kinase by first binding the glycosylphosphatidylinositol-anchored GDNF family receptor GFRa1" has a meaning to him. By the late afternoon I had finished and sent it to the author.

The next morning (Thursday)

Lead author replied:

Hello Michael. Thank you very much for your fast and comprehensive revisions! I could follow all your comments and there was always a correct option (contentwise) among your suggestions. Also the comment from your statistician was very helpful. The parts in the introduction, that, as you mentioned, should be moved to the methods section, where "produced" during the major revisions. Otherwise, I will follow your suggestions closely (and try to memorize my false friends ;).

I can't believe that all my suggestions were correct content-wise. That's a really nice email to get. Much better than the one I got a few months ago about an analytical mistake I had made in a discussion section. That generated a published letter to the editor from other authors and necessitated the writing of a response saying *yes, you're right, but…* . The shame.

The *neurotrophic factor; encapsulated cells* paper was a nice diversion. I'm happy, the author's happy, R&D is, presumably, happy. I add it to my list of papers that went out but I'm not involved in the submission process. I hope I can add it to my published list soon. I have to shift myself my attention now to the other four papers I've put off. It's raining outside and the mountains are blocked by a thick gauze of clouds.

The colleague who was out sick is back in today. She thanked me for doing the 2-minute summary. She's going to be out for the next 5 weeks and her workload is being shifted to me and the new medical writer.

As I'm finishing this article an email comes in. An author I've been working closely with will send me the final version on Monday for me to proof; after 1+ years and rejections from a series of journals, we (or rather: he and the other authors) are very close to an acceptance.

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News from the EMA

The articles included in this section are a selection from the European Medicines Agency's News and Press Release archive from January 2017 to March 2017. More information can be found on the Agency's website: www.ema.europa.eu

Conditional marketing authorisations give patients access to important new medicines earlier

January 23, 2017 – Conditional marketing authorisation (CMA) can speed up access to medicines for patients with unmet medical needs in the European Union (EU). It allows the authorisation of medicines if the public health benefit of their immediate availability to patients outweighs the risk of an authorisation on the basis of less comprehensive data than normally required. The European Medicines Agency (EMA) has published a report on the CMA experience based on the data collected over 10 years since 2006. Since 2006, a total of 30 medicines have received a CMA. Over this 10-year period, no medicine with a CMA had to be revoked or suspended. Medicines that were granted a CMA target seriously debilitating or life-threatening conditions such as HIV infection, breast cancer, severe epilepsy in infants, or multi-drug resistant tuberculosis. Fourteen were orphan medicines, providing patients suffering from rare diseases with new therapeutic options.

A CMA is valid for 1 year. As part of the authorisation, the company is obliged to carry out further studies to obtain complete data. EMA's Committee for Medicinal Products for Human Use (CHMP) assesses the data generated by these specific post-authorisation obligations at least annually to ensure that the balance of benefits and risks of the medicine continues to remain positive. At the end of its assessment, the Committee recommends either the renewal or not of the CMA or its conversion into a standard marketing authorisation.

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The report shows that it took an average of 4 years to generate the additional data needed and to convert a CMA into a full marketing authorisation. This means that patients with life-threatening or seriously debilitating conditions can access promising medicines earlier.

The report identifies a number of possible areas for improvement. These include:

- Prospective planning of CMAs and early dialogue with EMA to support the generation of high-quality data, timely discussion of additional post-authorisation studies and their feasibility, and better data generation for completion of specific obligations.
- Engaging other stakeholders involved in bringing a medicine to patients, in particular Health Technology Assessment bodies, to facilitate the generation of all data needed for decision-making through one development programme.

The full report together with an infographic that highlights the key findings of this analysis is available online on the EMA website.

It's time to reduce, replace, and rethink the use of antimicrobials in animals

January 24, 2017 – Reducing the use of antimicrobials in food-producing animals, replacing them where possible, and rethinking the livestock production system is essential for the future of animal and public health. Antimicrobial resistance (AMR) is one of the world's most pressing public health issues and the use of antimicrobials in animals contributes to this problem.

Experts from the European Food Safety Authority (EFSA) and EMA have reviewed the measures taken in the EU to reduce antimicrobials use in animals and stress that there is no one-size-fits-all solution. Successful strategies follow an integrated, multifaceted approach which takes into account the local livestock production system and involves all relevant stakeholders – from governments to farmers.

Measures

Control strategies that have been important drivers for change include setting of national targets to reduce antimicrobial use. The use of antimicrobials in animals should be reduced to the minimum that is necessary to treat infectious diseases. Other than in exceptional cases, their use to prevent such diseases should be phased out in favour of alternative measures. Critically important antimicrobials for human medicine should only be used in animals as a last resort.

Alternatives to antimicrobials that have been shown to improve animal health and thereby reduce the need to use antimicrobials include vaccines, probiotics, prebiotics, bacteriophages, and organic acids.

Further, there is a need to rethink the livestock system by implementing farming practices that prevent the introduction and spread of the disease into farms and by considering alternative farming systems which are viable with reduced use of antimicrobials. Education and awareness of AMR should be addressed to all levels of society but in particular to veterinarians and farmers.

What is the impact on animals and food?

Experts concluded that it is reasonable to assume that reducing antimicrobial use in food-producing animals would result in a general decrease in antimicrobial resistance in the bacteria that they carry and the food products derived from them. However, they could not quantify the impact of single reduction measures or alternatives to antimicrobials on levels of antimicrobial resistance in food-producing animals and food due to lack of data.

