Regulatory news

Vision statement

Japan announces Rational Medicine initiative

Japan – The Pharmaceuticals and Medical Devices Agency (PMDA) has announced its “Rational Medicine” initiative, which aims to serve the best overall interests of the patient through an all-inclusive approach to medicine that is thoroughly based on the latest science and most advanced technology in all relevant areas.

This holistic, patient-centred approach to medicine is intended to advance regulatory science and to create an environment where medical care is strictly evidence-based. To this end, the PMDA plans to continue its initiatives in four areas: (1) innovation through product approval reviews of enhanced rigour and rationality; (2) further promotion of regulatory science; (3) increased sophistication of safety measures through the use of real-world data; and (4) enhanced international partnerships.

Through this approach the PMDA will ensure that patients receive optimal medical treatment, including treatment based on innovative new technologies.


Scientific integrity was also named by the WHO Director-General as one of four priorities that should guide health policies in the next decade. In delivering the keynote address at the 10th anniversary of the University of Washington's Department of Global Health, she said: “Regulatory agencies everywhere must resist the push to replace randomized clinical trials, long the gold standard for approving new drugs, with research summaries provided by pharmaceutical companies. As some argue, making this change would speed up regulatory approval, lower the costs to industry, and get more products on the market sooner. This kind of thinking is extremely dangerous. We must not let anything, including economic arguments or industry pressure, lower our scientific standards or compromise our integrity.”


Pre-market assessment

Ten years of EMA conditional marketing authorizations

European Union – The EMA has published a report on its ten years of experience with conditional marketing authorizations since their introduction in 2006 until June 2016. Thirty products were granted a conditional marketing authorization during that period, and none of them were subsequently revoked or suspended. On average, it took four years to convert the conditional approval into a full marketing authorization based on additional data. The report concludes that conditional marketing authorization enables patients with life-threatening or seriously debilitating conditions to access promising medicines earlier.

The report characterizes the data on which conditional approvals have been granted and the additional data generated through specific obligations. Some areas for improvement are identified, notably with
regard to prospective planning and early dialogue between stakeholders, including health technology assessment bodies that make decisions on reimbursement.


### Post-market monitoring

**Australia to publish laboratory testing results**

**Australia** – The TGA has announced that it will begin publishing the outcomes of its laboratory testing on its website from mid-2017.\(^1\) Where products fail any aspect of testing, details of the test(s) that failed and outcomes of any follow-up action will also be provided. Results will be published in May and November of each year, allowing six months after the end of each reporting period for follow-up on any non-compliant findings.

The TGA tests approximately 2000 samples of therapeutic goods annually. The planned publication of the results is part of the TGA’s response to a 2015 expert review of medicines and medical devices regulation, which had recommended to establish a more comprehensive post-market monitoring scheme for medical products in Australia. Similar information is also published by the U.S. FDA \(^2\) and the EMA \(^3\).

► (1) TGA Statement, 7 February 2017.

(2) FDA. Drugs > Science & Research (Drugs) > Drug Quality Sampling and Testing Programs.

(3) EMA website. Human regulatory > Overview > Compliance > Sampling and testing.

**India releases medicines quality survey results**

**India** – The Central Drug Standards Control Organization (CDSCO) and the Ministry of Health and Family Welfare have released the report of a nationwide medicines quality survey.

The survey was conducted by the National Institute of Biologicals and covered the period 2014-2016. With almost 48000 samples from all major therapeutic categories collected across the country, it was the largest-ever such survey to be conducted in India. A specially designed in-house software was used for collection, transmission and analysis of data. Testing was done at India’s seven Central and three State Government drug testing laboratories.

Overall the survey found that 3.16% of samples were not of standard quality, and 0.0245% were spurious drugs.

Of 33656 samples from Indian retail outlets tested in the survey, 1011 (3%) failed one or more tests. Dissolution accounted for a third of the failures, followed by assay. The list of molecules with the most non-compliant samples was led by four antibacterials: erythromycin (28.7%), gentamicin (21.1%), ceftriaxone (19.8%) and amikacin (19.5%).

Samples taken at government facilities had above-average failure rates. Of 8369 samples analyzed, 839 (10%) failed one or more tests. The most frequently failed tests were assay and dissolution, followed by related substances. Non-compliance in the latter test accounted for about every seventh failure, occurring almost twice as frequently as in samples collected at retail outlets.

