information is issued by Japan's Ministry of Health, Labour and Welfare (MHLW) or Pharmaceuticals and Medical Devices Agency (PMDA) to healthcare professionals regarding the safety of pharmaceutical agents and/or medical devices. Examples of such information may include "MHLW Urgent Safety Information", "Dear Healthcare Professional" letters, and notifications of revised precautions, among other relevant information.

At the end of March 2016, the PMDA enhanced the functions of PMDA Medi-navi and its additional feature ("My Drug List for Safety Updates"), which can be utilised by users registered on PMDA Medi-navi. However, separate registrations are required to use each of these services.

Approximately 135,000 users have registered to receive PMDA Medi-navi, as at the end of March 2016.

From early June this year, registration forms for PMDA Medi-navi have been distributed to medical institutions (mainly general clinics and pharmacies, where the service is currently not well utilised), with cooperation of the member companies of the Federation of Pharmaceuticals Manufacturers' Associations of Japan (FPMAH) and the Japan Pharmaceutical Wholesalers Associations (JPWA).

The PMDA stated that "PMDA Medi-navi is an important tool for accessing important information promptly and reliably". Further information can be obtained from the PMDA Medi-navi website (https://www.pmda.go.jp/safety/info-services/medi-navi/0007.html).

Pharmaceuticals and Medical Devices Agency of Japan. Use of "PMDA Medi-navi" and "My Drug List for Safety Updates". Pharmaceuticals and Medical Devices Safety Information 333: 4–9.

7 Patient-Reported Data Important to Current and Future PV Activities

Patient-reported safety information makes an important contribution to current pharmacovigilance (PV) activities—but more can be done to enhance the value of this information.

Dr. Linda Härmark from the Netherlands Pharmacovigilance Centre Lareb, and her colleagues, noted that patient reports provide first-hand information about the suspected adverse drug reaction (ADR) and the circumstances under which it occurred, as well as a better understanding of the patient's experience of the ADR. They noted that since the introduction of the new PV legislation 3 years ago in the EU, the time is right to evaluate if the current PV methods make the best use of such patient-reported data.

The researchers noted that it may be worthwhile considering if ADR reporting forms for healthcare professionals (HCPs) and patients "should be clearly differentiated in order to better capture the different kinds of information that the reporter can provide".

Further value could also be added to current PV methodologies if reports of suspected ADRs could be differentiated by severity (i.e. patient reports are helpful in determining this) and seriousness (i.e. as determined by the Council for International Organizations of Medical Sciences [CIOMS] definition).

Although PV database structures have been primarily developed based on primary information from HCPs, further development of the coding and structure of these databases could maximise the value of patient-reported data.

7.1 Full Potential Yet to be Realised

Dr. Härmark and her colleagues also highlighted that "a major issue to be addressed if the potential of patient reporting is to be realised is that awareness about ADR reporting systems is in general quite low among the general public". They noted that one way of dealing with this issue would be to actively approach patients. Another way could be to use social media data, but ethically-sound policies would need to be developed as this is a new methodology of obtaining patient data.

"When raising awareness about pharmacovigilance, it is important to show the general public what is done with their information and how that contributes ultimately to

safer use of medicines and better patient care", stated Dr. Härmark and her colleagues. They noted that patient representatives are included in the EMA's Pharmacovigilance Risk Assessment Committee, and that the agency plans to hold public hearings in 2016 whereby drug safety issues and any risk-minimisation options will consider the patients' perspectives.

The researchers concluded that "it is time for a renaissance of pharmacovigilance", and that active promotion of patient-oriented ADR reporting "is necessary and those organisations responsible for the processing and assessing of these reports should develop the means to do this".

Härmark L, Raine J, Leufkens H, et al. Patient-reported safety information: a renaissance of pharmacovigilance? Drug Saf. Epub 5 Jul 2016. doi:10.1007/s40264-016-0441-x. Accessed 8 Aug 2016.

8 EMA: Single Platform for Drug Safety Updates Now Mandatory

All periodic safety update reports (PSURs) for EU-authorised medicines must now be submitted to a single central platform (repository), says the EMA.

This repository—which has been developed by the EMA, in collaboration with EU Member States and the pharmaceutical industry—will contain PSURs (and related documents) that will be available for use by regulatory authorities and pharmaceutical companies within the EU.

PSURs provide an evaluation of the benefit-risk balance of a medicine, and marketing authorisation holders are required to submit these reports at defined time points after the medicine has been approved.

As of 13 June, submissions to the repository became mandatory, and PSURs should no longer be submitted to individual national competent authorities. The EMA has stated that "the PSUR repository provides an important simplification for marketing authorisation holders" and that "it also facilitates the assessment of the reports by ensuring that national competent authorities, EMA and its scientific committees have timely and secure access to all relevant documents".

The PSUR repository was initially released in January 2015. After a phased implementation approach, feedback from users, and an independent audit, the EMA approved use of the repository in June 2015.

European Medicines Agency. Single, central platform now mandatory for all periodic safety update reports. 2016 Jun 10. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002547.jsp&mid=WC0b01ac058004d5c1. Accessed 8 Aug 2016.

9 Survey Volunteers Wanted for European Web-RADR Project

Volunteers are needed for a survey as part of the European Web-RADR project—which is led by the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

This "ground-breaking" 3-year Web-RADR project (which reached its mid-point at the end of April this year) aims to "digitally revolutionise the way adverse drug reactions are reported and monitored", stated the MHRA.

As part of this project, two different surveys are available—one is for completion by healthcare providers and another survey may be completed by patients or medicine consumers. Results from these surveys will be used to make enhancements to the MHRA's Yellow Card app, and to increase the general knowledge about ADR reporting and receiving medicines safety information.

The surveys may be completed anonymously and will take around 15–20 min to complete. Survey participants will be eligible to enter a prize draw to win a €50 coupon, as a token of appreciation.

Medicines and Healthcare products Regulatory Agency. Volunteers wanted to help determine the future of pharmacovigilance. 2016 Jul 11. Available from URL: https://www.gov.uk/government/news/volunteers-wanted-to-help-determine-the-future-of-pharmacovigilance. Accessed 8 Aug 2016.

