BMJ 2018;362:k3855 doi: 10.1136/bmj.k3855

EDITORIALS

Regulatory response to contaminated valsartan

Regulators took rapid action, but exposed patients still require long term monitoring

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Despite being limited by its short follow-up, the registry based cohort study by Pottegård and colleagues (doi:10.1136/bmj.k3851) provides reassuring interim evidence about the risk of cancer in patients treated with valsartan products contaminated with a probable human carcinogen (N-nitrosodimethylamine, NDMA).[1] This study was planned, conducted, analysed, and published within three months from the notification of this quality issue to regulatory authorities.[2] It would not have been possible without linking data from four Danish nationwide registries collecting information on prescriptions, cancer diagnoses, hospital admissions, mortality, and migration. The authors report no increase in overall cancer risk among users of potentially contaminated valsartan products followed up for a median of 4.6 years.

This study alone cannot dispel doubts about the potential risk for patients in the longer term, but it helps inform decision making around this episode. It also illustrates the usefulness of national registries for examining the relations between risk factors and health problems and how research can give a prompt response whenever public health concerns emerge.

How did regulatory agencies react to the safety concern affecting medicinal products containing valsartan? Europe, the United States, Canada, and Japan rapidly started their own investigations, with some international collaboration. Firstly, they mapped all the licensed medicines containing the active substance valsartan—an angiotensin II receptor blocker—supplied by the company that detected the impurity. They recalled the contaminated lots, amounting to more than 3000 products licensed at the national level or centrally by the European Medicines Agency.[3] Branded medicinal products, not just generics, were affected. The Italian medicines agency, for instance, recalled more than 700 lots pertaining to about 100 medicinal products, licensed by 15 marketing authorisation holders.[4] This affects a large number of patients, as valsartan alone or in combination with hydrochlorothiazide accounted for a total of 25.1 defined daily doses per 1000 inhabitants per day in Italy in 2017.[5]

Secondly, regulatory authorities are collecting information on the cause of this contamination; possibly related to a change in the manufacturing process in 2012. Although this needs confirmation, some will wonder whether the impurity could have been detected earlier. Possibly it could. Manufacturing processes must be checked and monitored for any known impurities that imply a risk—as with NDMA, which is a recognised probable human genotoxic compound. This task is the responsibility of the manufacturers themselves, but the marketing authorisation holders are responsible for the quality of the finished medicinal products they put on the market. Public authorities are called to authorise production sites and supervise the quality of pharmaceuticals with frequent, thorough inspections.[6 7]

The European Medicines Agency has mainly a coordinating and harmonisation role, and the national drug agencies have final responsibility for inspections. However, it must be kept in mind that the relationship with industry is mainly based on trust. This applies to clinical efficacy and safety data too, not just quality. Misleading, incomplete, or delayed reporting on clinical efficacy and safety may have a much worse impact on public health than quality.[8]

Thirdly, regulatory authorities are trying to estimate the theoretical risk of the NDMA exposure after the use of contaminated valsartan. The EMA estimated there might be one extra case of cancer for every 5000 patients using the highest valsartan dose (320 mg) every day for seven years.[9] This is based on the average levels of this impurity detected in the active substance (60 ppm, more than 1000 times the amount one might take with water daily) and the possible cancer risk extrapolated from animal studies. Similar estimates by the US Food and Drug Administration report one extra case of cancer for every 8000 patients treated for four years.[10] The Danish cohort covers about one fifth of the person years of exposure required to confirm the EMA estimation. Therefore, patients exposed to this impurity need continued monitoring.

Active pharmacovigilance research programmes, ideally at the European level, may be useful to clarify the potential impact on valsartan safety. Had the Danish study extended to a larger European population, we might already have a conclusive answer. Registry based cohort studies, which are often inappropriately proposed to solve uncertainties on clinical efficacy, would in this case be the ideal methodological approach to deal with safety concerns in the long term.

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The EMA response to these safety concerns seems to have been prompt and transparent.[11] One hopes it will be effective too. Pharmaceutical companies that had used the contaminated active substance in their valsartan medicines are now required to test samples they hold to determine the actual NDMA levels in the final products. Additional checks are being done by European official control laboratories, and other manufacturers are under investigation too.

The outcome of the Article 31 pharmacovigilance referral procedure, dealing with safety concerns of medicinal products authorised in the European Union,[12] is expected later in September. International cooperation between regulators has become important to ensure effective oversight and to respond to the challenges of the increasingly complex global supply of medicines.

Regulatory actions coupled with the generation of robust evidence are the keys to responding promptly to emerging public health concerns.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following: none.

Provenance and peer review: Commissioned; not peer reviewed.

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