

DATE 15 APRIL 2010

BEFORE THE HEALTH SELECT COMMITTEE:

**RE: IMPROVING NEW ZEALAND'S ENVIRONMENT TO SUPPORT INNOVATION
THROUGH CLINICAL TRIALS**

SUBMISSIONS OF NEW ZEALAND BIOTECH 2003 INCORPORATED

1. Wish to be heard

- 1.1. Bronwyn Dilley the Chief Executive of NZBIO wishes to speak to our submission. She would wish to be accompanied by Dr Doug Wilson and up to two other members of NZBIO to provide expert opinions from industry.

2. About New Zealand Biotech 2003 Incorporated (NZBIO)

- 2.1. This submission is made by NZBIO on behalf of our members. In preparing this submission NZBIO has consulted its members. NZBIO is New Zealand's National Industry Association for bio-based industries. NZBIO receives some supportive funding through the Ministry of Economic Development (administered by New Zealand Trade and Enterprise) to assist its development into a sustainable industry association.
- 2.2. NZBIO has three hundred members that include individuals, micro-companies (bio-based companies and service providers with less than 10 staff), government agencies, large international companies and New Zealand based small and medium sized enterprises (SMEs). Members' commercial interests span the entirety of the bio-based business spectrum, from agricultural biotechnology, environmental and energy, food and nutraceuticals and human health - including the development of human therapeutics, medical devices and diagnostics and the running of clinical trials.
- 2.3. A main objective of NZBIO is to assist the economic expansion of the bioeconomy sector by working with its members, the Government, and domestic and international partners to realise opportunities and remove barriers to growth. A key goal of NZBIO is to represent member views to Government to assist in the development of policy that is internationally competitive and encourages private investment, commercialisation of innovation and sector growth.

Questions regarding this submission should be directed to:

Bronwyn Dilley, Chief Executive Officer

NZBIO

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- 2.4. Bronwyn Dilley was appointed Chief Executive of NZBIO in March 2008. She has over 10 years experience in strategic marketing and management for start-ups and developing SMEs across a broad range of industries, and has spent the past five years working in the Australian biotech sector. Previous roles include senior Marketing and Business Development positions at Neurosciences Victoria, the National Neuroscience Facility and Grey Innovation in Melbourne.
- 2.5. Dr Doug Wilson has an experience in clinical trials that is matched by few, if any, other New Zealanders. He has been involved in hundreds of clinical trials in many different

geographies. As Senior Vice President for Medicine and Regulatory Affairs for Boehringer Ingelheim in the USA, Doug oversaw multiple drug development projects from conception to successful registration. He was responsible for all interactions with the FDA. He participated or headed teams registering over 10 New Drug Applications (NDA) in the USA and multiple others in Europe and elsewhere. Doug became Head of worldwide medicine and regulatory affairs for Boehringer Ingelheim, based at the head office in Germany, and chaired or co-chaired the International Committees for Clinical drug development, and for drug labeling. Doug is experienced in projects for cancer, HIV, anti-virals, respiratory drugs, hypertension, urology, central nervous system (CNS), stroke, many cardiac drugs and others.

3. NZBIO supports the general comments made by the Health Committee

- 3.1. NZBIO congratulates the Health Committee on recognising the need for an inquiry into improving the environment for clinical trials in New Zealand.
- 3.2. The Health Committee has stated that Phase 1-IV trials are worth \$450 million per year in Australia but only \$12 million to \$30 million in New Zealand.
- 3.3. NZBIO believes that the benefits to New Zealand are more broad than the economic contribution through service revenue from trials:
 - 3.3.1. A profound benefit is through improvements to the healthcare system. The Committee is referred to a summary of benefits by Dr Joshua Funder, published in the NZBIO Journal BIOACTIVE, October 2009, pp30-31, key points are repeated below:
 - 3.3.2. Each patient on a clinical trial receives the best standards of care in addition to getting access to potentially improved new medicines.
 - 3.3.3. In undertaking clinical research, doctors, research nurses and many other health professionals are trained in better diagnosis and new treatment modalities, as well as improved patient management, monitoring and measurement of clinical outcomes. Involvement in clinical trials enables physicians and nurses to stay up to date on the rapidly changing world of medicine.
 - 3.3.4. The next patient treated by carers with research experience will get higher quality health care whether or not they are on a clinical trial.
 - 3.3.5. Linking our clinical trials with medical research is also a great benefit in improving the outcomes of our research, shaping the directions of biomedical research and providing a clear path for future technologies to further improve our health.
 - 3.3.6. The alternative is grim; without clinical research on new therapies, medical practice slips to second rate and there is nowhere for local biomedical research to go.
 - 3.3.7. Currently, most DHBs and hospitals discourage involvement in clinical trials as secondary to clinician's employment. Consequently, there is a migration of

some physicians from New Zealand to nations where they are able to conduct clinical research as well as attend to their duties to patients as part of their daily lives.

