Same difference?

When a drug patent expires, other manufacturer can make generic versions of it – but this does nc necessarily mean it is the same, or will have the same effect on the patient, as Richard Shrubb explains

Tracee Cossey, a freelance teacher and PR consultant from Luton, had had her psychotic illness under control for a decade thanks to the antipsychotic drug she took, Risperdal (risperidone). But when this medication's patent expired in 2010, she was given generic versions instead – which had very different effects on her.

Generic medications come onto the market after the patent of a compound has expired, 10 years after it has been licensed. They are cheaper options for the NHS and many patients will be asked to take them after the original patent has expired. But they do not always have the same effect on a patient, despite being the same active compound.

people react differently to different formulations of the same active compound

When taking Risperdal, Cossey says: "I get jittery for an hour so found that I am alright if I go to the gym and burn off the energy."

This is her favourite preparation as it meant that she could work and lead a normal life. But when she started taking two generic versions of risperidone, Teva and Activis, she found that one sedated her and the other stimulated her.

For example, with Activis: "I could think very clearly but couldn't sleep, so I balanced this by having a glass of wine before bed."

But taking Teva disabled her. "I was given this at Christmas 2011 for the first time and had a brain fog. I couldn't think or concentrate for six months."

Later in 2012, she got a prescription for Activis again. "I was OK instantly – I could operate effectively, though again sleep is an issue. You get used to that, however."

In her experience, having a two-week supply of Activis and Teva would be ideal so she can work like crazy then catch up on sleep. But Cossey's chief issue is getting hold of the right drugs. Different pharmacies supply only one generic preparation each – very few in Luton supply Teva. As a result, she now buys her drugs privately from an American website.

Different formulations

Cossey's experience is by no means unique. While it might be assumed that generic and patent drugs would work the same, this is not always the case because the efficacy and tolerability of these drugs have variation and people react differently to different formulations the same active compound, even though clinical tria should ensure they react in the same way as they do the patent formulation.

The reason for this variation is down to th bioavailability of the medication. Bioavailability a descriptor for the amount of a compound that w be used by your body when you take it. The sam formulation will be absorbed differently according the preparation.

For example, in a recent case in the US, Zyprex (olanzapine) administered as an intramuscular dep injection was withdrawn from use after two peop died when injected and were found to have hig levels of olanzapine in their system postmorten The US Food and Drug Administration investigatio is on-going, but essentially it is looking at why th bioavailability was too high and the patients die from olanzapine poisoning.

Generic formulations are tested for their bioequivalenc to the original patent versions. Bioequivalence is term for whether the two preparations will work in a equivalent way in the patient's body. Professor Mun Pirmohammed, a psychopharmacologist at the Universit of Liverpool, explains: "Generic manufacturers have t show exposure to their formulation is equivalent to th patent drug."

A spokesperson for the Medicines and Healthcar products Regulatory Agency (MHRA) explains tha "the applicant is able to 'abridge' (or refer to) th safety and efficacy data generated by the innovato [patent] product if they can demonstrate that the product 'has the same qualitative and quantitativ composition in active substances and the sam pharmaceutical form as the reference medicina product, and whose bioequivalence with th reference medicinal product has been demonstrate by appropriate bioavailability studies.'"

Professor Pirmohammed adds that absorption o all medications is down to the law of averages. "Ove 100 days the absorption rates should be similar. Ove a shorter period – say 10 days – it might be different."

This could be down to, for example, what you ea in that time. "If you eat a lot of fruit in that period, fo example, you would absorb the medication differently, says Professor Primohammed. "Eating a steady, averag

Richard Shrubb is a freelance journalist and mental health service user

diet would be very boring so you're not expected to eat the same thing week in, week out!" This absorption variability applies to all medications, including patent formulations so isn't specific to generic compounds.

Number of testers

But when testing the bioequivalence of a generic formulation, the number of people used in the sample can be quite small, according to Monika Benstetter of the European Medicines Agency (EMA), which sets testing guidance for the MHRA and its equivalent agencies across the European Union. "The number of evaluable subjects in a bioequivalence study should not be less than 12," she says.

With large numbers of people taking many of the medications on the market, this should ring alarm bells – 12 people will not accurately represent, say, 10,000 people who have been switched from a patent to a generic drug. The MHRA spokesperson leavens this, stating: "Whilst the minimum number of subjects is stated as 12, this number is rarely used as studies are designed to ensure there is sufficient statistical power to allow for the demonstration of bioequivalence."

Professor Pirmohammed adds: "Across 50 people tested, the effects would be expected to be similar overall. It is possible that within this number, people will respond differently as individuals."

generic manufacturers have to show exposure to their formulation is equivalent to the patent drug

This law of averages is known as a window of tolerability. With illnesses such as epilepsy the variation among individuals has to be very similar as those taking the compound may have a seizure if there is significant variation in the way people react. Psychiatric medication is not considered to be in this group – people on it are less likely to black out, for instance.

A full explanation of European Union regulations around bioequivalence testing is available online. The EMA *Guideline on the investigation of bioequivalence* states that in batches tested: "The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified." This suggests that such batches have to fulfil the law of averages by being made on a similar scale to full production.

Essentially, within a window of tolerability, people will react differently to the same drugs for reasons not fully understood. Professor Pirmohammed's main line of research is into why people react so differently to the same psychiatric medication despite having the same illness.

Regulations on the bioequivalence of generic drugs minimise the problems encountered for patients taking those generics but there will be variations within the cohort taking them. Simply, people will react differently to different formulations of the same drug because we are different to one another! ■

Gever J (2013) FDA investigates Zyprexa depot deaths. *Medpage Today* June 18, 2013. Available at: http://www.medpagetoday.com/Psychiatry/Schizophrenia/39925

European Medicines Agency (2010) *Guideline on the investigation of bioequivalence*. London: EMA.