The highest percentages of non-compliant samples were seen for bisacodyl (66.7%), zinc sulfate (51.3%), amikacin (43.3%), oxytocin (41.3%) and gentamicin (40.2%); ceftriaxone ranked 9th with 24.6%.

A breakdown by manufacturing units from which at least 25 samples were tested showed some particularly high failure rates in the retail outlet part of the survey: four sites, including an Indian manufacturing site...
of a well-known multinational company, had failure rates >50%.

Of 4987 samples taken at ports none failed any tests.

Thirteen samples tested in the survey were found to be spurious as defined in Indian legislation. These samples failed to meet the identification test of the labelled drug or had zero active ingredient. The molecules concerned were amoxicillin with or without clavulanic acid (7 samples), prednisolone or methylprednisolone (3 samples), sulfamethoxazole/trimethoprim fixed-dose combination (2 samples) and cefixime (1 sample).


WHO has published guidelines which outline the steps to consider when preparing and conducting a survey of medicines quality. The guidelines provide recommendations and examples of methodological approaches with a discussion of their advantages and disadvantages, and suggestions on how to prepare reports on the results obtained from such surveys. An overview of WHO guidelines on medicines quality is provided in the Norms and standards section (pp. 15-26)


Antimicrobial resistance

(See also page 46: WHO has published its first-ever list of antibiotic-resistant priority pathogens)

Two reports on antimicrobial resistance in Europe

European Union – Experts from the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have reviewed the measures taken in the European Union (EU) to reduce antimicrobials use in food-producing animals. In their report they emphasize that there is no one-size-fits-all solution. The experts conclude that reducing and replacing antimicrobials can reasonably be assumed to decrease antimicrobial resistance; however, due to lack of data they were unable to quantify the impact of single measures. In addition to reduction measures the experts recommend to rethink the livestock production system and to introduce innovative solutions to prevent and control infectious diseases in animals.


In February 2017 EFSA and the European Centre for Disease Prevention and Control (ECDC) published their annual report on the levels of antimicrobial resistance in food, animals and humans across the EU. The findings underline that antimicrobial resistance remains high and poses a serious threat to public and animal health. Infections caused by bacteria that are resistant to antimicrobials lead to about 25000 deaths in the EU every year. Countries where actions have been taken to reduce, replace and re-think the use of antimicrobials in animals, show lower levels of antimicrobial resistance and decreasing trends.

Regulatory statement and new guidelines on antibiotic use in India

India – The Central Drugs Standard Control Organisation (CDSCO) of India has released an advisory statement with recommendations about the rational use of antibiotics to limit antimicrobial resistance. The statement outlines the measures implemented by CDSCO and lists the steps to be taken by other stakeholders. It calls on the regulators of each of India’s States to enforce compliance with laws and regulations and to raise public awareness about the consequences of misuse of antibiotics. The statement further asks the All India Organization of Chemists and Druggists to educate its members on the licensing conditions for medicines sales and cooperate with regulatory authorities, and calls on the pharmaceutical industry to use its network to discourage the sale of antibiotics without a prescription.(1)

In February 2017 the Indian Council of Medical Research (ICMR) released its guidelines on antimicrobial use. As stated in the foreword to the guidelines, an estimated 50% or more of hospital antimicrobial use is inappropriate. The document is intended to guide treatment in order to bring down the burden of antimicrobial resistance in India.(2)

FDA guidance on naming of biologicals

United States of America – The FDA has released its guidance for industry titled Nonproprietary Naming of Biological Products. The guidance provides for nonproprietary names to include a core name and a distinguishing FDA-designated suffix that is devoid of meaning and composed of four lowercase letters. The guidance applies to previously licenced and newly licenced originator biological products, related biological products and biosimilar products. FDA is still considering the appropriate suffix format for interchangeable biological products.

In commenting on the guidance at the draft stage, many responders suggested that a meaningful, distinguishable suffix may help to improve pharmacovigilance, enhance safety and facilitate identification between biological products. Some supported the use of a random suffix to avoid creating an unfair advantage for specific manufacturers. Several comments stated that the current practices of FDA and non-FDA entities for identifying products is sufficient for the purpose of pharmacovigilance, and designation of a suffix is not needed.

Biosimilars

EMA advice on development of biosimilars

European Union – The EMA will launch a pilot project in February 2017 to test the added value and feasibility of tailored scientific advice for the development of biosimilar medicines. The advice will support the stepwise approach recommended in EU guidelines, where the level and robustness of previously accumulated quality, analytical and functional data should determine the extent and nature of the required studies and tests.

