# Botox: An extended case study

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## Introduction

Mention botox and most people will immediately think of the increasingly popular aesthetic procedure that reduces the appearance of wrinkles. Others may know it as a medicine to treat such ailments as migraines and spasms. It is due to the dual use that regulating botox being tested on animals is so convoluted in the current legal framework in the UK.

'Botox' (with a capital B) is a specific brand and registered trade mark of botulinum toxin. However, the term 'botox' (with a small B) is used throughout the article to refer to all botulinum toxin products (think of Hoover and hoover or Biro and biro). The term 'aesthetic' is also used rather than 'cosmetic,' due to a rather limited EU definition of the latter as outlined below.

## Botox testing

Firstly, it is worth explaining what the animal test entails. Botox is overwhelmingly tested on mice in the UK using what is known as the Lethal Dose 50 test (LD50), so-named because it aims to determine how much of substance is needed to kill half the group to which it is given. An alternative model has been developed, but this is product-specific and the extent to which it is being used to replace the mouse test is uncertain. The LD50 involves groups of mice being injected with differing dilutions of the product. After being injected, the mice are placed back into their cages in small groups for the duration of the test (usually 72 or 96 hours). The numbers of mice who have died by the end of the test period are counted. Approximately 90% of the mice in the highest concentration group are expected to die, 10% in the lowest.[1]

For those animals receiving a sufficient dose of toxin, signs of poisoning start to show within hours. The main effect is paralysis of the lower body; affected mice begin to stagger and those more severely affected are unable to walk. As the paralysis develops over the first 24 hours, it affects the ability to breathe. The cause of many deaths is asphyxiation. In addition, the more severely affected mice cannot reach food or water and may therefore die as a result of dehydration and weight loss and not the toxin per se.

Every batch released onto the market must be tested for potency and consistency (botox is a biological product and therefore very variable; it is also highly toxic). Compounded by the fact that the use of botox has continued to increase, the number of mice tested on per year is vast. The total number of mice used in batch potency tests in the UK was 144,957 in 2015 and 130,973 in 2016[2] and the vast majority of these will have been for botox.

## The administering of botox

Botox cannot be lawfully given to individuals in the UK without a prescription. It is possible to divide its uses into three categories reflecting when medicines can be prescribed:

1. On-label uses: this is where the medical indication i.e. the particular purpose to which a medicine can be put, is expressly authorised by a medical licence called a 'marketing authorisation' granted by the Medicines and Health Regulatory products Agency

[1] (Adler et al. 2010)

[2] Statistics of scientific procedures on living animals https://www.gov.uk/government/collections/statistics-of-scientific-procedures-on-living-animals

('MHRA').[3] With botox, examples are spasticity and moderate to severe glabellar (frown) lines when this has 'an important psychological impact on the patient [under 65].' The latter, although it has an aesthetic element, is addressing a medical condition;

2. Off-label medicinal uses: this is where a doctor (or other prescribing medical professional e.g. dentist, nurse, pharmacist) lawfully prescribes botox to treat a medical condition, although that condition is not expressly authorised by the market authorisation e.g. squints, migraines and urinary bladder muscle relaxation. These are therefore 'off-label' medical uses;
3. Off-label non-medicinal uses: this is where botox is prescribed by a medical professional but for an aesthetic e.g. reducing the appearance of wrinkles to improve facial appearance. This regularly occurs in private beauty clinics, for example. The General Medical Council has confirmed to Cruelty Free International (CFI) that doctors can prescribe botox based on a patient's perceived need (e.g. cultural or aesthetic) without there being any diagnosed medical condition.

## Legal framework

Testing cosmetics on animals is banned in the EU under Regulation (EC) No 1223/2009. Unfortunately, botox is not covered by this ban by virtue of the definition of 'cosmetic product' under Article 2(1)(a), which states:

*'cosmetic product' means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours*

The definition refers to external application; as botox is

[3] There is an equivalent system for veterinary products

injected it is not caught by the definition.

