

## **CHO Seminar #6 Dr David Graham.**

### **Dr David Graham, National Manager of the Therapeutic Goods Administration**

I'm not always sure how much people know about the TGA.

TGA's primary role is to protect your safety and your health when using therapeutic products and it has a number of mechanisms for doing that. It has a fairly low profile normally, except when things hit the fan, which they did a couple of years ago with Pan Pharmaceuticals. That made people aware that the TGA has a very important public protection role.

You may not have seen the TGA building, but if you go along Narrabundah Lane in Canberra you'll see a building that looks a bit like a crematorium. It's noticeable because it has lots of stacks going up into the air. This is because in the days when it was built, the Australian standard required a separate exhaust for each chemical containment cupboard. I don't know how many exhausts the building has, but it's probably in the order of about a hundred or so. It looks modern and it's a very nice building with a very nice environment. About 450 people work there, many of them highly qualified as pharmacists, doctors or have a science degree of one sort or another and, it has a strong international presence.

One of the things Australia's done well is to operate in a conceptual framework called the national medicines policy, which has four arms to it (slide 2).

One arm is to have a viable industry which puts medicines onto the market; otherwise there's not much reason for the other three arms. A viable industry should also be a responsible industry; in how it promotes its products, how it supplies its products and manufactures them.

The second role is that of TGA in ensuring the quality, safety and efficacy of those products that go onto the market, and this involves products that range from vitamins and minerals through to prescription drugs.

And if you have products available for supply on the market, people have to be able to access them. One means is the Pharmaceutical Benefits Scheme. But there are many other products that need to be accessible such as those supplied in a health food shop. Do you for example, make things available over the counter or restrict them to prescription only?

The fourth arm of the national medicines policy covers the aim that, if you have medicines available how do you ensure their appropriate use? These are foreign chemicals which we are putting into our bodies and so it's probably not surprising that we do have adverse reactions many of which may be caused because we are not using the medicines well. The aim of this arm is to encourage people to use medicines wisely. Antibiotic use is a good example of this because Australia tended to use antibiotics very liberally in the past. In recent times there's been a lot of effort put into education about how to use antibiotics carefully so we don't create resistance and in fact defuse the drugs that are helping us.

Medicines are one component of therapeutic goods which also include medical devices, blood products, biological products etc

The three aspects we must ensure for therapeutic goods are quality, safety and efficacy. It's very important that regulators can prove that they regulate according to risk on the one hand

without making it risky regulation because they are under-regulating and on the other hand without adversely affecting the industry through over regulation.

Slide 3. How does the TGA regulate therapeutic goods? The power is given by the Therapeutic Goods Act, which goes back to the early 1990s.

In fact, the origins of the regulation of the therapeutic goods in Australia dates from the 1950's with an organisation called the National Biological Standards Laboratories, which was established to assay the quality of pharmaceutical benefits (the Pharmaceutical Benefits Scheme had started about that time), to make sure they complied with monographs of the British Pharmacopoeia, the gold standard for the quality of products. The whole thrust of regulation was toward testing the suitability of products through taking samples and testing them in the laboratories.

Then in the 1960s and 70s, thalidomide came along and people realised you couldn't base suitability just on the quality of products, you also had to consider evidence to establish that products were safe. And so the pre market evaluation function evolved.

Now there is another development in ensuring suitability. In a global market manufacturers are putting their product onto the world market pretty well simultaneously. Whereas in the past Australia could perhaps monitor a drug's performance in overseas markets, that information is not available. Post market monitoring is becoming increasingly important as an early detector of adverse effects that may not show up in clinical trials using limited numbers of subjects. While premarket evaluation, analysis of samples and post market monitoring for adverse outcomes are very important tools in regulation, there are also other tools.

The TGA licenses manufacturers. Whoever manufactures a product either in Australia or overseas has to demonstrate compliance with good manufacturing standards.

We make sure that the industry promotes its products correctly. Our approach in Australia is through co-regulation where we allow the industry to manage and police the advertising of therapeutic goods while we provide the legislative support. The Industry Associations know the importance and significance of making sure that their products are used well in the market place.

Another increasingly important mechanism of good regulation is the reporting of adverse reactions. There is the obligation on suppliers to report adverse events and doctors are encouraged to report adverse reactions with their patients. There is some debate about whether or not consumers should have a separate process to report adverse reactions and the quality and usefulness of that reporting.

We also have provisions to recall products from the market place. You have probably seen the advertisements in the papers where we recall a product at the consumer level. However, depending on the circumstances, the product might be recalled at the manufacturing level, the wholesaler level, the retailer level or, in extreme cases, the consumer level.

To underpin these mechanisms we need the teeth to prosecute offenders who breach the legislation. In TGA we have a team of surveillance staff who monitor the marketplace and investigate breaches.

On occasions, individuals need access to therapeutic goods which are not available on the market. A doctor may decide that an unregistered drug is essential for a patient and there is not a marketed alternative. We have a special access scheme where a doctor can use the unregistered drug with the informed consent of the patient.

Clinical trials are also important to give people access to the new experimental drugs as well as to gather the evidence that they are safe in our market. We also have personal import provisions where people can bring in limited quantities of their drug they might have used overseas for their own personal use.