10 ABPI Publishes Details of Industry Payments to Health Professionals

On the back of research showing the majority of healthcare professionals support greater transparency, the Association of the British Pharmaceutical Industry (ABPI) has for the first time published details of payments or benefits in kind made to doctors, nurses and pharmacists, as well as other health professionals and healthcare organisations in the UK on a publicly accessible database—Disclosure UK.

The database outlines payments from 109 pharmaceutical companies in the UK, and shows that in 2015, the industry paid a total of £340.3 million to health professionals and organisations, of which 67 % (or £229.3 million) was for activities related to the research and development of new medicines. The remaining £111 million of non-research and development activities was made as payments made to individual healthcare professionals and healthcare organisations, for a range of activities, such as registration fees (£4 million), sponsorship agreements with healthcare organisations and third parties (£16.6 million), donations and grants (£30.3 million), and fees (£39.8 million).

Around 70 % of individual healthcare professionals gave consent for the information to be disclosed on a named basis, and the database can be searched according to the recipient's name, profession or professional address. The database also includes information on payments made to companies and organisations.

Chief Executive for the ABPI, Mike Thompson, said "this is a milestone moment for transparency in our industry and for the vital partnerships we have with health professionals and organisations across the UK…We're committed to transparency—we believe it's right that the public has the opportunity to see some of the detail behind how we work with doctors, nurses, pharmacists and organisations".

Association of British Pharmaceutical Industry. Pharmaceutical industry spends GBP340.3m on working in partnership with leading UK health experts and organisations to improve patient care. 2016 Jun 30. Available from URL: http://www.abpi.org.uk/media-centre/newsreleases/2016/Pages/Pharmaceutical-industry-spends-Lstg340.3m-on-working-in-partnership.aspx. Accessed 8 Aug 2016.

11 English Patients Set to Benefit from Accessing Their Online GP Records

As a result of the General Practice (GP) Forward View launched by National Health Service (NHS) England in April 2016, over 55 million patients in England will now be able to view test results as they come in, and monitor their glucose levels and cholesterol on their smartphones, allowing them to have better control of their care and manage their health.

Over 95 % of GP practices are now set up to offer online access to detailed GP records including test results and diagnoses as well as referrals, immunisations, procedures and medications history.

In March 2016, 8.5 million patients have signed up to book appointments online, with 1.4 million appointments booked or cancelled, an increase of over 100 % from April 2015.

Benefits of these services reported by GP practices and patients include: empowered patients, reduced workload for GP practices, and a more convenient service for both patients and GPs.

Commenting on the initiative, NHS England National Director for Commissioning Operations and Information, Matthew Swindells, said "we want to give people the tools they need to confidently manage their health. Encouraging patients to access their GP record online helps put them in the driving seat of their care".

NHS England. Over 55 million patients in England set to benefit from accessing their GP record online. 2016 Jul 4. Available from URL: https://www.england.nhs.uk/2016/07/gp-records-online. Accessed 8 Aug 2016.

12 Adverse Event Collection by Questionnaires

Results of a study reported in *Vaccine* revealed that a paper-based questionnaire to collect adverse event information following influenza vaccination is more representative of the target group than a web-based questionnaire. However, a web-based approach seems to be more suitable "for situations where information about adverse events on a national level is desirable".

Active surveys were conducted in the Netherlands following the administration of seasonal vaccination with influenza virus vaccine (Vaxigrip or Influvac) and/or 1–2 doses of pandemic influenza A virus vaccine H1N1 (Focetria) in 2009/2010. The National Institute of Public Health and the Environment (RIVM) used a paper-based questionnaire to collect data from patients who attended primary care practices in the province of Utrecht. Influenzanet used a web-based questionnaire to collect data from their participants throughout the country.

Data analysis was restricted to patients >24 years of age. Patient age was significantly higher in patients who completed the paper-based questionnaire compared with those who completed the web-based questionnaire, with 79 vs 37 % of patients aged ≥60 years of age ($p < 0.001$).

Overall, the incidence of local events, such as redness, swelling and/or pain at the injection site, was similar following completion of the paper-based or web-based questionnaires, after adjustment for differences in age, gender and comorbidity [odds ratio (OR) 0.98; 95 % CI 0.88, 1.10; $p = 0.78$]. The incidence of systemic events, such as fever, dizziness, myalgia and/or fatigue, was also similar (OR 1.12; 0.99, 1.27; $p = 0.06$). Nevertheless, approximately twice as many adverse events were reported following pandemic vaccine administration from the web-based questionnaire compared with the paper-based questionnaire. In both groups of patients, there was a decreasing trend in local reactions with consecutively administered vaccination.

The advantage of the web-based questionnaire is patient recruitment from throughout the country, note the authors, which would be a major logistical operation for a paper-based questionnaire. However, they add that "attention should be paid to the representativeness" of the web-based questionnaire.

Kemmeren J, Honsbeek M, Dijkstra F, et al. Comparison of different collection methods for reported adverse events following pandemic and seasonal influenza vaccination. Vaccine. 2016; 34 (34): 3961–6.

13 INTERPOL Targets Illicit Sale of Fake Medicines, Products Online

Over 12 million fake and illicit medicines, and more than 270 000 medical devices, have been seized as part of INTERPOL's Operation Pangea IX. The operation was coordinated by INTERPOL and supported by a number of other organisations (including the World Customs Organisation, the Pharmaceutical Security Institute, the Center for Safe Internet Pharmacies) as well as private sector companies from the internet and payment industries (e.g. PayPal, MasterCard and VISA).

During the recent International Internet Week of Action (30 May to 7 June), several raids took place at addresses linked to illegal pharmaceutical websites, as well over 170 000 seizures by customs and regulatory agencies. At least 40 cases worldwide were found to be directly linked to organised crime, and close to 5000 websites have been suspended for selling illicit pharmaceuticals.

Operation Pangea has resulted in almost 400 arrests worldwide, and >$US53 million worth of potentially dangerous medicines/products have been seized—such as anticancer medicines, slimming pills, antimalarials, cholesterol medications, erectile dysfunction pills, hair loss treatments and nutritional products. Authorities in Singapore also seized illicit anabolic steroids, pregnancy test kits and infertility drugs.