3.3.8. Clinical research capabilities are also important to support New Zealand's large food industry. A growing number of products in New Zealand's global food and ingredients markets carry health claims to promote sales. The global trend is to tighten the regulation of health claims so that the ability to make a claim is dependent on clinical-type trials to prove the benefit.

3.3.9. Clinical trials conducted in New Zealand support other local industries, including the following:

3.3.9.1. Biopharmaceuticals

3.3.9.2. Pharmaceuticals

3.3.9.3. Medical devices

3.3.9.4. Health IT

3.3.9.5. Bioactives (including nutraceuticals, supplements and functional foods)

3.4. NZBIO believes that New Zealand has many of the elements required for an ideal clinical trials location, including the following:

3.4.1. excellent standard of health and care.

3.4.2. ability to rapidly and efficiently recruit study subjects.

3.4.3. superior health IT systems for data collection.

3.4.4. world renowned lead investigators and key opinion leaders in significant areas of medical research and clinical practice.

3.4.5. a population largely unexposed to certain medicines, making it attractive for Stage III trials of products for diseases such as Cystic Fibrosis.

4. Terms of reference

4.1. NZBIO supports the general terms of reference published by the Health Committee as follows:

4.1.1. a coordinated, nationwide approach to clinical trials and performance measures.

4.1.2. streamlined ethics approvals systems.

4.1.3. national patient referral networks, and better ways to approve establish and conduct clinical trials.

4.1.4. removal of unnecessary barriers.

4.1.5. benefit to New Zealand patients through clinical trials, as well as the New Zealand innovation system, health system, and economy.

4.1.6. ***NZBIO recommends that "Establish a national priority for clinical trials" is added to the Terms of Reference***

5. **The principal recommendation from NZBIO is for *New Zealand to develop a notification system for regulating clinical trials*. The current CTN/CTX system used by Australia provides a good competitive model.**

NZBIO offers to help convene a workshop of users to develop recommendations for the details of a scheme.

NZBIO members believe a CTN/CTX system would benefit the economy, the investigators, the patients, the standard of New Zealand medicine, the morale of New Zealand medicine, and the ability to attract and retain doctors with research interest and abilities. The rationale for this recommendation is presented below:

5.1. Australia is recognized as having the most internationally competitive clinical trials environment.

5.1.1. Australia uses a Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) Scheme. Australia is ranked by the Economist Intelligence Unit as the best location for conducting clinical trials, compared to the USA, UK, Germany, Japan, Singapore and India.

5.1.2. Prior to 1991, every study in Australia had to be approved by the Therapeutic Goods Administration (TGA) through a slow Investigational New Drug (IND, USA) type approval path, even though almost all drugs had previously had an EU or US regulatory review. This system caused major delays so companies did few trials in Australia.

5.1.3. In May 1991, Australia introduced the CTN system, alongside the CTX scheme. The CTN scheme allowed for clinical trials of unapproved products without the need for regulatory review by the TGA. The CTN system requires three decisions for trials to proceed: 1) the investigator approves, 2) the investigator's host institution approves, 3) the local Human Research Ethics Committee (HREC) approves. There are general guidelines for these groups to follow. Trials can begin as soon as the TGA is notified and the TGA does not play any part in the approval process. Therefore, approvals can be obtained very quickly. It is realistic to obtain HREC approval within 30 days, then lodge a notification (CTN) to the TGA, and immediately begin the trial. This change has enabled Australia to build its clinical trial industry very rapidly, and increasingly big companies are trialing drugs there. The overall benefit to the medical research community is huge, and for those clinicians keen to advance their academic careers these trials are perfect drivers into the international world of research. Australia does require certain drug classes to follow the CTX system, which requires a TGA review first. However, the great majority of drugs likely to be under trial in New Zealand would be outside these more limited classes and fall under CTN.

