

# News from the EMA

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## EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans

**July 7, 2017** – The European Medicines Agency (EMA) has concluded its review of gadolinium contrast agents, confirming recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the authorisations of others. The recommendations – confirmed by EMA's Committee for Medicinal Products for Human Use (CHMP) – follow a review that found that gadolinium deposition occurs in brain tissues following use of gadolinium contrast agents.

There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition.

The intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid given intra-articularly

(into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.

All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the European Union (EU). Another class of gadolinium agents known as macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

The suspensions or restrictions on linear agents can be lifted if the companies concerned



provide evidence of new benefits in an identified patient group that outweigh the risk of brain deposition or if the companies can modify their products so they do not release gadolinium significantly or cause its retention in tissues.

EMA's final recommendations will be sent to the European Commission (EC), which will issue a final legally binding decision applicable in all EU Member States.

## Revised guideline on first-in-human clinical trials: Strategies to identify and mitigate risks for trial participants

**July 25, 2017** – The EMA has revised its guidance on first-in-human clinical trials to further help stakeholders identify and mitigate risks for trial participants.

First-in-human trials are a key step in medicines development, where a medicine already tested in vitro, in animals or in other preclinical studies is administered to people for the first time. Participants in these trials, often healthy volunteers, face an element of risk as the ability of researchers to predict the effects of a new medicine on people is limited before it is actually studied in humans. Only on very rare occasions, however, have participants experienced serious harm.

The safety and well-being of trial participants should always be the utmost

priority when designing early clinical trials. The guideline puts emphasis on the sponsor's responsibility to define the uncertainty associated with the medicine tested at each step of the development and to describe how the potential risks that might arise from this uncertainty will be addressed within the design and conduct of the trial. The approach must be supported by a well-documented scientific rationale from the outset and be responsive to data emerging over the course of the trial itself.

The revision takes into account the fact that in the past 10 years trial protocols have become increasingly complex and now often include different parts within a single clinical trial protocol, aimed at assessing for example single and multiple ascending doses, food

interactions, or different age groups.

The strategies to mitigate and manage risks for trial participants described in the guideline refer specifically to the calculation of the starting dose to be used in humans, the subsequent dose escalations, and the criteria for maximum dose. Guidance is also provided on criteria to stop a study, the rolling review of emerging data with special reference to safety information for trial participants, and the handling of adverse events in relation to stopping rules and rules guiding progress to the next dosing level.

This guideline was revised in cooperation with the EC and the representatives of the Member States of the EU through the EU Clinical Trials Facilitation Group (CTFG).

## EU report: More evidence on link between antibiotic use and antibiotic resistance

**July 27, 2017** – A new report from the three agencies, the European Food Safety Authority, the European Medicines Agency, and the European Centre for Disease Prevention and Control, presents new data on antibiotic consumption and antibiotic resistance and reflects improved surveillance across Europe.

The Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report highlights that there are still important differences across the EU in the use of antibiotics in animals and humans. Overall antibiotic use is higher in food-producing animals than in humans, but the situation varies across countries and according to the antibiotics.

In particular, a class of antibiotics called polymyxins – which includes colistin – is used widely in the veterinary sector. It is also increasingly used in hospitals to treat multidrug-resistant infections. Other antibiotics are more often used in humans than in animals. These include third- and fourth-generation cephalosporins and quinolones, antibiotics that are also considered critically important for human health.

The report notes that resistance to quinolones, used to treat salmonellosis and campylobacteriosis in humans, is associated with use of antibiotics in animals. The use of third- and fourth-generation cephalosporins for the



treatment of infections caused by *Escherichia coli* and other bacteria in humans is associated with resistance to these antibiotics in *E. coli* found in humans.

The conclusions are in line with those of the first report published in 2015. However, the

availability of better quality data allowed for a more sophisticated analysis. Experts of the three agencies recommend further research to better understand how the use of antibiotics and resistance affect one another.

## EMA encourages tailored development of medicines for older people

**August 1, 2017** – The EMA is inviting comments from the public by January 31, 2018, on a reflection paper on how medicine developers can better address the needs of older people who take medicines.

In general, older people are the highest users of medicines. According to Eurostat, they are expected to make up almost a third of all Europeans by 2050, and they take more medicines than the rest of the population. Yet, medicines are rarely developed or packaged to take into account their specific needs. For example, some older people can face challenges such as difficulty opening boxes or bottles, reading instructions, swallowing or breaking tablets and capsules, which can result in medicines not being taken as intended, medication errors, and

ultimately a reduced quality of life.

The reflection paper describes aspects that medicines developers may consider when designing medicines for older people, such as selecting appropriate routes of administration and dosage forms, dosing frequency, excipients, container closure systems, devices and technologies, and user instructions in the product information.