The testing of botox on animals in the UK is subject to the general law that applies to all animal testing, the Animals (Scientific Procedures) Act 1986 (ASPA). The Secretary of State for the Home Department (Secretary of State/Home Office) is the regulator.

ASPA regulates experimental or other scientific procedures applied to living vertebrates (mammals, birds, reptiles, amphibians and fish) where the procedure may have the effect of causing the animal pain, suffering, distress or lasting harm over a certain threshold: ss. 1(1) and 2(1).

Before animal experiments can be carried out, there must be in place (*inter alia*) a project licence, which is granted by the Secretary of State under s 5(1):

> *(1) A project licence is a licence granted by the Secretary of State which specifies a programme of work and authorises the application, as part of that programme, of specified regulated procedures to animals of specified descriptions at a specified place or specified places.*

By s5B(1), a project licence cannot be granted unless the Secretary of State has carried out a favourable evaluation of the programme of work. Section 5B(3) then provides:

> *In carrying out the evaluation of a programme of work the Secretary of State must—*
>
> *(a) evaluate the objectives of the programme of work and its predicted scientific benefits or educational value;*
>
> *(b) assess the compliance of the programme of work with the principles of replacement, reduction and refinement;*
>
> *(c) classify as "non-recovery", "mild", "moderate" or "severe" the likely severity of each regulated procedure that would be applied as part of the programme of work;*
>
> *(d) carry out a harm-benefit analysis of the programme of work to assess whether the harm that would be caused to protected animals in terms of suffering, pain and distress is justified by the expected outcome, taking into account ethical considerations and the expected benefit to human beings, animals or the environment…*

Therefore, in assessing an application for a project licence, the Secretary of State must apply a 'harm:benefit' test and the Three Rs, namely reduction, refinement and replacement[4] (s5B(3)(b)), and classify the project according to its severity (non-recovery, mild, moderate and severe): s 5B(3).

The testing of botox in the UK has historically been carried out by Wickham Laboratories in Hampshire, which has had (and may well still have) a project licence classified as 'severe' in terms of s 5B(3)(c), the highest level of severity. Only a small handful of projects are given this classification. Section 10 of, and Schedule 2C to, ASPA make provision as to conditions to be imposed on licences. In addition to mandatory conditions, the Secretary of State may impose such other conditions as she thinks fit, a broad discretion: s 10(2). Breach of a condition does not invalidate a licence (s 10(3)).

## Policy ban

In addition to the EU cosmetic ban, the UK Government has a long-standing policy that it does not license the testing of cosmetics on animals, reflecting its view that the 'benefits' from these products do not justify the 'harm' caused to animals. This extends to botox. In a Parliamentary answer on 12 November 2009, the Minister said:

> *…under [ASPA] the Home Office grants licences for the testing on live animals of [botox] for*
>
> *products licensed for clinical purposes as a prescription-only medicine. The Home Office does not license the use of animals for the testing of cosmetic ingredients or products.*

[4] Reduction being the use of less animals, refinement being less suffering, replacement being the use of non-animal models

It is presumably for these reasons why the Home Office included a condition in the project licence it granted Wickham in 2009 to test botox:

> *To undertake testing procedures to ensure the safety, efficacy, stability and overall quality of botulinum toxins and associated proteins used for medicinal products in accordance to registered marketing authorisations held with national and international regulators and in accordance with Good Manufacturing Practice.*

## Cruelty Free International (CFI) Judicial Reviews

CFI (then BUAV) carried out two investigations at Wickham, one in 1992 and one in 2009. The investigations revealed not only the extent of the suffering endured by the mice, but also a variety of problems in the way Wickham was run.