5.2. The system in the USA is expensive and burdensome, but has some desirable attributes.

- 5.2.1. In the USA, an IND application approval is required from the FDA before a drug can be trialed in the USA, even if it has been tested elsewhere. This can be preceded by a pre-IND meeting, where advice is given on the submission. This advice is often very useful when a study is complex because the FDA sets the rules by which they will assess the study once complete. This meeting is very interactive and there can be an ongoing informative dialogue.
- 5.2.2. The FDA is currently very busy and understaffed so for many drugs there is no pre-IND meeting. Therefore, the sponsor has to prepare the IND before learning that their drug can or cannot proceed. Preparation of the IND is usually a massive project, taking many months to assemble, requiring many hundreds of pages of documentation, requiring detailed reviews by US based experts and then filing by a US agent. The FDA is required to identify any safety issues within a 30-day period after which, if the FDA does not raise concerns, the study can proceed. The study also has to have the approval of the investigator before the IND is filed and then goes to the ethics committee - as is the case for all other countries, and the host institutions and their lawyers.
- 5.2.3. While the 30-day IND approval timeframe might sound like a quick approval process, the reality is different. There are often delays so it takes up to 18 months before a new drug or even an old drug can progress to final approval. It can also be expensive. Just to get to a Phase I trial, the toxicology study in the USA can cost US\$1.5 million, and there are many other costs on top of this. Sponsors use the USA because their drugs have been approved in the USA to be a commercial success. The USA also has the experts and the facilities needed for many complex studies. Therefore, companies accept the high cost and delays as part of the life cycle of their drugs.
- 5.3. Many countries in the EU, such as Sweden, Netherlands, France, have FDA style pre-IND-type meetings.
 - 5.3.1. When the studies are complicated, these meetings are valuable because they are interactive and can provide useful information.
- 5.4. The current New Zealand system is too complicated and slow.
 - 5.4.1. In New Zealand, the process has many layers, which limits our ability to participate in the international R&D world. New Zealand's approach is unnecessarily over-cautious. All countries conduct studies under Good Clinical Practice (GCP) and follow the rules of the ICH, International Committee on Harmonization. Any trial that does not follow ICH/GCP rules will compromise an entire project. Therefore, the sponsors are highly motivated to ensure that trials are done right and comply with ICH/GCP guidelines.
 - 5.4.2. New Zealand has too few skilled people and too few resources to support a full-blown internationally competitive system for conducting clinical trials. Further, there is no inherent need for every a country to have its own system. Europe, for

example, has a central review body, EMEA, that represents 26 countries and over 500 million people.

5.4.3. Under the current New Zealand system, the clinical trial protocol has to have the approval of the investigator, the investigator's host institution, SCOTT (or GTAC), the Maori review, and finally the ethics committees.

5.4.4. The experience of NZBIO members is that the SCOTT review can cause delays that outweigh the potential value of the review.

5.4.5. NZBIO acknowledges that Maori should have input into the approval process to represent Maori cultural issues. However, NZBIO is aware that this input is a) extending the time for approval and b) increasing the financial cost to the applicants. NZBIO requests that the manner and criteria for Maori input be reconfigured in order to ensure that it does not become a financial or time burden on either applicants or the Maori required to be involved. This input should be on Maori cultural issues only. The process could be streamlined by incorporating Maori input as part of the ethics review process. The ethics committees could include members with a clear mandate to provide representation on Maori cultural issues.

5.4.5.1. NZBIO recommends that the manner and criteria for Maori input be reconfigured in order to ensure that it does not become a financial or time burden on either applicants or the Maori required to be involved. For example, the process might be streamlined by include members on the ethics committees with a clear mandate to provide the Maori review

5.4.6. Trial approval by local ethics committees is common practice internationally and would still be required if New Zealand adopted a scheme similar to the TGA CTX/CTN scheme. Some, but not all, committees can suffer a shortage of relevant skills.

5.5. The multi-region ethics committee is highly valued by NZBIO members and is considered a real strength of the current New Zealand system.

5.5.1. NZBIO recommends that the multi-region ethics committee mechanism be retained as part of any future scheme.

Additional changes.