The advice is intended to inform the development strategy for biosimilars. It will not constitute a formal pre-assessment of the data submitted as part of the marketing authorization application.


(1) CDSCO Advisory, 1 February 2017.
Substance use

**Opioid control in Canada**
Canada – Following the launch of the Canadian Drugs and Substances Strategy in December 2016, which reinstates harm reduction as a core pillar of Canada’s drug policy, the Government of Canada has announced new funding of 65 million Canadian dollars (approximately US$ 50 million) over five years to be used to support the federal government’s ongoing implementation of the Opioid Action Plan.\(^1\)

To raise awareness on the safe use of opioids Health Canada will put forward a regulatory proposal to make warning stickers and patient information handouts mandatory with all opioids dispensed in Canada. The sticker on the medicine container would warn patients about the risks of addiction and overdose with opioid use. The handout would contain broader information on the safe use of opioids and important risks.\(^2\)

\(^1\) Health Canada News release, 17 February 2017. 

Collaboration

**Landmark EU–U.S. agreement on inspections**
European Union, United States of America – EMA and FDA have agreed to mutually recognize inspections of manufacturing sites for human medicines conducted in their respective territories. This will enable better use of inspection resources with greater focus other parts of the world where there may be greater risk. Around 40% of finished medicines marketed in the EU come from overseas and 80% of the manufacturers of active pharmaceutical ingredients for medicines available in the EU are located outside the Union.

The agreement is an annex to the EU-U.S. mutual recognition agreement which was signed in 1998. Many provisions of the agreement are already effective, and others will enter into force on 1 November 2017. To reach the agreement on inspections the two regulatory authorities have worked together closely since May 2014 and have been auditing and assessing the respective supervisory systems.

\(\triangleright\) EMA Press release, 2 March 2017. 

**IGDRP roadmap to 2020**
The Steering Committee of the International Generic Drug Regulators Programme (IGDRP) has released the Programme’s Roadmap to 2020. The document describes the five overarching strategic priorities for the initiative as well the key objectives for each of these priorities.

The IGDRP was launched in 2012 as a pilot to increase the efficiency of review procedures for generic medicines and reduce regulatory burden without comprising the safety, efficacy, and quality of products. Availability of quality generic medicines plays an increasingly important role in helping to address rising health care costs.

\(\triangleright\) IGDRP News, 21 December 2016.

**IGDRP biowaiver template**
The IGDRP Bioequivalence Working Group has developed a template for biowaiver assessment reports to ensure that the relevant information for a biowaiver is consistently taken into account during assessment, despite the IGDRP members’ differing requirements for biowaivers based on the Biopharmaceutics Classification System.
Under discussion

European Union – The European Commission has invited comments on its revised guidelines on excipients in the labelling and package leaflet of medicinal products for human use. The purpose of the guideline is to define requirements on how excipients must feature on the labelling of medicinal products. The original guidance was adopted in 2003.


European Union – The EMA has launched a public consultation on the proposed revision to its 2010 policy on access to documents. The new version extends the scope of the policy to include explicitly corporate documents and takes into account the move towards more transparency that has led to the publication of additional documents on the EMA website since 2010.


European Union – The EMA has released a concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product. Such requirements are intended for situations where a medicinal product is used along with a specified medical device, and there is no intention to duplicate the CE marking process for medical devices.


United States of America – The FDA has released three texts regarding different types of manufacturers’ communications about medical products, including: communications with funders and similar entities, communications conveying content that is not included in the product information; and communications on unapproved uses of approved products.


New Zealand – Medsafe has launched a public consultation on labelling requirements for over-the-counter miconazole products to include a compulsory warning about

System (BCS). As this template can also benefit applicants and the broader regulatory community it has been made available on the IGDRP website.


ASEAN joint assessment pilot
The medicines regulatory authorities of the Association of Southeast Asian Nations (ASEAN) have developed a new procedure for joint assessment of marketing authorization applications. The procedure will be implemented, with support and technical advice from WHO, for a pilot period of up to two years starting in January 2017. Participation by applicants and regulators is voluntary for each product to be assessed. The procedure is intended lead to faster review of priority medicines throughout ASEAN while respecting existing national decision-making processes.

a known interaction with warfarin. The revision is proposed because potentially life-threatening events continue to be reported in New Zealand in patients taking the two medicines concomitantly.

  Closing date: 13 April 2017.