In addition, Hungarian police seized approximately 65,000 anti-anxiety tablets hidden in the back seat of a car and in the spare tyre, and similar smuggling efforts involving narcotics were foiled in Austria. An underground laboratory producing illicit medicines and steroids was also uncovered in Austria.

A US Food and Drug Administration (FDA)-led investigation between August 2013 and January 2014 revealed that one US customer died in October 2013 after ingesting a 2, 4-dinitrophenol (DNP)-containing weight loss product that had been purchased on eBay; the seller pleaded guilty in May this year to one count of introduction of an unapproved drug into interstate commerce. In May 2015, the FDA had issued an Orange Notice about the dangers of DNP, following the death of one person in the UK, and another person from France who was left seriously ill, after ingesting a substance purchased over the internet.

Tim Morris, Executive Director of Police Services at INTERPOL, commented that "raising public awareness about the dangers of buying medicines online is essential if we are to choke off this source of funding for organized crime which is making significant profits at the cost of people's health and safety".

INTERPOL. Online sale of fake medicines and products targeted in INTERPOL operation. 2016 Jun 9. Available from URL: http://www.interpol.int/News-and-media/News/2016/N2016-076. Accessed 8 Aug 2016.

14 ICER Calling for Input on Value Assessment Framework

The US Institute for Clinical and Economic Review (ICER) is calling for suggestions on how to improve its value assessment framework. ICER will accept comments until 12 September 2016, and will use the suggestions to guide internal review and discussions with stakeholders, before finalising an updated version of the value framework.

The purpose of the value framework is to support dialogue between healthcare stakeholders, including clinical experts, companies, insurers, patient groups, and other interested parties, on "how best to use evidence as the cornerstone of improvements in clinical practice, coverage policies, and pricing". The most recent iteration of the framework has been used for over 12 months, during which time it has evolved based on feedback and experience.

Priority areas for potential revision include:

- methods to integrate perspectives of patients and clinicians on the value of interventions not adequately reflected in published literature, which may have "additional benefits or disadvantages" or "contextual considerations";
- appropriate cost-effectiveness thresholds, and best practice in capturing health outcomes for determining incremental cost-effectiveness ratios;
- methods of estimating market uptake and the potential short-term budget impact of new interventions;
- methods to set a threshold for short-term budget impact that alerts policymakers to the need to address affordability through the introduction of measures to improve the impact of a new intervention on the overall healthcare system.

Comments should be emailed to: publiccomment@icer-review.org

Institute for Clinical and Economic Review. ICER opens national call for proposed improvements to its value assessment framework. 2016 Jul 14. Available from URL: https://icer-review.org/announcements/improvements-value-framework. Accessed 8 Aug 2016.

15 Germany to Extend Price Brake on Reimbursed Drugs

Under a new draft law in Germany, the price brake introduced in 2009 on drugs covered by statutory health insurance is to be extended for another 5 years after 2017,

says Reuters. This extension is expected to achieve savings of €1.5–€2 billion, the health ministry estimated.

In addition, under the draft law, the German government wants to reduce prices of new drugs within the first year if sales exceed €250 million.

Reuters. Germany plans to extend price brake for drugs under statutory insurance. 2016 Jul 25. Available from URL: http://www.reuters.com/article/us-germany-pharmaceuticals-idUSKCN1051RS. Accessed 8 Aug 2016.

16 Criteria for Using Expert Judgement in Economic Studies

Reporting criteria for two types of study design that use expert judgement in model-based economic evaluations (EE) have been recommended in guidelines published in *PharmacoEconomics*.

The aim of this study was to produce reporting criteria for two types of study design to use expert judgement in model-based EE: an expert elicitation quantitative study, and a Delphi study to collate qualitative expert opinion. A two-round online Delphi survey was used to identify the degree of consensus on four core definitions (expert; expert parameter values; expert elicitation study; expert opinion) and two sets of reporting criteria, in a panel of 12 experts. Data analysis summarised the extent of agreement based on a pre-defined 75 % threshold for consensus.

Consensus was achieved for definitions of expert (88 % agreement), expert parameter values (83 %), and expert elicitation study (83 %). The panel recommended 16 criteria to use when reporting an expert elicitation study (research rationale, research problem, measurement of uncertain quantities, definition of an expert, number of experts, preparation, piloting, data collection, administration, the exercise, data aggregation, measures of performance for data aggregation, ethical issues, presentation of results, and interpretation of results); and 11 criteria to use in a Delphi study to collate expert opinion (research problem, research rationale, literature review, data collection, the survey, number of rounds, the expert sample, ethical issues, data analysis, presentation of results, and interpretation of results).

"Further research is required to develop and apply the methods to elicit parameter values and/or their distributions and collate expert opinions. Specifically, it is necessary to conduct empirical research on whether mathematical or behavioural aggregation methods are robust and practical when used in model-based EE of healthcare interventions," commented the authors.

Iglesias CP, Thompson A, Rogowski WH, et al. Reporting guidelines for the use of expert judgement in model-based economic evaluations. Pharmacoeconomics. Epub 30 Jun 2016. doi:10.1007/s40273-016-0425-9. Accessed 8 Aug 2016.

17 European HTA Agencies Require Robust Evidence in Oncology

Health technology assessment (HTA) agencies in Europe require robust evidence of the clinical benefits of drugs in cancer patients in order to make reimbursement decisions, say authors of a study published in the *Annals of Oncology*.

This cross-sectional analysis compared HTA guidelines and relative effectiveness assessments (REAs) used to make pricing or reimbursement decisions in jurisdictions in England, France, Germany, the Netherlands, Poland and Scotland on anticancer drugs that received marketing authorisation in Europe between 2011 and 2013, and for which four or more national REAs were available. In total, 79 REAs were included.

Overall, HTA guidelines preferred clinically-relevant endpoints such as overall survival (OS) and patient-relevant endpoints such as QOL assessments, and did not favour surrogate endpoints. Most guidelines did not clarify whether progression-free survival (PFS) was considered a surrogate endpoint or a patient-relevant endpoint.

