

**STARGATE INTERNATIONAL**  
**SUBMISSION TO THE NEW ZEALAND LAW COMMISSION**

**"Controlling and Regulating Drugs"**

**30 April 2010**

**PART A: INTRODUCTION AND SUMMARY**

1. This is Stargate International's ("**Stargate**") response to the New Zealand Law Commission's ("**Commission**") Issues Paper on controlling and regulating drugs ("**Issues Paper**").
2. The Commission has invited submissions from the industry and the public on the issues raised in its Issues Paper and Stargate is grateful to the Commission for the opportunity to participate in the consultation process and to contribute to the development of an appropriate regulatory regime for control of drugs. Stargate welcomes the Commission's balanced and sensible approach to the manufacture, sale and supply of recreational psychoactive substances in New Zealand.
3. Stargate's contact for matters regarding this submission is:

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**About Stargate**

4. Stargate is a private organisation dedicated to minimising the harms associated with drug use across the community. Stargate's key functions include:
  - (a) The development and bringing to market of safer, legal alternatives to addictive and dangerous drugs;
  - (b) The development and introduction of nutritional biochemistry solutions for existing or recovering alcohol and drug users;
  - (c) Advocating more effective, evidence-based drug policy through the political process;
  - (d) Representing the interests and issues of those communities most effected by drug use to government and the public;
  - (e) Developing and providing innovative drug education programmes; and
  - (f) The development of 'on the ground' harm minimisation strategies to provide physical help for people experiencing drug related difficulties.

5. Stargate's commitments to harm minimisation are aligned with the New Zealand Government's National Drug Policy,<sup>1</sup> and are in line with the latest international standards and research in this area.
6. Stargate's work in harm minimisation complies with protocols recommended by the United Nations and the World Health Organization. Stargate also makes itself available to work with health and treatment agencies worldwide to implement advanced drug harm minimisation techniques.
7. Matt Bowden, the founder of Stargate, has been a consistent advocate for harm minimisation approaches to drug regulation since BZP was introduced into the New Zealand market in the early 2000's.

### **The Commission's general policy approach**

8. The Commission's review of drug regulation is carried out against the backdrop of the Government's National Drug Policy 2007-2012, which is based on the principle of harm minimisation. The Commission endorses this principle, and Stargate entirely supports harm minimisation as a key objective for drug regulation.
9. Stargate has reviewed the proposals in the Commission's Issues Paper, and is particularly interested in engaging with the Commission on its proposals for the regulation of the manufacture, sale and supply of recreational psychoactive substances (eg non-convention substances). While Stargate largely supports the Commission's treatment of the issues, Stargate wishes to emphasise that for a new regulatory framework to achieve the greatest degree of harm minimisation, there needs to be greater recognition that the availability of low risk products in a controlled and regulated environment can assist to deter people from abusing illicit "black market" substances that cause significant disruption and harm to the community.

### **Restricted substances**

10. Stargate's submission focuses on regulation of restricted substances (eg drugs that are not prohibited). Stargate proposes that any substance which is intended to be administered to humans for a purpose which is not a therapeutic purpose (ie not a medicine), but nevertheless produces a specific pharmacological action or effect in the body,<sup>2</sup> should fall into a separate class of substances (non-medical pharmaceutical products).
11. This would encompass "restricted substances" (ie legal recreational substances) but the scope would potentially have to be broader than this, as it may also potentially include non-recreational "lifestyle" drugs such as nootropics (ie study drugs), aphrodisiacs, some cosmetics (eg tanning drugs like melanotan II), and the wide and growing range of substances used in athletics and bodybuilding to increase bulk, endurance, oxygen capacity and so on. At present, the trend is to classify such compounds as medicines, but this seems incongruent given that they are not being used to treat any recognised medical condition, with the medicines classification effectively being used to ban them rather than regulate their use.
12. The test for a compound to be placed into this non-medical pharmaceutical products class would be simple. If the compound:
  - (a) does not fall within any other class (eg is not a medicine, illicit drug etc);

<sup>1</sup> Ministry of Health, *National Drug Policy 2007-2012*, 2007.

<sup>2</sup> This can be phrased very broadly, cf Medicines Act 1981, section 4(f).

- (b) is intended for human consumption via any route (but excluding topical products that are not significantly absorbed through the skin); and
- (c) has a pharmacological effect in the body;

the substance would be defined as a non-medical pharmaceutical product or restricted substance.

