greater proportion of those molecules to pass through regulated preclinical development. Efficacy pharmacogenetics will add focus to clinical development that will make it faster and less expensive. Safety (adverse event) pharmacogenetics will facilitate prescribing products for the right patients in whom the drugs will have a favorable benefit-to-risk ratio. It might also enable products to stay on the market by improving their safety profile in post-approval use[7]. The genes and the SNP map are now available. The race to apply these genetic dictionaries to write the poetry of life begins now. Start your engines.

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# Is there a future for GMO medicines in New Zealand?

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In June 2000, a recall of a cholera vaccine was initiated in New Zealand. However, this was not an issue of the safety or effectiveness of the vaccine, but a lack of review of the potential environmental risks. Because the vaccine contained a genetically modified live organism, recent legislation requires approval by an environmental risk management agency. Rather than being just a scientific issue, political grandstanding has created an atmosphere that could hamper the future introduction of genetically modified medicines in New Zealand.

The product recalled is Orochol® Berna, a live, single-dose, oral vaccine for active immunization against cholera (see Box 1). It contains a genetically modified organism (GMO), strain *Vibrio cholerae* CVD I03-HgR, is manufactured by Swiss Serum and Vaccine Institute (Berne, Switzerland) and is registered in several countries. An application was made to the Ministry of Health (MoH) for approval of the product in April 1998. Approval was granted on 2 March 2000. However, the product has been supplied to the New Zealand market since June 1998 under legal exemption. During this period, about 1400 people have used the vaccine.

To fully understand the background to the situation, it is necessary to appreciate the political environment in New Zealand.

## Political background

Currently, there is a centre–left Labour coalition government, which was elected in November 1999. This coalition includes the left-wing Alliance party and the Green party. In order for the government to progress legislation, it requires the support of both the Alliance and the Greens. This support comes at a price, with the Greens (who have been a very strong anti-genetic engineering lobby) being in a position to advance its own agenda. The culmination of this pressure was agreement that the Government would initiate a Royal Commission on Genetic Modification. This Commission was also accompanied by a voluntary moratorium that effectively halted applications made under the Hazardous Substances and New Organisms Act 1996 (HSNO) for field testing, import or release of GMOs until after 31 August 2001.

It was provisions of the HSNO Act that resulted in the recall of Orochol Berna. Although drafted in 1996, the Act did not take effect until 28 July 1998, after the filing of the new medicine application with the MoH, and after the product had already been imported and distributed in New Zealand. To add further confusion, only parts of the Act specific to new organisms came into effect at this time, and the sections relating to hazardous substances are still not in effect. It must be said that the Environmental Risk Management


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Authority (ERMA), the body that administers the HSNO Act, has had some difficulty communicating its regulatory requirements to the scientific community. This has been evidenced by continued revelations of experiments involving genetic modifications being conducted within research establishments. Furthermore, the MoH consented to the distribution of Orochol Berna without noting the requirement for further approval under the HSNO Act.

Prior to the recall of Orochol Berna, there were frank and meaningful discussions between the importer of the medicine, the MoH, the Ministry of the Environment (MoE) and ERMA on how the recall should be progressed and of publicity arrangements. The recall decision was to be made by the Minister of the Environment and the Minister of Health following approval by the Cabinet. Unfortunately, even the best-made plans come to grief, and news of the recall was leaked to the Greens who issued an emotive and inflammatory press release entitled *First release of GE organism an outrage*. In this release, the Greens suggested that the engineered bacteria could survive passing through the body, and live for some time in the environment, and might even then mutate. One wonders whether the Greens were actually serious in their concerns or whether such an event enabled them to take the moral high ground and hold the media spotlight.

The early release of the Greens' press statement overshadowed the later release of statements by the Ministers of Health and of the Environment and by the importer. Furthermore, it achieved number one billing on the evening television news programmes. The Ministers took a far more pragmatic approach to the situation, having to act on breach of the HSNO Act by ensuring withdrawal of the product, yet maintaining supply of the medicine for those in need, particularly as Orochol Berna is the only effective cholera vaccine available in New Zealand. This was achieved by the MoH establishing criteria for what was termed 'emergency use' for people who require cholera vaccination. Under these provisions, the clinician is responsible for ensuring that the vaccine is only used in the following instances:

- In cholera endemic areas by civilian or defence force personnel involved in humanitarian, military or peace keeping activities.
- In areas where the WHO or CDC have declared that a cholera epidemic is present, by civilian or defence force personnel involved in humanitarian, military or peace keeping activities, and by travellers who will be resident in the epidemic area for prolonged periods of time.

### Box 1. What is Orochol Berna and how does it work?

Orochol Berna is a vaccine for oral administration against cholera. The principal active ingredient is attenuated *V. cholerae* bacterin (strain *V. cholerae* CVD 103-HgR). In this non-toxic vaccine strain, the gene for the biologically active A subunit of the toxin has been removed by recombinant DNA technology.