The number of REAs included per jurisdiction ranged from 7, in the Netherlands, to 18, in Germany. Although all REAs included OS data (the preferred endpoint of HTA agencies), the data were not robust in all REAs. OS data had a positive (48 %) or neutral (35 %) impact on reimbursement. Only 54 % of REAs included QOL data, and this had a limited impact on reimbursement recommendations. Most REAs (70 %) included PFS data, but the extent to which this was considered relevant varied between HTA agencies.

"Divergences are…seen between HTA bodies and drug regulatory agencies because the regulator is willing to accept a higher degree of clinical uncertainty to expedite access to therapies," said the authors. "A multi-stakeholder debate would be essential to align concrete robust evidence requirements in oncology and standardise the definition of 'relevant clinical benefit', which will benefit patients and society in general," they said.

Kleijnen S, Lipska I, Leonardo Alves T, et al. Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. Ann Oncol. Epub 20 Jun 2016. doi:10.1093/annonc/mdw233. Accessed 8 Aug 2016.

18 AMCP Recommends Improved Sharing of Product Information

The Academy of Managed Care Pharmacy (AMCP) has published recommendations that would allow biopharmaceutical companies to more easily share healthcare economic information (HCEI) with formulary and coverage decision makers—a move that the AMCP believes will address the growing move towards value-based pricing.

The recommendations (developed at a stakeholder partnership forum held by AMCP) address restrictions in the sharing of product information that is not on the drug label, a prohibition that hinders decision makers from accessing HCEI on new therapies.

More specifically, they clarify section 117 of the 1997 FDA Modernization Act, which is a regulatory safe harbour for the dissemination of HCEI to formulary decision makers but is little used because of wording ambiguity and a lack of implementation guidance from the FDA.

The FDA announced that it plans to release guidance this year. To help inform the FDA's current thinking on development of new guidance, AMCP suggests that: factors beyond costs are considered, such as healthcare utilisation, patient benefits, quality of life; evidence forming the basis of HCEI should be "truthful and non-misleading tests, analyses, research, studies, models, or other evidence"; HCEI from pipeline drugs should be disseminated 12–18 months before approval; HCEI could be disseminated to other entities beyond just pharmaceutical and therapeutic, and formulary committees; and, that the AMCP's Format for Formulary Submissions and the eDossier system could be well suited to seek HCEI from manufacturers.

Details of the recommendations are reported the forum proceedings, published in the July issue of AMCP's *Journal of Managed Care & Specialty Pharmacy*, and AMCP will also lead the development of a draft guidance document to share with the FDA.

Academy of Managed Care Pharmacy. AMCP releases consensus recommendations to improve sharing of HCEI used in pharmaceutical coverage decisions. 2016 Jun 24. Available from URL: http://www.amcp.org/Newsletter.aspx?id=21177. Accessed 8 Aug 2016.

19 ISPOR Publishes Guidance on Patient-Preference Data

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has announced that its latest Good Research Practices Task Force Report is published in the June 2016 issue of *Value in Health*.

The report, titled "Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force Group", is the third ISPOR report of this type and provides guidance on the interpretation and analysis of patient preference data in light of the increased movement of the health sector towards patient-centric care and improved patient engagement. Specifically, the report focuses on data gathered by discrete-choice experiments (DCEs) which are a stated-preference survey method used to quantify the values and priorities of patients, medical professionals, caregivers and other healthcare decision makers. DCEs quantify patients' priorities and the relative importance placed on various aspects of treatment or health services using a score calculated by asking patients what they would decide when faced with a real-life situation that involves trade-offs.

The Task Force included a solid description of DCE data fundamentals as part of the report to address the importance of ensuring the validity of results through proper analysis and interpretation of DCE data. They have also developed the ESTIMATE Checklist for researchers, which consists of questions to consider when choosing and describing the analysis method, and interpreting the results. Lead author and Task Force Chair, Dr A. Brett Hauber, commented that "we determined that a pragmatic introduction to different statistical analysis methods was needed—highlighting the differences among methods and identifying the strengths and limitations of each method".

International Society for Pharmacoeconomics and Outcomes Research. ISPOR Task Force provides guidance on statistical methods for analyzing patient preference data. 2016 Jun 21. Available from URL: http://press.ispor.org/index.php/ispor-task-force-provides-guidance-on-statistical-methods-for-analyzing-patient-preference-data. Accessed 8 Aug 2016.

20 New EMA and FDA Cluster on Patient Engagement

The EMA and the US FDA have established a new 'cluster' collaboration on patient engagement, to share experiences on patient involvement in regulatory processes.

"The cluster will provide a forum to share experiences and best practices on the way the two agencies involve patients in development, evaluation and post-authorisation activities related to medicines," according to the EMA. "We look forward to increasing our collaboration with FDA in this area in order to benefit from each other's experiences, and to advance patient involvement," said Guido Rasi, Executive Director of the EMA.

The first cluster teleconference meeting on patient engagement was held on 22 June 2016.

Previously established EMA and FDA clusters discuss issues related to topics including biosimilars, cancer drugs, orphan medicines, paediatric medicine and pharmacovigilance.

European Medicines Agency. EMA and FDA reinforce collaboration on patient engagement. 2016 Jun 22. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002554.jsp&mid=WC0b01ac058004d5c1. Accessed 8 Aug 2016.

21 ASCO Value Framework: Responses & Revisions

Revisions have been made to the American Society of Clinical Oncology (ASCO) Value Framework following feedback received during the public comment period, reports an article in the *Journal of Clinical Oncology*.

More than 400 responses were received during the 60-day public comment period following publication in June 2015 of the ASCO Value Framework, which was developed to enable patients and physicians to assess the value of a cancer treatment regimen based on the individual preferences and circumstances of the patient.

Firstly, in response to the perception by some readers that the net health benefit score calculated by the framework was "arbitrary", the authors concurred that it is an artificial construct but note that it is derived from key efficacy elements and is "the very element that patients seek to understand as they consider treatment options and that most oncologists use to make treatment recommendations". Concerns were also raised that the cost focus was on the prescription drugs rather than cancer care as a whole. The authors acknowledged that although drug costs are a fraction of the total expenditure, there is a lack of available or quantifiable cost data and suggest that discussion of alternative regimens allows the patient to facilitate a personalised treatment plan that "takes into account goals of care and financial realities". Additionally, the omission of patient-reported outcomes (PRO) from the framework was raised, which the authors concede is "an important deficiency" due to lack of clinical trial data. They hope that this will be addressed by the inclusion of PRO endpoints in cancer clinical trials in the future. Other responses included questions regarding the dual intent of the framework to drive both policy decisions on drug pricing and shared clinical decision making; concerns over the practicality of the framework; and concerns that personalised decision making would not be allowed within the framework.