13. As the Commission notes (at paragraphs 5.74 and 5.109 to 5.112), difficulties in classification might arise at the borderline, particularly with substances such as herbal remedies and dietary supplements, as these products already avoid making any therapeutic claims to avoid being classified as medicines, yet are nevertheless implied to have some beneficial effect in the body. However an effective restricted substances regime could help to ensure that such substances are regulated under the appropriate regime, rather than being forced into an ill-suited regime (as sometimes occurs now).
14. In response to question 12, we think that it is more important to get the relevant definitions right for the various regimes, rather than introduce formal coordination processes between the regulatory bodies responsible for foods, medicines, hazardous substances and restricted substances.

#### **Overview of our submission**

15. Stargate supports the following proposals regarding the regulation of recreational psychoactive substances:
  - (a) The regulatory regime for new recreational psychoactive substances should follow the approach that is currently adopted under the Hazardous Substances and New Organisms Act 1996 ("**HSNOA**"). That is (in response to question 2 and 3), no recreational psychoactive substances can be imported or manufactured until positive approval has been given by the relevant regulatory authority. This model is consistent with Stargate's preference for a controlled supply environment;
  - (b) The reasonable criteria for approval suggested by the Commission, which appear to mirror the criteria in the existing legislation;
  - (c) Having a separate regulatory regime for recreational psychoactive substances and hazardous substances, rather than both substances being regulated under the hazardous substances regime. Stargate strongly agrees with the Commission's conclusion that the current criteria under the HSNOA are not appropriate to apply to recreational psychoactive substances; and
  - (d) The conditions and restrictions that the Commission considers should be attached to any approval, on the basis that these measures are consistent with Stargate's objective of ensuring a controlled environment for the manufacture and supply of psychoactive substances.
16. In summary, and in response to question 1, we strongly endorse the general approach adopted by the Commission, which proposes a regulatory model where the import and manufacture of non-convention drugs are subject to conditions and restrictions, and prohibition is available as a last resort only. Specifically, Stargate supports Commission's view that "regulation of drug use is only justified to the extent necessary

to prevent harm to others, and even then, the benefits arising from the reduction in harm must outweigh the costs arising from regulation itself".<sup>3</sup>

17. Stargate would, however, like to bring to the attention of the Commission a few important issues that require further consideration. This submission therefore elaborates on Stargate's recommendations that:
- (a) As part of the approval process, there be a statutory presumption that new recreational psychoactive substances will be classified as restricted substances unless, following the application of the relevant statutory criteria, the relevant regulatory authority can demonstrate that such a classification is not appropriate (and that substance a should instead be prohibited);
  - (b) The relevant statutory test must include sufficient constraints to promote objective decision-making, such as a requirement that the relevant regulatory authority deny approval only on "reasonable grounds". This would require all approval decisions to be made on evidenced-based assessments; and
  - (c) The regulatory authority that is charged with classifying new substances place particular weight on the possible displacement effects of not approving recreational psychoactive substances.

## **PART B: COMMENTS ON THE COMMISSION'S PROPOSALS**

### **Requirement for approval**

18. The default status for compounds which are not considered to be medicines, hazardous substances, illicit drugs, foods or dietary supplements is at present best described as "undefined". This creates a loophole that has allowed a thriving industry to develop, based around party pills and other legal recreational drug products. Some benefits have undoubtedly resulted from this, notably the reduction in harm that has been possible thanks to users being able to have the choice to substitute safer legal alternatives for harmful prohibited drugs.
19. Stargate's concern is that in recent years, it has increasingly seen the unregulated market become dominated by profiteers with little concern for public welfare. Consequences of this are that:
- (a) relatively safe substances have been sold but have been consumed at unsafe dosages;
  - (b) substances that would ordinarily require precautionary labels are sold without such warnings; and
  - (c) substances that would not otherwise have been approved for public sale had they been required to undergo safety and toxicity testing prior to marketing and distribution have become more available.
20. Stargate acknowledges that this situation cannot continue indefinitely and therefore (in response to questions 2 and 3) endorses the Commission's proposal to adopt a regulatory framework whereby no recreational psychoactive substances can be imported and manufactured until positive approval has been given by the relevant regulatory authority. As discussed below, approval would mean the substances are

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<sup>3</sup> Issues Paper, paragraph 7.14.

subject to extensive controls to ensure they are sold in the safest possible way, with the potential for abuse minimised to the greatest extent possible.