6. NZBIO believes that greatest beneficial impact to the New Zealand environment for clinical trials would be achieved through the CTN/CTX system outlined above. However, in the interim other improvements could be made to improve the operation of the current system, as discussed below:

6.1. A major impediment to smooth and rapid clinical trial approvals is the inability to have meaningful dialogue with the SCOTT Committee (or potentially GTAC):

- 6.1.1. NZBIO members find that it is not possible to have meaningful dialogue with the SCOTT or GTAC either before an application is submitted or after an application is considered. Therefore, sponsors are unable to address concerns that may arise, and thereby design better studies with better outcomes and less risk of the study being declined. Sponsors are also unable to clarify for understanding issues that SCOTT (or GTAC) raise through their review.
- 6.1.2. It is unrealistic to expect applications to be fit for unqualified approval without any prior consultation with SCOTT. This fact is recognized by other countries, where dialogue is encouraged and expected.
- 6.1.3. NZBIO members have lost several millions of dollars of clinical trials revenue to Australian providers because effective dialogue between sponsors and MEDSAFE has not been possible.
- 6.1.4. **NZBIO recommends that operating guidelines to MEDSAFE, SCOTT and GTAC expressly encourage meetings with sponsors before an application is submitted and after it has been reviewed.** The FDA pre-IND consultation process is an example that New Zealand might draw from in developing operating guidelines
- 6.2. The terms of reference for appointments to SCOTT should be tightened to ensure no perception of conflict of interest is possible:
 - 6.2.1. NZBIO recommends that SCOTT members should not work for, consult to, or have a financial interest in clinical research organizations or companies that use clinical trials where the interest is in a competing outcome area, geography, or stage of trial.
 - 6.2.2. **NZBIO recommends that Rules for defined terms of service on the committees, without rollover, should be defined and enforced.**
- 6.3. New Zealand has a very small pool of suitably experienced reviewers.
 - 6.3.1. **NZBIO recommends that overseas experts should be considered to expand the talent pool for SCOTT.**
- 6.4. Decision times need to be shortened. New Zealand could gain a significant competitive advantage by requiring binding review decisions be delivered within a shorter time frame.
 - 6.4.1. **NZBIO recommends that New Zealand allow no more than 30 Calendar days for an application to be declined.**
- 6.5. NZBIO recommends that a special process be implemented for clinical-type trials on foods that do not require the costly toxicity studies required for new medicines.
 - 6.5.1. Much of the regulatory requirements involve toxicity. This is true for both Australia and New Zealand.
 - 6.5.2. Foods that are based on ingredients with a long history of safe use should not be required to have extensive toxicity studies.

6.5.3. Functional foods and nutraceuticals have lower profit margins than therapeutics and cannot bear the high cost of extensive toxicity studies as part of their regulatory requirements.

6.5.4. ***NZBIO recommends that the process for trials involving functional foods be separated from the therapeutic clinical trials process and simplified to remove non-relevant requirements such as toxicology studies on foods with a long history of safe consumption.***

7. NZBIO is aware that Jim Mervis and the other individuals who comprise the Health Strategic Initiatives Review Committee have submitted a number of recommendations. Below is a list of their recommendations that NZBIO members support:

7.1. Improve New Zealand's Competitive Advantage for Clinical Trials.

7.1.1. Include clinical research incentives and outcomes in hospital performance measurements, to ensure that a portion of budget, time and facilities are spent on staff development and clinical research, allowing the hospitals to choose how best to do this and in what therapeutic areas to specialize.

7.1.2. Uncouple the link between Pharmac's remit and clinical research, by providing other incentives to encourage clinical research to be conducted in NZ.

7.1.3. Remove "NZ-only" criteria from international trials, and apply only best-practice international standards e.g. International Conference on Harmonisation – Good Clinical Practice (ICH-GCP).

7.1.4. Establish a dedicated national Ethics Committee (EC) for commercial trials which can be sent the applications electronically and respond more quickly, e.g. within a week, and charge a fee for this.

7.1.5. Support implementation of a single indemnity contract template and/or checklist agreed with insurance companies for NZ, as a source of competitive advantage.

7.1.6. Provide incentives for a laboratory to be established in New Zealand to process and store tissue samples, meaning fewer risks with having to transport samples, development of local expertise and business, and obviating cultural issues that are making it difficult to participate in an increasing number of trials.