Changes made to the framework included: establishing the hazard ratio as the preferred efficacy variable; modifying the scoring system to more accurately assess survival measures; and inclusion of all adverse events into the framework rather than just the high-grade toxicities.

"In publishing this revision to the ASCO value framework, we have tried to respond to the many constructive suggestions we received", say the authors. "In doing so, we are adhering to our goals of stimulating debate and forging a broad consensus on how to define the value of a cancer treatment—putting the patient at the center".

Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology value framework: revisions and reflections in response to comments received. JCO. Epub 31 May 2016. doi:10.1200/JCO.2016.68.2518. Accessed 8 Aug 2016.

22 Drones Offer Promise for Vaccine Transport

Unmanned aerial vehicles (UAVs), otherwise known as drones, could potentially increase vaccine availability and decrease transport costs compared with land transportation, according to an article published in *Vaccine*.

The authors utilised the Highly Extensible Resource for Modeling Event-driven Supply Chains (HERMES) software platform to generate a simulation model of the WHO Expanded Program on Immunization supply chain in Gaza, a province in southern Mozambique. The impact of vaccine distribution via a traditional multi-tiered land transport system was compared with distribution via UAVS, which were assessed as unmanned aerial systems (UAS) to encompass the total associated costs of purchasing, maintaining, operating, launching and recovering UAVs, as well as infrastructure requirements. Costs were reported in 2015 US dollar values.

The model demonstrated that UAS vaccine delivery across the province increased vaccine availability (96 vs 94 %, respectively) and reduced the cost per dose administered ($US0.33 vs $0.41, respectively), compared with traditional land transport. Subset analysis of vaccine delivery for distances under 75 km demonstrated a further increase in vaccine availability with UAS versus traditional land transport delivery (100 vs 97 %), with corresponding costs per dose administered of $0.22 versus $0.31, respectively.

The minimum UAV payload (i.e. the maximum volume of vaccines each UAV can carry in a single shipment) required to achieve cost savings ranged from 0.20 to 0.40L, which was considerably smaller than current estimates of 1.5L. Additionally, analysis of cost saving thresholds showed that savings could be achieved with a UAS cost that was higher than currently assumed values, when operated under realistic flight conditions.

"Immunization programs in low and middle income countries…face numerous challenges in getting life-saving vaccines to the people who need them", say the authors. "Implementing a UAS could increase vaccine availability and decrease costs in a wide range of settings and circumstances if the drones are used frequently enough to overcome the capital costs of installing and maintaining the system".

Haidari LA, Brown ST, Ferguson M, et al. The economic and operational value of using drones to transport vaccines. Vaccine 2016; 34 (34): 4062–7.

23 Important Differences Between Antidiabetic Drugs

There are "clinically important differences" in the risks of cardiovascular (CV) disease, heart failure (HF) and all-cause mortality between different diabetes drugs, according to UK researchers.

This population-based cohort study involved 469,688 eligible patients with types 2 diabetes mellitus (aged 25–84 years) who were registered at eligible UK general practices between April 2007 and January 2015. The primary exposures of interest were new use of dipeptidyl peptidase-4 inhibitors (gliptins) and new use of thiazolidinediones (glitazones). Also, six different classes of diabetes drugs (glitazones, gliptins, metformin, sulfonylureas, insulin, and other oral diabetes drugs)—administered alone or in combination with other agents—were compared with no drug treatment.

Use of glitazones was associated with significantly decreased risks in all three outcomes (23 % reduction for all-cause mortality; 26 % reduction for HF; 25 % reduction for CV disease), compared with non-use of glitazones. However, corresponding use of gliptins was only associated with significantly decreased risks of all-cause mortality (18 %) and HF (14 %), but no significant change in the risk of CV disease.

Compared with no current treatment, significantly decreased risks in all three outcomes were seen following dual treatment with gliptins + metformin, and triple treatment with gliptins + metformin + sulfonylureas. There were no significant associations between monotherapy with gliptins and the risk of any of the three outcomes.

Monotherapy with glitazones was associated with a 50 % reduction in the risk of HF, and significant reductions in all three outcomes were seen with dual treatment (i.e. glitazones + metformin) and triple treatment (glitazones + metformin + sulfonylureas), compared with no treatment.

The study researchers concluded that "these results, which do not account for levels of adherence or dosage information and which are subject to confounding by indication, may have implications for prescribing of diabetes drugs".

Hippisley-Cox J. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. BMJ. 2016;354:i3477.

24 Update on New EudraVigilance System Implementation

The EMA's Management Board has approved an updated schedule for implementation of its new adverse reaction monitoring system, EudraVigilance.

EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance) is the system for managing and analysing information on suspected ADRs to medicines that are undergoing clinical trials, or have been approved, in the European Economic Area.

This new system is expected to go live in November 2017, and "will offer enhanced functionalities for the reporting and analysis of suspected adverse drug reaction to all stakeholders", stated the EMA.

The agency has indicated that the 4-month delay in implementation of the new system is primarily due to the need to optimise its performance prior to launch. "A high level of system performance is crucial", said the EMA, given that it processes very large number of reports and transactions on a daily basis. Use of the system is also expected to increase significantly once the new functions are made available.

Details of the planned enhancements to the EudraVigilance were previously published in October 2015.

European Medicines Agency. EMA Management Board: highlights of June 2016 meeting. 2016 Jun 17. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002552.jsp&mid=WC0b01ac058004d5c1. Accessed 8 Aug 2016.

25 Mobile Tools to Detect AEs Successfully Used in Germany

Use of mobile applications at the point of care can allow physicians to ascertain and report potential adverse events (AEs) in a timely manner, according to a study published in *Drug Safety*.