21. An exception to requiring approval ought to apply to the limited importation, by adults, of unapproved compounds for personal use amounts (ie 10 grams or less), with requirements that personal use quantities be subject to specific storage requirements and inventory recording to ensure importation was genuinely for personal use. Any sale or distribution of these products would, however, continue to be an offence.

#### **Criteria for approval**

22. The Commission considers that the relevant criteria for the regulatory authority to consider before approving a new psychoactive substance would be as follows:
- (a) The nature of the harm caused by the substance and any benefits associated with its use;
  - (b) Whether that harm can be effectively managed by the imposition of regulatory controls;
  - (c) The likely consequences of any proposed regulatory controls or prohibiting the substances (including cost considerations); and
  - (d) Any possible displacement effects that might occur because of the way other substances are regulated.
23. The Commission confirms in its Issues Paper that the HSNO criteria are not appropriate to regulate recreational psychoactive substances, and Stargate strongly agrees with this conclusion. A specific harm-based assessment is appropriate for restricted substances.
24. Stargate's view is that the criteria proposed by the Commission for approval of restricted substances are reasonable, given that they reflect the criteria under the Misuse of Drugs Amendment Act 2005 ("**MDAA**") for classifying a substance as a "restricted substance".
25. However, Stargate is concerned that the regulator could adopt a default position of declining applications, ostensibly on the basis that it is not possible to conclusively determine the harmful effects of a substance. As the Commission has noted, assessing harm involves a high degree of value judgment. As the Commission has also recognised,<sup>4</sup> evidence of harm or otherwise in relation to recreational psychoactive substances is a vexed matter. As the positive effects of a recreational psychoactive substance are much less tangible than other regulated substances, the Commission's current proposal risks a situation where substances are declined, even where there is no evidence that a substance is harmful.

#### *Evidence-based decision-making*

26. Accordingly, Stargate submits that the onus should not be on the applicant to show that new recreational psychoactive substances are not harmful. Rather the onus should be on the Expert Advisory Committee on Drugs ("**EACD**") and the relevant regulatory authority to show that new substances are harmful, before declining an application. This would effectively mean there is a (rebuttable) presumption that a substance will be approved as a restricted substance. On the other hand, applicants should be required to provide full evidence about the substance, and there should be an ability to refuse an application if there is no evidence upon which a decision can reasonably be made. The

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<sup>4</sup> Issues Paper, paragraph 8.6.

legislation could also allow the regulatory authority to prescribe the type of evidence that must be provided with an application.

27. Stargate therefore agrees with the Commission that as part of the approval process, the importer or manufacturer of a substance should be required to provide to the regulatory body all available information about the composition of the substance and its known health effects, in order to assist in the determination of what regulatory controls are appropriate.<sup>5</sup> For its part, Stargate is happy to conduct clinical trials and provide any available evidence on the use and safety of psychoactive substances where possible.
28. Stargate believes it is essential that the relevant statutory test, which the regulatory authority must apply before deciding to approve a substance, be based on evidenced-based assessments. The power to grant approval (or not) must be sufficiently constrained to require objective decision-making to the greatest extent possible (we acknowledge the Commission's point at paragraph 9.78 that a purely objective assessment is not possible). Stargate therefore proposes that the relevant statutory test for classification should expressly state that the regulatory authority must approve a substance as restricted, unless he or she is satisfied that there are reasonable grounds not to. This requirement will also ensure that no decisions will be made without careful consideration of the appropriate evidence available. This will help address the problem, recognised by the Commission (at paragraph 9.78), that the controversial and emotive nature of drug issues can undermine good regulatory decision-making. In response to question 11, Stargate accepts that the Minister of Health is the appropriate person to issue approval under the restricted substances regime, so long as there is a sufficient constraint on his or her power.
29. The evidence to be provided with each application would vary, depending on the degree to which the substance has been used by humans.
30. Psychoactive substances that are novel to New Zealand, but have an extensive history of human use overseas with no significant problems associated with their use, would still have to be approved, but this should be a formality requiring only that the applicant can prove a history of use, and provide a detailed summary of the known toxicity, adverse effects and possible drug interactions. The relevant statutory test would allow the regulatory authority to refuse approval if the evidence produced is manifestly inadequate or if there are grounds for concern. In this case, additional tests might be required, but this should be the exception rather than the standard practice.
31. Novel substances without any significant history of human use could, however, require much more stringent safety testing as part of the approval process. The appropriate safety test could essentially be a simplified version of the pre-clinical testing carried out on new medicines prior to Phase I clinical trials, followed by limited trials on humans (see the **attached** Appendix for a brief explanation of an appropriate testing process). With recreational psychoactive substances, there should be no requirement to prove efficacy; if consumers choose to use a product for which there is no or dubious evidence for efficacy, this should be their choice. Where the role of government is important is to ensure that substances are suitably safe for public sale, and determine, where there are risks involved, if these risks are manageable, or whether the risk is so great that public sale should not be permitted at all.
32. Finally, Stargate also suggests that the expert committee that advises the Minister (currently the EACD) be required to place particular weight on the possible displacement effects of not approving recreational psychoactive substances. This approach is entirely consistent with the Government's principle of harm minimisation for drug regulation.