7.1.7. Maintain NZ's advantages in areas that matter for trials, which are quality data, quick reliable applications (scientific, ethics, indemnity) and patient recruitment by conducting clinical research to international best-practice, having a streamlined application process, and keeping accurate data on patient populations.

7.1.8. Provide access to population data to ascertain the prevalence of medical conditions for clinical research purposes; if being understood that such data shall not identify individual patients.

7.2. Support Clinical Research Education.

- 7.2.1. Train universities and private companies in the clinical research industry, in each other's skills and requirements for the research and development lifecycle, and establish forums for them to work together.
- 7.2.2. Organise workshops for hospitals, e.g. a roadshow, to train staff in best-practice clinical trials – managers, investigators, research nurses, lawyers (indemnity) – and to answer concerns and highlight the benefits to sites, patients, access to health information and technologies, expertise and careers.
- 7.2.3. Organise training on funding sources (commercial and non-commercial), how to apply, business skills, and regulatory and ethics applications, for clinical research sites and new investigators.
- 7.2.4. Organise regular training on clinical research for Ethics Committees, to keep them up-to-date with developments that affect their deliberations in assessing clinical studies.
- 7.2.5. Promote forums and publications for clinical researchers in New Zealand to exchange information, such as MedSci, MTANZ, NPNZ, NZBIO, New Zealand Association of Clinical Research (NZACRes), and others.
- 7.2.6. Work with the New Zealand Immigration Service (NZIS) to add clinical research occupations to skill shortages lists and work with bodies e.g. Kiwi Expats Abroad (KEA) to locate and encourage New Zealanders with such skills to return from overseas.
- 7.2.7. Pool the demand for training and bring overseas trainers to New Zealand to offer training for study co-coordinators, clinical research associates, investigators and other research staff.
- 7.2.8. Commission an economic study of the costs and benefits of clinical trials against healthcare delivery.

7.3. Promote Domestic Innovation for further Competitive Advantage.

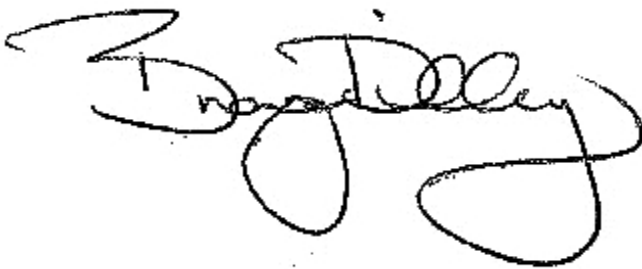
- 7.3.1. Support Information Technology (IT) developments, already a strength in New Zealand, to facilitate clinical trial data management and bioinformatics, through targeted funding for Health IT firms.
- 7.3.2. Support Key Opinion Leaders (KOL's) in the development and promotion of their research facilities, staff and expertise.
- 7.3.3. Create a more attractive environment for pharmaceutical companies to scale up in New Zealand and forge links with hospitals and medical schools, to provide a sustainable environment in which clusters once established, continue to thrive.
- 7.3.4. Provide effective financial incentives to attract and develop clinical research and related industries, e.g. laboratories, in NZ, whether that be R&D or other tax breaks, paying a subsidy for drugs, bioactives, medical devices and IT reflecting

the amount invested into New Zealand by companies for clinical research and/or requiring investment for products to be eligible for subsidy.

7.4. Promote New Zealand Competitive Advantage Internationally.

- 7.4.1. Encourage and assist New Zealand research staff to belong to and attend international events, especially as a group in order to make more impact.
- 7.4.2. Develop international interest in New Zealand biotechnology through attracting international companies to New Zealand and promoting New Zealand companies offshore through tradeshows and other means.
- 7.4.3. Develop and promote Key Opinion Leaders (KOL's), including attracting New Zealanders back and others from overseas, to build niche areas of expertise.
- 7.4.4. Attract international companies to provide the environment, training and career opportunities, to allow clinical research and the associated skills to grow and develop in New Zealand.

Dated in Wellington this 15th day of April 2010

A handwritten signature in black ink, appearing to read 'Bronwyn Dilley'. The signature is stylized with large loops and a prominent initial 'B'.

Bronwyn Dilley

Chief Executive New Zealand Biotech 2003 Incorporated