First hormone replacement therapy for parathyroid disorder recommended for conditional marketing authorisation

February 24, 2017 – The EMA has recommended granting a CMA in the EU for Natpar (parathyroid hormone) that is proposed as a treatment for patients with chronic hypoparathyroidism who cannot be adequately controlled with standard treatment with calcium and vitamin D. It is the first approved replacement therapy with parathyroid hormone for this rare condition, for which no treatment options are available currently.

Hypoparathyroidism is a hormone disorder where the parathyroid glands in the neck produce too little parathyroid hormone, in most cases because of damage to the parathyroid glands during surgery. This results in too little calcium and too much phosphate in the blood, which affects the normal functioning of nerves and muscles leading to symptoms such as tingling sensations and muscle spasms or even seizures and heart rhythm disorders. In the longer term, uncontrolled hypoparathyroidism increases the risk of bone fractures and calcium deposits, particularly on the kidney, brain and eye lens.

The safety and effectiveness of Natpar were evaluated in a clinical trial of 124 participants who were randomly assigned to receive Natpar or a placebo, in addition to the standard treatment with calcium and vitamin D. The trial was designed to determine whether Natpar can be used to help reduce the amount of calcium or vitamin D taken by the participants, while maintaining acceptable calcium and phosphate serum levels. Results showed that 54.8% of participants treated with Natpar were able to reduce the doses of calcium and vitamin D supplements by more than 50% while maintaining acceptable blood-calcium levels, compared to 2.5% of participants who received the placebo treatment.

As part of the CMA, the applicant for Natpar is required to conduct a 26-week clinical trial to further study the safety and efficacy of the medicine, confirm the dosing schedule and assess the effects of treatment on symptoms of the disease and on patients' quality of life. The study will also look at how calcium and phosphate are processed in the body during treatment.

Because hypoparathyroidism is rare, Natpar received an orphan designation from the Committee for Orphan Medicinal Products (COMP) in 2013. Orphan designation is the key instrument available in the EU to encourage the development of medicines for patients with rare diseases. Orphan-designated medicines qualify for 10 years' market exclusivity. In addition, orphan designation gives medicine developers access to incentives, such as fee reductions for marketing authorisation applications and for scientific advice.

European and US regulators agree on mutual recognition of inspections of medicines manufacturers

March 02, 2017 – Regulators in EU and the United States (US) have agreed to recognise inspections of manufacturing sites for human medicines conducted in their respective territories on both sides of the Atlantic.

Each year, national competent authorities from the EU and the US Food and Drug Administration (FDA) inspect many production sites of medicinal products in the EU, the US and elsewhere in the world, to ensure that these sites operate in compliance with good manufacturing practice (GMP). Under the new agreement, EU and US regulators will rely on each other's inspections in their own territories. In future, the need for an EU authority to inspect a site located in the US, or vice versa, will be limited to exceptional circumstances.

The agreement will enable both the EU authorities and the FDA to make better use of their inspection resources to help them to focus on other parts of the world where active pharmaceutical ingredients (APIs) and medicines for the EU or US markets are manufactured. This will ensure that patients can rely on the quality, safety and efficacy of all medicines, no matter where they have been produced. Around 40% of finished medicines marketed in the EU come from overseas and 80% of the manufacturers of APIs for medicines available in the EU are located outside the Union.

In the EU, inspections of manufacturing sites are carried out by national competent authorities from EU Member States. The EMA plays an important role in coordinating these activities in collaboration with Member States.

The agreement is underpinned by robust evidence on both sides of the Atlantic that the EU and the US have comparable regulatory and procedural frameworks for inspections of manufacturers of human medicines. Teams from the European Commission, EU national competent authorities, EMA and the US FDA have been auditing and assessing the respective supervisory systems since May 2014, and have worked closely together to reach this agreement.

PRAC review finds evidence of gadolinium deposits in the brain after MRI body scans but no signs of harm: suspension of marketing authorisations recommended for some gadolinium agents

March 10, 2017 – EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) has recommended the suspension of the marketing authorisations for four linear gadolinium contrast agents because of evidence that small amounts of the gadolinium they contain are deposited in the brain. The agents concerned are intravenous injections of gadobenic acid, gadodiamide, gadopentetic acid and gadoversetamide, which are given to patients to enhance images from magnetic resonance imaging (MRI) body scans.

The PRAC's review of gadolinium agents found convincing evidence of accumulation of gadolinium in the brain from studies directly measuring gadolinium in brain tissues and areas of increased signal intensity seen on MRI scan images many months after the last injection of a gadolinium contrast agent. The companies concerned by this review have the right to request the PRAC to re-examine its recommendations.

Although no symptoms or diseases linked to gadolinium in the brain have been reported, the PRAC took a precautionary approach, noting that data on the long-term effects in the brain are limited. Deposition of gadolinium in other organs and tissues has been associated with rare side effects of skin plaques and nephrogenic systemic fibrosis, a scarring condition in patients with kidney impairment. Furthermore, non-clinical laboratory studies have shown that gadolinium can be harmful to tissues.

The four agents recommended for suspension are referred to as linear agents. Linear agents have a structure more likely to release gadolinium, which can build up in body tissues. Other agents, known as macrocyclic agents, are more stable and have a much lower propensity to release gadolinium. The PRAC recommends that macrocyclic agents be used at the lowest dose that enhances images sufficiently to make diagnoses and only when unenhanced body scans are not suitable.

For those marketing authorisations recommended for suspension, the suspensions can be lifted if the respective companies provide evidence of new benefits in an identified patient group that outweigh its risks or show that their product (modified or not) does not release gadolinium significantly (dechelation) or lead to its retention in tissues.