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<sup>5</sup> Issues Paper, paragraph 8.31.

The Commission also appears to have recognised the important role that alternative substances may play in harm minimisation, specifically noting in its Issues Paper that this criterion, although covered under the proposed "likely consequences of regulation" criterion, was "important enough to be expressly included".<sup>6</sup> Stargate also agrees with the Commission that it is important to ensure that the expert committee is independent and transparent.<sup>7</sup>

### **Separate regimes for hazardous and restricted substances**

33. In response to question 10 of the Issues Paper, Stargate strongly supports the Commission's position that a separate regime for regulating recreational psychoactive substances is appropriate.
34. However, as the Commission identified in its Issues Paper, fundamental inconsistencies between the misuse of drugs regime and the HSNOA legislation has meant that it has not possible to have separate regimes for regulating psychoactive substances and hazardous substances. The definitions of "hazardous substance" and "restricted substances" mean that all psychoactive substances fall under the definition of hazardous substances under HSNOA, and hazardous substances cannot be classified as a restricted substance under the Misuse of Drugs Act 1975 ("**MDA**"). There is therefore no way in which any substances can come within the restricted substances regime.
35. As the Commission anticipated, the Government has now introduced a bill (the Misuse of Drugs Amendment Bill) into Parliament, which purports, among other things, to remove the exclusion that a hazardous substance, as defined in the HSNOA, cannot be a restricted substance under the MDA regime. If the Bill is passed, this would mean that newly introduced (and current) recreational psychoactive substances can be regulated as restricted substances. At this point, Stargate reiterates that it will be important for the Commission to follow the Bill's progress closely to ensure that there is consistency between the Bill and the development of the regulatory framework for controlling and regulating drugs.

### **Restrictions and conditions attached to approval**

36. Stargate accepts that as part of the Commission's preferred regulatory regime for recreational psychoactive substances, once a substance is approved, this approval will be subject to certain restrictions and conditions on how the substance will be manufactured, sold, supplied and advertised.
37. The Commission is of the view that while differences between psychoactive substances may mean that different controls are required, there also needs to be some regulatory requirements that should apply to all recreational psychoactive substances if they are to be approved. For example, the Commission proposes that the following generic conditions be included in primary legislation before approval as a restricted substance is given:
  - (a) Age restriction;
  - (b) Advertising and promotional restrictions;
  - (c) Places of sale restrictions;

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<sup>6</sup> Issues Paper, paragraph 8.93.

<sup>7</sup> Issues Paper, paragraph 9.86.

- (d) Restrictions on who can supply recreational psychoactive substances; and
  - (e) Other restrictions, such as child-proof and tamper-proof containers and sufficient labelling and warnings on all products.
38. To clarify, we understand the Commission's recommendation that 18 be the statutory minimum age for the supply of any psychoactive substance to mean that this prohibits under 18 year olds from being sold or supplied psychoactive substances, but does not restrict the entry of under 18 year olds into premises where psychoactive substances are sold and where there are non-restricted products also available for sale.
39. Similarly, we understand that the Commission's support of the type of restrictions found in the Smoke-free Environments Act 1990, which would effectively prevent the advertising of psychoactive substances on the Internet, would not prevent online retailers from selling products via their retail websites. We also note that selling products directly via a retailer's own website can be done in a way to ensure the sale and supply restrictions are complied with (eg check of driver's licence and distribute to the address on that licence).
40. The Commission also proposes that the relevant regulatory authority have the power to impose additional tailored conditions as part of an approval to manufacture or import a recreational psychoactive substance, such as:
- (a) Additional place of sale restrictions;
  - (b) Labelling restrictions and requirements;
  - (c) Packaging restrictions and requirements;
  - (d) Health warning requirements;
  - (e) Signage requirements;
  - (f) Quantity, dosage, form and serving requirements;
  - (g) Storage and display restrictions;
  - (h) Record-keeping requirements; and
  - (i) Any other requirements necessary or desirable to minimise the harm that might occur as a result of use of the substance.
41. The above conditions and restrictions that the Commission proposes for recreational psychoactive substances represent a combination of restrictions that already exist under the restricted substances regime, as well as conditions similar to those that feature under the tobacco and liquor regulatory regimes.
42. Stargate considers that the above conditions are consistent with what Stargate advocated during the previous reform process. We therefore do not see any immediate concerns with the conditions proposed and support this element of the Commission's proposal. Stargate engaged fully with the Ministry of Health during the last legislative reform process, particularly on the appropriate controls that were to be imposed on restricted substances. Stargate was also heavily involved in assisting with the development of a code of practice, which was submitted to the Director-General of Health for approval. Stargate therefore remains committed to ensuring a controlled and