**United Kingdom** – The MHRA is developing a strategy for the creation of *pharmacopoeial public quality standards for biological medicines* and has launched a consultation to seek input on the strategy, and on how the standards are used and can be improved.

- MHRA Open consultation, 9 January 2017.
  Closing date: 10 April 2017.

**Australia** – The 2015 *Review of Medicines and Medical Devices Regulation* in Australia included three recommendations to improve access to unapproved therapeutic goods through changes to existing schemes. The recommendations made are to decrease duplication of work and to streamline access to unapproved therapeutic goods considered to have an established history of use.

- TGA Consultation, 15 February 2017.
  Consultation closed 29 March 2017.

**Australia** – The TGA has released a consultation paper on reforms to its *complementary medicines regulation*. The document proposes a three-tiered risk-based framework, introducing a new assessment pathway sitting between the existing pathways for listed medicines (low risk) and registered medicines (high risk).

  Consultation closed 28 March 2017.

**United States of America** – The FDA has published its draft guidance on the data and information expected for a *biological product* to meet the standard for interchangeability. The availability of biosimilar and interchangeable products will provide more treatment options, potentially driving down costs to give more patients access to needed medicines.

  Consultation closed 20 March 2017.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has released its *reflection paper on Good Clinical Practice (GCP) Renovation*. The paper proposes a revision of the ICH E8 General Considerations for Clinical Trials, as well as further revisions to the E6 Guideline for GCP.

  Consultation closed 11 March 2017.

**European Union** – The EMA has published a summary of *ideas on advanced therapy medicinal products (ATMP)* put forward at a May 2016 workshop. While revisions to the legislation on ATMPs in Europe are currently not foreseen, the workshop outcomes will be considered for a wider EU plan to be developed.


**European Union** – In response to a European Commission consultation on the development of *good manufacturing practice (GMP) guidelines for ATMPs*, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) has expressed its concern about proposed lowered GMP standards for ATMPs, leading to an internationally non-harmonized approach in this area.

- (1) EC. Summary of the responses to the targeted stakeholder consultation.
**Approved**

**Plecanatide for chronic idiopathic constipation**

**Product name:** Trulance®
**Dosage form:** Tablets
**Class:** Guanylate cyclase-C agonist, human uroguanylin analog
**Approval:** FDA
**Use:** Treatment of chronic idiopathic constipation (CIC) in adults.
**Benefits:** Additional treatment option for adult patients with CIC.
**Safety information:** Plecanatide should not be used in children under six years due to the risk of serious dehydration. Its use should be avoided in patients aged 6-18 years, as its safety and effectiveness have not been established in these patients. The product should not be used in patients with known or suspected mechanical gastrointestinal obstruction. The most common and serious side effect was diarrhoea. If severe diarrhoea occurs, patients should stop taking the medicine and contact their health care provider.


**Telotristat ethyl for carcinoid syndrome diarrhoea**

**Product name:** Xermelo®
**Dosage form:** Tablets
**Class:** Serotonin synthesis inhibitor
**Approval:** FDA (fast-track designation, priority review; orphan drug designation)
**Use:** Adjunctive treatment of carcinoid syndrome diarrhoea in adults when the condition is inadequately controlled with somatostatin analog therapy alone.
**Benefits:** Inhibits the production of serotonin by carcinoid tumours and reduces the frequency of carcinoid syndrome diarrhoea.

**Safety information:** Patients should be monitored for severe constipation. If a patient experiences severe constipation or severe, persistent or worsening abdominal pain, they should discontinue telotristat ethyl and contact their healthcare provider.


**Crisaborole for atopic dermatitis**

**Product name:** Eucrisa®
**Dosage form:** Ointment
**Class:** Phosphodiesterase 4 (PDE-4) inhibitor
**Approval:** FDA
**Use:** Treatment of adults and children over two years of age with mild to moderate atopic dermatitis.
**Benefits:** Additional treatment option for adult patients with CIC.
**Safety information:** Serious side effects include hypersensitivity reactions to crisaborole.