This proof-of-concept study explored the use of a mobile application called VACC-Tool (ViVI Automated Case Classification Tool) by German physicians to classify clinical cases of neuroinflammatory adverse events (NIAE), based on 14 predefined case algorithms. The beta-version (2.0) of the VACC-Tool was utilised from July 2013 to October 2014 as part of a quality management programme at the Charité Universal Medical Center, in collaboration with the Robert Koch Institute, in Berlin. 243 children (mean age 8.5 years) were hospitalised due to suspected NIAE and participated in this programme.

Using the VACC-Tool in the emergency department (ED), 209 of 243 children (86 %) were classified successfully as having NIAE. Such events included cases of fever (51 %), fatigue (29.2 %), acute disseminated

encephalomyelitis (17.3 %), convulsive seizure (16.9 %), peripheral facial nerve palsy (13.6 %), aseptic meningitis (9.9 %), encephalitis (9.9 %) and persistent crying (0.4 %). However, comparison of the VACC-Tool results with International Classification of Diseases, 10th revision (ICD-10) admission diagnoses revealed that 89 (36.6 %) cases of NIAE had been missed, and a total of 79 (32.5 %) cases were misclassified, in the ED reports.

Longitudinal follow-up assessments using the VACC-Tool demonstrated that an additional eight cases of NIAE were classified successfully (six were initially 'negative' and two were 'indeterminate').

The researchers highlighted that within 20–40 min, "repeated use of the VACC-Tool 2.0 provided a dynamic 'moving image' of longitudinal data rather than a singular 'snapshot' of the patient's initial presentation". They added that use of this tool for consecutive follow-up assessments "also revealed new adverse events that would have otherwise been missed or misclassified".

Hoppe C, Obermeier P, Muehlhans S, et al. Innovative digital tools and surveillance systems for the timely detection of adverse events at the point of care: a proof-of-concept study. Drug Saf. Epub 27 Jun 2016. doi:10.1007/s40264-016-0437-6. Accessed 8 Aug 2016.

26 AHA Warns of Medications Which Worsen Heart Failure

Many commonly used medications may cause or exacerbate heart failure, according to an American Heart Association scientific statement published in *Circulation*, often by direct myocardial toxicity, drug-drug interactions, or both.

Statement preparation involved analysing case reports and case series, prospective and observational trials, meta-analyses and package inserts to identify medications that may be associated with myocardial dysfunction or toxicity.

Patients with heart failure often experience multiple comorbidities, comprising both cardiovascular and non-cardiovascular chronic conditions. On average, patients receive 10.1 doses of 6.8 prescription medicines daily. Frequently, the also use over-the-counter (OTC) and complementary or alternative medicine (CAM) products, possibly without the knowledge of their healthcare providers.

A wide variety of prescription medications may be associated with heart failure induction or exacerbation, including anaesthetics, analgesics, antiarrhythmics, anti-hyperglycaemics, antihypertensives, anti-infective, anti-neoplastics, antiplatelets, antirheumatics, decongestants and neuropsychotherapeutics. It is estimated that 35 % of adult Americans use OTC drugs, mainly for allergies, coughs/colds, headache and heartburn. Many of these medications have high sodium levels, or contain ingredients such as NSAIDs or vasoconstrictors which may exacerbate heart failure. Patients may use higher-than-recommended doses, or not consult the package labelling before use, and many do not inform their health care providers. Similarly, about 38 % of adult Americans use CAMs, despite the lack of quality efficacy and safety data. There is also a lack of manufacturing oversight, and "adulterated products abound". It is recommended that healthcare providers question patients about their use of OTC products and CAMs.

Currently, heart failure guidelines recommend that no naturoceuticals, with particular mention of ephedra-like products, should be used to manage heart failure symptoms or for the prevention of cardiovascular events. Products which interact with digoxin, anticoagulants, β-blockers, antiarrhythmic agents or vasodilators, such as St John's wort, ginseng and black cohosh, should not be used. The AHA statement notes that the risks and benefits of prescribed medications need to be carefully evaluated, "with an attempt made to reduce or eliminate optional medications".

Page RL II, O'Bryant CL, Cheng D, et al. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation. Epub 11 Jul 2016. doi:10.1161/CIR.0000000000000426. Accessed 8 Aug 2016.

27 STOPP/START Criteria Reduce ADRs and Drug Costs in Elderly

Use of the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria reduces the incidence of ADRs and medication costs in elderly patients with acute illness, according to the findings of a study published in the *Journal of the American Geriatrics Society*.

This single-blind, cluster-randomised study, conducted between May 2011 and May 2012, investigated the impact of using STOPP/START criteria for reducing potentially inappropriate prescribing on the incidence of ADRs, the duration of hospitalisation and medication costs in 732 elderly patients (≥65 years) hospitalised with acute illness in Cork University Hospital, Ireland. In the intervention cluster, 14 attending physicians in six specialties were given a presentation on adjusting medications according to STOPP/START criteria. The control cluster included 13 consultants in eight specialties.

The proportion of patients experiencing at least one ADR during index hospitalisation was reduced in the intervention group compared with the control group (11.7 vs 21.0 %; OR 0.50; 95 % CI 0.31, 0.79; $p = 0.001$). The median duration of hospitalisation was 8 days in both

groups. Median medication costs extrapolated over a 28-day period were significantly lower in the intervention group than in the control group (€73.16 vs €90.62; $p < 0.001$).

"STOPP/START version 2 will…be the central component of a novel software engine called SENATOR designed specifically for prevention of ADRs in older adults that will be tested in a randomized clinical trial in six hospital centers in Europe starting in 2016," commented the authors.

O'Connor MN, O'Sullivan D, Gallagher PF, et al. Prevention of hospital-acquired adverse drug reactions in older people using screening tool of older persons' prescriptions and screening tool to alert to right treatment criteria: a cluster randomized controlled trial. J Am Geriatr Soc. Epub 1 Jul 2016. doi:10.1111/jgs.14312. Accessed 9 Aug 2016.

28 UK Women Surveyed About Use of Medicines During Pregnancy

A woman's beliefs and her perception of any associated risks play an important role in the actual use of medicines during pregnancy, according to a UK-based study.