responsible environment for the manufacture and supply of recreational psychoactive substances, and believes that the Commission's conditions and restrictions listed above will help achieve this objective.

43. By way of elaboration, the following summarises our views on the appropriate controls that should apply to restricted substances. A key point is that we suggest appropriate licensing requirements in addition to the controls suggested by the Commission:

(a) Minimum standards should start with **purity of the ingredients**. Pharmaceutical grade ingredients are required to be of an extremely high standard,<sup>8</sup> but it is important to consider that setting these standards too strictly could amount to prohibition by proxy, by setting a purity standard that is effectively impossible to meet. Nevertheless while it may be advantageous to allow a slightly relaxed standard compared to conventional pharmaceuticals, a minimum purity of 99%, identification of all impurities present, and maximum allowable levels of specific toxins such as heavy metals, dioxins etc are essential.

Purity standards for plant extracts containing a mixture of components will be more challenging to define, especially where there are multiple active components or the active components have not been identified. In this case the focus should be on proving that the claimed ingredients are actually present, which could involve measuring the relative quantities of characteristic "fingerprint" molecules present in the particular plant.

(b) The next standard should be on **accurate labelling**. All ingredients must be identified, although as with foods exact amounts need not be specified, with the exception of the amount of active ingredient(s) which must be stated clearly and accurately. Resistance to this in the past has stemmed largely from the lack of appropriate intellectual property protection available for products which cannot be patented, which causes a strong incentive to keep ingredients secret. Introducing a government regulated licensing system with scope for exclusivity for a limited period could prospectively address these issues.

(c) **Substances with low to moderate risk** of harm would be best suited to the restricted substances regime, and subject to all the associated limitations on age limit, points of sale and advertising established under the MDAA. Additional regulations should be put in place to tighten up and clarify the existing requirements, as well as introducing several new aspects. The main additional control envisaged would be licensing requirements both for the individuals selling the substances and for the premises from which they are sold, largely mirroring the scheme set up by the Sale of Liquor Act 1989, although with some modifications as needed. A single premise should not be allowed to hold both a liquor licence and a restricted substances licence at the same time (although this would not restrain an individual from acquiring both licences and thus having the option of working at either type of establishment at different times).

(d) **Restriction on age, place of sale, and advertising** should depend on the degree of risk associated with the particular product. Many substances in the "herbal remedy" and "dietary supplement" classes have some kind of pharmacological effect on the body and should be subject to the purity and labelling standards, but have low toxicity and virtually zero potential for abuse

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<sup>8</sup> >99% pure if dose is 1mg or below, >99.9% pure if dose is between 1mg and 10mg, >99.95% pure if dose is above 10mg, all impurities above 1 part per million must be identified.

or overdose, so for these “lowest risk” substances clearly there is no need for restrictions on who can buy them or on where and how they are sold.