**Parathyroid hormone replacement therapy**

**Product name:** Natpar®
**Dosage form:** Injection
**Class:** Hormone; ATC code: H05AA03
**Approval:** EMA (conditional marketing authorization; orphan designation)
**Use:** Adjunctive treatment of patients with chronic hypoparathyroidism who cannot be adequately controlled with calcium and vitamin D
**Benefits:** Ability to reduce the need for calcium and vitamin D supplements while maintaining adequate serum calcium levels.
**Regulatory news**

**Approved**

**Note:** This is the first EMA-approved hormone replacement therapy for parathyroid disorder.


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**Rucaparib for certain ovarian cancers**

**Product name:** Rubraca®

**Dosage form:** Tablets

**Class:** Poly ADP-ribose polymerase (PARP) inhibitor; **ATC code:** L01XX55 (temporary)

**Approval:** FDA (accelerated approval, breakthrough therapy, priority review; orphan drug designation)

**Use:** Treatment of advanced ovarian cancer in women who have been treated with two or more chemotherapies and whose tumours have a specific gene mutation (deleterious BRCA) as identified by an FDA-approved companion diagnostic test.

**Benefits:** Additional treatment option for women with BRCA-mutated ovarian cancer.

**Safety information:** Serious risks associated with rucaparib include myelodysplastic syndrome, acute myeloid leukaemia and foetal harm.


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**Nusinersen for spinal muscular atrophy**

**Product name:** Spinraza®

**Dosage form:** Injection

**Class:** Survival motor neuron-2 (SMN2)-directed antisense oligonucleotide

**Approval:** FDA (fast-track designation, priority review; orphan drug designation)

**Use:** Treatment of adults and children with spinal muscular atrophy (SMA)

**Benefits:** Improvement in motor functions such as head control, sitting, ability to kick in supine position, rolling, crawling, standing and walking.

**Notes:** This is the first medicine approved in the U.S. for the treatment of SMA, a rare and often fatal hereditary condition affecting muscle strength and movement. According to an article in the New York Times, treatment could cost US$ 625,000-$750,000 in the first year, and about $375,000 annually after that.


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**Sublingual dust mite allergen extract**

**Product name:** Odactra®

**Dosage form:** Sublingual tablet

**Class:** Allergen

**Approval:** FDA

**Use:** Treatment of house dust mite-induced allergic rhinitis.

**Benefits:** Reduction in allergy symptoms

**Safety information:** Boxed warning about the risk of severe allergic reactions, some of which can be life-threatening. As with all sublingual allergen extracts, patients should be prescribed auto-injectable epinephrine (adrenaline).


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**Sodium zirconium cyclosilicate for hyperkalaemia**

**Product name:** Lokelma®

**Dosage form:** Powder for oral suspension; **ATC code:** V03AE10

**Approval:** EMA/CHMP recommendation

**Use:** Treatment of hyperkalaemia in adult patients.

**Benefits:** Ability to lower serum potassium levels.

Two adalimumab biosimilars

Product name: Amgevita®
Reference product: Humira®
Approval: EMA recommendation

Product name: Solymbic®
Reference product: Humira®
Approval: EMA recommendation
Use: Treatment of rheumatoid arthritis, enthesitis-related arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis.

Three clinically important generics approved in China
The China Food and Drug Administration (CFDA) has announced the approval of three clinically important generics manufactured by Chinese companies, as well as the active pharmaceutical ingredients contained in the products. The medicines concerned are the anti-cancer medicine gefitinib and the antiretrovirals efavirenz and tenofovir disoproxil fumarate (TDF). TDF can also be used to treat hepatitis B. (1)

This follows a drive by the CFDA to raise the standards of generic drugs developed, produced and sold in China. In late 2015 the authority had released draft guidance calling for manufacturers of approved generics to perform conformity assessments of their products. (2) Draft guidelines on inspections for generic medicines were released in January 2017. (3)
(3) RAPS. Asia Regulatory Roundup. 3 January 2017.

Two tests for guiding antibiotic use
The FDA has cleared two tests that can help to guide the use of antibiotics. The Vidas Brahms PCT Assay was cleared for expanded use in guiding treatment in lower respiratory tract infections, in addition to its use in sepsis. The test measures procalcitonin (PCT), a protein associated with the body’s response to a bacterial infection. It is intended to be used in the hospital or emergency room setting. The FDA also cleared the PhenoTest BC Kit, which can identify various infective agents causing bloodstream infections and provide sensitivity results for selected antibiotics.
► (1) FDA News release, 23 February 2017.
(2) FDA News release, 23 February 2017.

Extension of indications

Elvitegravir & cobicistat & emtricitabine & tenofovir for children over 12 years of age
Product name: Stribild®
Approval: FDA
Newly approved use: Treatment of HIV in children over 12 years of age weighing at least 35 kg.
► FDA. What’s new in HIV and AIDS. 31 January 2017.