Now, I will describe further the risk-based approach we use for therapeutic goods.

One of the dilemmas when we set up the legislation was, how do you cover vastly different products with different risks? For example, the range is from homeopathic medicines to prescription medicines. If people want access to a homeopathic medicine - how do you give access to them when they are part of a regulatory system designed to deal with prescription medicines?

Nearly all therapeutic goods must originally be registered on the Australian Register of Therapeutic Goods before they can be supplied (slide 5). The Register is structured in two levels of registered products and listed products: High level registration is for prescription drugs. They go through the full gamut of premarket evaluation of their quality, safety and efficacy. There is also a lower level for over-the-counter drugs. They go through a lower level registration of pre-market evaluation of quality, safety and efficacy. They are supplied over the counter because they have a lower risk. (We use a process that schedules drugs either as prescription or over-the-counter as one of the criteria for the risk-based approach)

Listing on the Register applies to many of the vitamin, mineral and herbal products. All have a long and established history of use, both through being in the marketplace and through empirical knowledge. Even with their lower risk, we require that they have the same quality of manufacture as registered medicines.

Listable products have a long history of the safe use and the ingredient must be on a permitted list. We require the company to hold information of the efficacy of the product. If a herbal product, for instance, contains a scheduled herb or a scheduled drug, then it automatically goes up into the registrable category and has to go through that higher level of pre-market clearance.

A listable product can only make claims for simple, selflimiting illness. As soon as a manufacturer wants to make claims about treating for example, chronic pain or chronic pain management then the product has to be evaluated as a registered product before it can go onto the market.

It's similar with therapeutic devices with the same sort of decision tree approach.

How many drugs are listed on the Australian Register of Therapeutic Goods (slide 6) ? For high level registered medicines, about 10,000. For listed medicines, about 19,000 and export only medicines (which are going into other countries) just over 3000. Export only medicines are checked to make sure that they comply with quality standards in this country which protects both the user and Australia's reputation, but of course the way they are used in another country might be different.

Then we have the registered devices and listed devices. Overall on the Australian market there are in the order of 64,000 therapeutic goods.

The TGA is structured (slide 7) into regulating areas dealing with prescription medicines, non-prescription medicines, complementary medicines, and an office that deals with devices. We also cover blood, tissues and organs. Support areas include the laboratories which carry out analysis of products and the manufacturer licencing group.

We have two other parts to the TGA Group of Regulators. One is the Office of the Gene Technology Regulator, which is the regulator of genetically modified products which might be crops or drugs. We also have Office of Chemical Safety which is the area that regulates industrial chemicals. You could say that TGA is a one stop shop for chemicals that either go into the body or are used in crops, agriculture or industry in some way.

There are some interesting interfaces of therapeutic goods with other areas. The separation between a medicine and a cosmetic that might be making claims of relieving wrinkles or anti-aging claims and where that overlaps with a therapeutic good is often a hard one to define. Likewise with foods. The food area is evolving and health claims are appearing on food with more frequency. The demarcation between a therapeutic good and the food that is making claims about reducing cardio-vascular risk can be a difficult area to define.

TGA does a lot of work in the international area. The pharmaceutical and medical devices industry are international we have several agreements with regulators in other countries where we exchange information, skills and knowledge.

We are keen to be more transparent. But there are restrictions on what information we can release. We are keen to push the boundaries with industry about what they regard as a commercial in confidence information and the extent of what we can disclose to the public. Not everything should be automatically stamped by a company as commercial in confidence.

Where are we going in the future? I'd like to mention just a couple of trends (slide 9). One is that we are setting up a joint agency with New Zealand. Increasingly one of the expectations when operating in the international market place, and rightly so, is that regulators will harmonise their requirements so there won't be unique country requirements except where essential. The logical extension is to collapse down the number of regulators. We are actively working with New Zealand to set up one regulator across the Tasman.

However, this creates interesting dilemmas about meshing together, for example, different Freedom of Information requirements, different staffing structures and different legal compliance structures. One example is that New Zealand allows direct promotion of prescription products to consumers which we don't allow in Australia and there is good rationale behind this. Also we will be reporting to two different Ministers and two different

Parliaments. It's a new ballgame, but we're working through it and the expectation is that we should be ready to go by mid 2007.

If we go forward 100 years we will find fewer regulators in many areas as the markets become more global. Initiatives like free trade agreements are also breaking down barriers at a very fast rate.

Another trend is post market monitoring. Increasing prominence is being given to how we monitor products when they get into the market place. Recently a company removed an anti-inflammatory product from the market world-wide after there were problems with it. But it was only after it got into the market that there was sufficient exposure to enough patients to start to show cardio-vascular side effects. There was a huge expense for the company and now as well there are class actions against the company by patients who suffered adverse effects.

That incident begs the question, is that a product-isolated event or is it a class event across a whole range of products? We're working through that question but often data doesn't come from the clinical trials on very select groups of patients, it only appears following exposure to the whole population. The real challenge is how can we identify problems early enough and how we can collect robust information that allows us to make a decision. Partly it is a matter of building up the skills and information systems that can detect these trends at a very early stage.

As you can see, the world of therapeutic goods regulation is becoming increasingly complex and interesting. I am confident the TGA will meet the challenges and fulfill its public protection role.

Thank you.