- (e) **Substances that have low, but not negligible risk**, might require additional controls. This might include mild herbal sedatives or mood enhancers such as valerian, St John’s Wort or kanna, which are unlikely to cause any degree of dependence or risk of overdose, but at the same time should not be used by children or by people who are elderly or have severely compromised health. These compounds should be able to be sold by anyone without any licence requirements, from any outlet, and should not be banned from advertising, but should be subject to an R18 age limit (ie a similar level of control to spray paint, butane gas etc) and training requirements might be needed in certain instances (eg for substances such as St John’s Wort, which have significant drug interactions with commonly prescribed medicines).
- (f) **Importers and manufacturers** would also be subject to a separate licensing regime, mainly focusing on storage, record-keeping and manufacturing practices, with requirements that records be kept and reported to the appropriate authority on a regular basis, concerning how much and of which compounds had been imported, how much was currently held in storage or had been sold, and who it had been sold to. Storage and labelling requirements could be loosely derived from existing legislation such as the various Hazardous Substances Regulations, although pure drug compounds are generally hazardous only through inadvertent exposure via ingestion, inhalation etc, and do not present any additional hazards. Therefore the focus of storage requirements is more likely to be on securing stockpiles against theft or unauthorised consumption or distribution.

Manufacture and formulation of dosage units, packaging and distribution should be compliant with the industry code of Good Manufacturing Practice,<sup>9</sup> which contains detailed requirements for hygiene, standardisation of doses (so all dosage units contain the same amount of active ingredient), and safe manufacturing processes. Enforcement provisions would include scope for audits of inventory stockpiles (to ensure no distribution had been made outside the licensing scheme) and both physical inspections of manufacturing sites and independent laboratory analysis of commercially marketed products to ensure compliance with GMP standards.

This scheme would envision that importers and manufacturers would primarily be wholesalers, who would then supply packaged product to retail stores, so the importer/manufacture licence would allow bulk sales to retail stores, which would hold the separate licences allowing sale to the public. In this instance there would not be any problem with the importer/manufacture to also be selling directly to the public, but they would need to hold all applicable licences. So in the case of a sole trader, three licences would be required, the importer/manufacture licence allowing the drug to be manufactured or imported and packaged into dosage units, the restricted substances outlet licence attached to the licensed premises from which the drugs are to be sold, and the individual Restricted Substances licence required to be able to serve customers.

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<sup>9</sup> Rules and Guidance for Pharmaceutical Manufacturers and Distributors. London: Pharmaceutical Press.

**Other issues**

44. The Commission is of the view that the Order in Council procedure that is in place for the upward classification of drugs under the MDA (which is also subject to an affirmative resolution procedure) is not justified, particularly because this kind of decision, which bears on individual liberty, should be subject to the full parliamentary process. The Commission also notes that this procedure also brings with it "an unacceptable risk of challenge" and should be abolished in favour of a more transparent legislative amendment process via the House.
45. In response to question 17 in the Issues Paper, Stargate agrees with the Commission's position and supports the abolition of the Order in Council process under the MDA on the basis that only Parliament should have the power to prohibit substances. Stargate has always held this view and is encouraged that the Commission has adopted a similar stance.
46. Stargate also supports the Commission's proposal that if the Order in Council procedure were to be abolished, there ought to be a requirement that the Minister present to the House a report from the expert committee at the time the legislation is introduced, or as soon as reasonably practicable thereafter in the case of a Member's Bill, to ensure Parliament's decisions are fully informed by independent and expert advice.

## APPENDIX

### PRE-CLINICAL SAFETY TESTING

- Pre-clinical safety testing should involve most of the same tests used when assessing the safety of new medicines, starting with test tube studies to assess mutagenic and carcinogenic potential, inhibition of liver enzymes such as CYP2D6, and screening against known antitargets such as the HERG channel and 5HT2B receptor.
- Animal studies then start, first involving preliminary studies in rodents to assess absorption, distribution and metabolism, and actions on the central nervous system, cardiovascular and respiratory systems. This is followed by acute toxicity studies using two species (ie rat and mouse) and two routes of exposure (one intravenous and one by the proposed route of administration) aiming to evaluate the minimum dose at which toxicity appears, and the maximum nonlethal dose. Dose ranges may be up to 100 times the highest dose anticipated for human use if toxicity has not become evident before this.
- Next is to repeat the dose toxicity study, again using two different mammalian species, one of which should not be a rodent. This should aim to model heavy human use of the drug, so dosage should be at the higher end of the therapeutic range, but below that established as the toxic dose in the earlier trials. Frequency of administration should model the expected human use pattern (ie twice daily, once daily, once a week etc) and the duration of repeat-dose trials may be anywhere between two weeks and six months, with a longer safety assessment period required for substances which:
  - are expected to be used often, at a high dosage or for a long time; or
  - for drugs which may be suspected of having a risk of chronic toxicity due to problematic structural elements or known toxicity of closely related drugs.