In addition, the insertion of a mercury-resistance marker into the *hlyA* gene appears to have diminished the ability of CVD 103-HgR to colonize the gastrointestinal tract. This means the vaccine organism secretes only the non-toxic B subunit that possesses all the immunogenic characteristics. Therefore, the vaccine strain can elicit a local intestinal and humoral immune response against both the vibrio and the cholera toxins.

## What really are the environmental risks of Orochol Berna?

The manufacturers state that *V. cholerae* CVD 103-HgR is a genetically well-characterized and stable attenuated strain designed as a live vaccine. From the available data, it can be concluded that CVD 103-HgR is safe for ingestion by humans as well as by animals, plants and protozoa. The spread and survival of the organism in the environment and exposure to humans is very low and is of no risk because of the non-pathogenic characteristics of CVD 103-HgR. The strain does not appear to be susceptible to, or to generate, further genetic modifications other than the one that could be expected from naturally occurring non-toxigenic *V. cholerae* strains. Such events are estimated to be extremely rare and would not lead to the creation of new organisms with unexpected characteristics.

The Swiss Serum and Vaccine Institute has examined the environmental risks of Orochol in some detail. After ingestion, it found that 20–30% of the vaccinees shed an average of $7\times10^4$ Orochol cells in their faeces distributed over a maximum period of 7 days, peak excretion of approximately $2\times10^2$ cells being on the third day. As about 1400 people have received the vaccine in New Zealand to-date, the total quantity of Orochol cells that have been released since 1998 is ~$1\times10^8$ Orochol cells. This number represents less than five colonies of Orochol growing in a Petri dish; in other words, the total quantity excreted is extremely small. Furthermore, once in the environment, Orochol is no longer culturable after 14 days and the cells cannot survive in the way their wild-type *V. cholerae* counterparts can. It has also been shown that Orochol is very stable genotypically and has no transfer system that would enable it to spread its genes in the environment. Similarly, *in vitro* and *in vivo* experiments have shown that it will not readily pick up genes from the environment. Altogether, and considering that usually the shed Orochol cells end up in sub-optimal ecological environments for its growth, it can be considered that the potential risk of a hazard occurring is 'effectively zero'.

The environmental impact of Orochol Berna was addressed in the new medicine application submitted to the MoH in

New Zealand and to overseas regulatory authorities. Authorities in Holland, Germany and Switzerland have certified that the product complies with environmental regulations and poses no special risks for man and the environment.

**So, what of the future?**

The only option for the importer to re-enter the market before the end of the moratorium was to apply to the MoE for an exemption from the moratorium so an application can be made under the HSNO Act. Procedures for applications for exemptions from the moratorium made in accordance with the HSNO Act for field-testing of GMOs have been published. However, there have been no such provisions for exemptions for release of GMOs, as would be necessary in the case of Orochol Berna.

On 9 July 2000, an application was made to the Minister for the Environment for such an exemption. Not surprisingly, the application was declined on the basis that a GMO release would divert attention from, undermine and pre-empt the Royal Commission. If, however, exemption from the moratorium was granted, an application could be lodged under the HSNO Act, which brings further difficulties. The process for approval of release of GMOs involves public consultation whereby the application is advertised and the public is invited to make written or oral submissions. There is also a special requirement for consultation with the indigenous Maori communities. As New Zealand Government departments operate a user-pays philosophy, the costs of the process are charged to the applicant, including the public consultation. We have received estimates from reliable sources that, for an application such as for Orochol Berna, the charges could be NZ$50,000–350,000 (US$22,500–157,500). Clearly, the importer and the manufacturers of Orochol Berna [who have already paid NZ$15,300 (US$6,900) in MoH fees] will not be enamoured with paying these sums for a low-sales niche medicine. This begs the question of what is the future for medicines that contain GMOs.

With ongoing advances in scientific research, we are surely going to increasingly see similar situations. In the short term, the moratorium should ensure that there will be no new such medicines introduced in New Zealand. In the longer term, will companies bother to register them in New Zealand when faced with huge compliance costs for a small market financial return? The crunch will come when the medicine is a life-saving vaccine for AIDS or cancer. Perhaps then we will see an effective pro-medicine lobby become active in New Zealand.

## What do you think the impact of the human genome sequence will be on drug discovery?

Have you had any experiences of data-mining the draft sequence, successful or otherwise?

Do you have comparable experiences of data-mining genome sequences from other species?

Please send your comments to Dr Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@current-trends.com

Publication of letters is subject to editorial discretion.

## What does the human genome sequence mean to you?

For a thorough and independent analysis of the meaning and importance of the February publications of the draft human genome sequences, visit http://news.bmn.com/hmsbeagle/96/notes/feature3.

To mark the importance of the event, we are pre-publishing all the articles for *Drug Discovery Today* and the *Trends* journals on these publications in our free, online magazine, *HMS Beagle*. You cannot afford to miss these up-to-the-minute commentaries, opinions and updates, written by leading players from across the whole of biology. And they're free!


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