For example, when there is evidence that older people find it difficult to break a tablet by hand, companies may find ways to improve the

breakability of the tablet or consider alternative administration approaches, such as small tablets in a dose dispenser. Similarly, companies may consider redesigning the containers so that older patients can open them easily without any assistance.

Comments are particularly invited on the accuracy of tablet breaking, the administration of medicines through feeding tubes, and on multiple compliance aids and multiple drug dispensing systems (containers that clearly state the name of the day or the moment when a medicine needs to be administered).

Depending on the outcome of the public consultation, the content of the reflection paper might be further developed into regulatory or scientific guidance.





## Platform for post-authorisation studies registered as EU trade mark

**August 7, 2017** – The European Union Intellectual Property Office (EUIPO) has approved the registration of “EU PAS Register” as a European Union trade mark (EUTM). A EUTM grants exclusive rights in all current and future Member States of the EU and can be renewed every 10 years.

Launched in November 2010, the EU PAS Register is a unique source of information on the safety and effectiveness of authorised medicines. It is an openly accessible platform with infor-

mation on observational post-authorisation research in medicines already marketed in Europe and includes study protocols, study results, related publications and other relevant information.

The information in the EU PAS Register helps to reduce publication bias through increased transparency of medicines research, improves the quality of post-authorisation studies by facilitating peer-review of protocols and results, promotes collaboration among stakeholders, and ensures compliance with EU pharmacovigilance legislation requirements.

By July 31, 2017, 1,145 studies had been registered on the platform. 583 (50.9%) have been requested by a regulatory authority, and 368 (32.1%) are finalised.

The trade mark, registered on July 10, 2017,

will reinforce the European Medicines Agency’s (EMA) legal control over the name of the platform and its content. The EU PAS Register is now acknowledged internationally as a repository of observational post-authorisation studies. The use of the platform is widely recommended in scientific publications, guidelines, and textbooks. Although initially the main aim of the EU PAS Register was to collect studies conducted in the EU, researchers from outside the EU are also registering studies to increase transparency of their research.

The EU PAS Register was developed through the European Network of Centres for Pharmacoeconomics and Pharmacovigilance (ENCePP), which is coordinated by EMA to support research in pharmacoepidemiology and pharmacovigilance.

## New commitment allows FDA to share full inspection reports with EC and EMA

**August 23, 2017** – The European Commission (EC), the United States (US) Food and Drug Administration (FDA), and the EMA have signed a new confidentiality commitment that allows the US regulator to share non-public and commercially confidential information, including trade secret information relating to medicine inspections, with EU regulators. This confidentiality commitment is a milestone in the ongoing implementation of the mutual recogni-

tion of inspections of medicine manufacturers, and it aims to strengthen the EU-US relationship. Ultimately it will contribute to a more efficient use of inspection resources by regulators for the protection of human and animal health.

The EU and the US have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information as part of their regulatory and scientific processes. However, complete exchange of information was

not possible under these arrangements.

The new confidentiality commitment formally recognises that FDA’s EU counterparts have the authority and demonstrated ability to protect the relevant information. This step now allows the sharing of full inspection reports, allowing regulators to make decisions based on findings in each other’s inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk.

## Factor VIII medicines: No clear and consistent evidence of difference in risk of inhibitor development between classes

**September 9, 2017** – The EMA has concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: Those derived from plasma and those made by recombinant DNA technology.

Factor VIII is needed for blood to clot normally and is lacking in patients with haemophilia A. Factor VIII medicines replace the missing factor VIII and help control and prevent bleeding. However the body may develop inhibitors as a reaction to these medicines, particularly when patients first start treatment. The inhibitors reduce the medicines’ effect, so that bleeding is no longer controlled.

EMA looked at data to assess whether there is a difference in the risk of inhibitor development between factor VIII medicines manufactured with DNA technology and those

extracted from human blood. EMA concluded that there is no clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines. Patients should therefore continue to use their factor VIII medicines as prescribed by the doctor.

EMA’s review was started following publication of the SIPPET study, which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines containing von Willebrand factor. The review concluded that the data did not show any statistically or clinically meaningful difference in inhibitor risk between factor VIII classes. The SIPPET study was designed to assess class effects and included a small number of factor VIII medicines, and the review considered that the results cannot be extrapolated to individual

medicines, especially since many were not included in the study. Therefore, the risk for each product will continue to be assessed as more evidence becomes available.

To reflect current knowledge, the prescribing information of factor VIII medicines will be updated to include, as appropriate, inhibitor development as a very common side effect in previously untreated patients, and as an uncommon side effect in previously treated patients. The warning on inhibitor development will be amended to state that low levels of inhibitors pose less risk of severe bleeding than high levels.