This study (i.e. a sub-study of the Multinational Medication Use in Pregnancy Study) recruited 1120 pregnant women and mothers within 1-year of giving birth, who were invited to take part in an online cross-sectional questionnaire-based study via a pregnancy website in the UK. 193 women (17.2 %) reported having a chronic condition (e.g. asthma, allergies, depression, anxiety, among others).

Overall, 856 women reported using medications (OTC and/or prescription drugs) to treat at least one of the eight common conditions (nausea, heartburn, constipation, common cold, urinary tract infections [UTIs], neck or pelvic pain, headache and sleeping problems) experienced during pregnancy. The study researchers stated that "although a significant number of respondents experienced these conditions during pregnancy, relatively few of them took medication for nausea (9.5 %), constipation (19.2 %) or sleeping problems (1.1 %)".

Over 65 % of women reported using OTC analgesics for a variety of conditions (including headache, neck pain and pelvic pain). The researchers highlighted that one of the most important concerns was the number of women who experienced a UTI (n = 191; 17.1 %), of whom 66 (65.4 %) did not receive any conventional treatment.

Overall, 815 women (72.8 %) reported deliberately avoiding the use of certain medicines during pregnancy—including paracetamol, ibuprofen (and combination products), cold and cough medicines, antihistamines and nasal decongestants.

Among women with heartburn and UTIs, there was a significant difference in the number of women who took medication (in terms of their perception of being overused, and being more harmful and less beneficial), compared with women who received treatment for these conditions.

The researchers highlighted that "more work needs to be done to determine if healthcare professionals have the tools available to them to allay concerns, assess severity of conditions and provide appropriate treatment advice for pregnant women".

Twigg MJ, Lupattelli A, Nordeng H. Women's beliefs about medication use during their pregnancy: a UK perspective. Int J Clin Pharm. 2016;38 (4):968–76.

29 Calcium Channel Blockers Not Associated With Breast Cancer

There is "no evidence of increased risk of breast cancer from 10 years or more of current calcium channel blocker use", according to the results of a prospective study reported in *Breast Cancer Research*.

The cohort study, named the Sister Study, included 50,757 eligible women from Puerto Rico or the USA who had a sister with breast cancer but had no personal history of breast cancer. Of the 17,068 women who had ever received an antihypertensive drug, 3316 were currently receiving a calcium channel blocker; 820 women had been treated with a calcium channel blocker for ≥10 years.

After a mean follow-up time of 5.3 years, 1965 women were diagnosed with breast cancer. The use of calcium channel blockers, or any antihypertensive, was similar in women who developed breast cancer and in those who remained cancer-free. In Cox proportional hazards regression analysis, the risk of developing breast cancer was similar for former users of calcium channel blockers compared with patients who had never received calcium channel blockers [hazard ratio (HR) 0.97; 95 % CI 0.63–1.49]. Results were similar for those who had received calcium channel blocker treatment for <5 years (HR 0.84; 0.66, 1.08), 5–10 years (HR 1.10; 0.80, 1.53) or >10 years (HR 0.86; 0.57, 1.28).

The authors note that the "lack of convincing biological evidence is consistent with the observed lack of association between calcium channel blocker use and breast cancer risk in this study". "Women who used calcium channel blockers in our study were more likely to have a history of smoking, to be overweight, to be postmenopausal, and to have used hormone replacement therapy", they add, and "these associations might help to explain the inconsistencies observed in past studies of breast cancer risk and antihypertensive drug use".

Wilson LE, D'Aloisio AA, Sandler DP, et al. Long-term use of calcium channel blocking drugs and breast cancer risk in a prospective cohort of US and Puerto Rican women. Breast Cancer Res. Epub 5 July 2016. doi:10.1186/s13058-016-0720-6. Accessed 9 Aug 2016.

30 ISMP's Monitoring Category Reports

According to the Institute for Safe Medication Practices (ISMP)'s annual report issue of QuarterWatch, the leading drug-related adverse events reported to the US FDA in 2015 in various categories included rivaroxaban for the highest number of serious events in the USA, adalimumab for the highest number of events submitted directly to the FDA, fluoroquinolones for the highest number of persistent events, and pioglitazone for the highest number of legal cases.

30.1 Rivaroxaban

The oral anticoagulant rivaroxaban (Xarelto) was associated with 10 674 reports of fatal, disabling or serious injury in the USA, including 1121 deaths and 4508 injuries requiring hospitalisation. This was the highest number of reports for the 1395 regularly monitored drugs; there were a median of 7 reports per drug. Haemorrhage was reported in 8643 events, with 1611 embolic-thrombotic or clot-related events. Marketing and promotional activities among anticoagulant producers may have increased the contact between health care professional or consumers and manufacturers, enabling manufacturers to learn more about adverse events. In addition, some reports may have related to previous years. Nevertheless, the large number of reports "remains a strong signal that improving the safety of oral anticoagulant treatments should be a major priority in drug safety".

30.2 Adalimumab

The biological product adalimumab (Humira), the most widely prescribed anti-tumor necrosis factor (anti-TNF) drug, was associated with 1581 direct reports to the FDA, mostly involving hypersensitivity, pain and injection site reactions. However, this was only a fraction of the 49 927 total reports involving adalimumab. The high cost of anti-TNF drugs and administration by self-injection may increase patient interaction with pharmacists and increase subsequent event reporting.

30.3 Fluoroquinolones

The fluoroquinolone antibacterials were associated with the highest number of persistent adverse events: 489 with levofloxacin (Levaquin) and 366 with ciprofloxacin (Cipro). The most frequent events were pain in extremity (n = 200), unspecified pain (n = 162) and tendon pain (n = 119); the patient was reported to be disabled by 65 % of the events. Interestingly, 99 % of the reports were direct to the FDA, even though direct reports only account for 4 % of the overall cases reported. Adverse event reporting rates are lower for generic versions of drugs such as fluoroquinolones than for brand-name drugs still on patent. "These data suggest the health problem of persistent injury from fluoroquinolones could be much larger than indicated by these case totals".

30.4 Pioglitazone

The oral anti-diabetes drug pioglitazone (Actos) was the most frequent suspect drug in cases identified as legal cases, with 3041 reports. Pioglitazone is suspected to increase the risk of bladder cancer. Takeda Pharmaceuticals, the manufacturer, agreed in April 2015 to pay $US2.4 billion to settle 9000 legal cases, following 5 of the first 8 cases resulting in verdicts against the company. However, most of the scientific evidence remains under seal. A company-sponsored epidemiological study "claimed to see no association," but there are unanswered questions about "whether their design was capable of detecting an association if one existed".

Institute for Safe Medication Practices. Quarter Watch: Monitoring FDA MedWatch Reports. Annual Report Issue. 2016 Jun 29. Available from https://www.ismp.org/quarterwatch/pdfs/2015Q4.pdf. Accessed 9 Aug 2016.

31 Biologics Associated With Gastrointestinal Perforation

In patients with rheumatoid arthritis, treatment with biologics is associated with gastrointestinal perforation (GIP), according to the results of a study published in *Arthritis & Rheumatology*. The risk is significantly higher for patients who receive tocilizumab or tofacitinib compared with those who receive an anti-TNF medication.

Data from health plan databases, Medicare in 2006–2013 and Marketscan in 2010–2014, identified 167,109 patients with rheumatoid arthritis who started receiving treatment with biologics and did not have a history of GIP. The incidence of GIP requiring hospitalisation per 1000 person-years was 1.29 in the 4755 tofacitinib recipients, 1.55 in the 11,705 tocilizumab recipients, 1.10 in the 31,214 abatacept recipients, 0.73 in the 4391 rituximab recipients and 0.84 in the 115,044 anti-TNF (i.e. adalimumab, certolizumab pegol, etanercept, golimumab or infliximab) recipients. The incidence of lower tract GIP was 1.29 for tofacitinib, 1.26 for tocilizumab, 0.76 for abatacept, 0.73 for rituximab and 0.46 for anti-TNF medications. The incidence of upper tract GIP was similar in all medication recipients. Death in hospital occurred in 16 % of patients.

Compared with anti-TNF recipients, the risk was significantly higher for tofacitinib recipients [adjusted hazard ratio (HR) 3.24; 95 % CI 1.05, 10.04] and tocilizumab recipients (HR 2.55; 1.16, 3.73). Lower tract GIP was also predicted by older age (HR 1.16 per 5 years; 1.10, 1.22), the presence of diverticulitis or other gastrointestinal conditions (HR 3.25; 1.62, 6.51) and receipt of prednisone at >7.5 mg/day (HR 2.24; 1.36, 3.70).

"Despite these differences in relative risk, the absolute rate differences between treatments were small," note the authors. They add that "the mechanisms whereby DMARDs and biologics might lead to lower GI tract perforations may include impairments in host defenses".

Xie F, Yun H, Bernatsky S, et al. Risk for gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologics. Arthritis and Rheumatol. Epub 2016 May 17. doi:10.1002/art.39761. Accessed 9 Aug 2016.

32 Neurocognition Not Affected By Anaesthetics

A single exposure to anaesthetics in young children does not have a significant effect on neurocognitive outcomes, according to study results published in the *Journal of the American Medical Association*.

The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) sibling-matched cohort study was conducted in four US university-based paediatric tertiary care hospitals between May 2009 and April 2015. The study included 105 sibling pairs; one of each pair (90 % boys) was exposed to general anaesthesia for elective inguinal hernia surgery at <36 months of age, while the other sibling (56 % boys) who was within 36 months of age to the exposed sibling was not exposed to anaesthetics. The exposed patients received inhaled sevoflurane and/or isoflurane; 28 patients also received intravenous (IV) ketamine, midazolam, propofol or thiopental. The duration of anaesthesia was 20–240 (median 80) minutes. The primary endpoint was global cognitive function (IQ), evaluated at 8–15 years of age.

There was no statistically significant between-group difference in mean full-scale IQ scores (−0.2; 95 % CI −2.6, 2.9), or in mean performance scores (0.5; −2.7, 3.7) or verbal scores (−0.5; −3.2, 2.2). Similarly, there were no significant differences between patients exposed to anaesthetics at 0–11, 12–23 or 24–36 months of age, or those exposed for 0–59, 60–119 or ≥120 min. There were no statistically significant differences in secondary outcomes including memory, learning, motor or processing speed, visuospatial function, attention, language, executive function and other areas of adaptive behaviour.

The authors note that "the sex imbalance of the exposed cohort may limit the generalizability of the results for female children". They add that "further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed".

Sun LS, Li G, Miller TL, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA. 2016;315 (21):2312–20.

33 DPP-4 Inhibitors Associated with Acute Kidney Injury

According to the results of a nationwide nested case-control study published in *Mayo Clinic Proceedings*, patients with type 2 diabetes mellitus who receive dipeptidyl peptidase-4 (DPP-4) inhibitors have an increased risk of developing acute kidney injury requiring hospitalisation.

The study included 6752 patients from the Longitudinal Cohort of Diabetes Patients data set from Taiwan's National Health Insurance Research Database (NHIRD), matched with 6752 controls. The 3811 men and 2941 women with a mean age of 69.0 years were hospitalised with acute kidney injury from 2010 to 2013. Use of DPP-4 inhibitors including sitagliptin, saxagliptin and vildagliptin was classified as current (≤30 days prior to the index date), recent (31–90 days prior) or past (91–365 days prior).

Overall, DPP-4 inhibitor use was associated with an increased risk of hospitalisation for acute kidney injury (adjusted OR 2.10; 95 % CI 1.05, 1.37; $p = 0.006$). Stratified analysis revealed a significant association with current DPP-4 inhibitor use (OR 1.26; 1.08, 1.48; $p = 0.004$) but not with recent or past use.

The authors note that these results "provide a signal for authorities concerned about the renal safety of DPP-4 inhibitor prescriptions". They add that the results "may not be generalized to patients with less severe forms of [acute kidney injury] based on changes in serum creatinine level, and neither to patients with acute on [chronic kidney disease] due to exclusion of preexisting [chronic kidney disease] in the current analysis".

Shih CJ, Lee YJ, Lo YH, et al. Association between use of dipeptidyl peptidase-4 inhibitors and the risk of acute kidney injury: a nested case-control study. Mayo Clin Proc. 2016;91 (7):867–72.