As a result of these discoveries, the Home Office reviewed Wickham and published a report[5], which was supported by the UK Government. The report found a range of potential breaches of licence conditions, including, but not limited to:

- Mice routinely found to have died in extremis rather than euthanised at an earlier and more appropriate end point; this caused unnecessary suffering. The proportion of mice humanely killed was as low as 0% and was typically around 20%;

- Incompetent application of humane killing methods to mice leading to unnecessary suffering. Killing methods included conducting cervical dislocation on corridor floors and putting more mice than recommended in a CO2 chamber; and,

- A potential conflict of interest due to the Named Veterinary Surgeon (NVS), Managing Director, majority share owner and the reporting manager for the Holder of the Certificate of Designation all being the same individual. The 2009 investigation led to years of engagement with the Home Office and two judicial reviews.

### 2011- 2012[6]

The issue in the first judicial review when initiated was whether the Home Office was required to take steps to enforce the 'medicinal products [7] limitation in the Wickham licence.

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During the course of the proceedings, the Home Office accepted what it had previously rejected, namely that it did. In doing so, the Home Office agreed with CFI that it:

> *(a) Has a duty to ensure that the terms and conditions of project licences are complied with;*
> *(b) Has a duty to take reasonable steps to satisfy herself that batches of [Botox] carry a marketing authorisation as a medicinal product and are used for medicinal purposes;*
> *And in pursuance of [this] the [Home Office] will:*
>
> *...*
>
> *(c) require licence holders to obtain and record information on the intended use of [botox] that is tested pursuant to the licence or clinical trial application*

[5] 'A review on the issues and concerns raised in the report The Ugly Truth - a BUAV investigation at Wickham Laboratories. Animals Scientific Procedures Inspectorate', November 2010 accessed at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/116820/wickham-laboratories.pdf

[6] There is no reference as the case did not reach a substantive hearing

[7] There was some confusion at this time with the licence condition. CFI was under the impression that the wording stated that the testing must be carried out for 'medicinal purposes' and was not corrected. The wording is in fact 'used for medicinal products.' However, the Home Office said it meant the same thing

The Home Office accordingly made a clear distinction between medical purposes (permitted) and aesthetic purposes (not permitted) and stated that licence holders had to obtain and record information about intended use, in order (it is assumed) to ensure that they could distinguish between batches.

### 2016-2017[8]

CFI and the Home Office entered into extensive correspondence after the 2011/2012 judicial review discussing how the Home Office actually enforced the licence condition. CFI successfully used the Freedom of Information Act request to ascertain what the department was (and, more relevantly, was not) doing. It was common ground throughout that the purpose of the limitation of the licence was to prevent laboratories testing batches of botox on animals intended for aesthetic purposes.

CFI was concerned that steps the Home Office claimed it was taking were not legally capable of enforcing the limitation. One example was the department's assertion that it checked that each batch of botox tested on animals was covered by a marketing authorisation. But since, all botox products have a marketing authorisation, even those destined for aesthetic use, this proves nothing. Similarly, the fact that botox could only be administered against a prescription is irrelevant, because that applies to beauty treatments as much as medical uses.

CFI was confident of its position and suggested to the Home Office that the organisations commission a joint opinion from a senior public law counsel, as part of the duty which all parties have, even in public law, to try to resolve disputes without litigation. The Home Office refused (though took a long time to do so). CFI therefore obtained its own opinion, which confirmed that the Home Office was doing nothing legally capable of enforcing the limitation.

The common understanding that animal-testing for aesthetic end-use was not permitted suddenly disappeared at a meeting between CFI and the Home Office on 4 May 2016 arranged to discuss enforcement. The Home Office claimed for the first time that laboratories could test for aesthetic end use only. This would this render the limitation pointless, as it could never apply. All the department could suggest, clutching at straws, was that animal testing was not permitted when the botox was destined for illegal back-street sale (in fact, testing for illegal purposes would never be permitted in any event). This was a complete shift in the Home Office's position. It seemed to represent recognition that CFI had demonstrated that the steps the department claimed to be taking to enforce the limitation were legally ineffective.

CFI subsequently gave the department the opportunity of reconsidering its *volte-face,* but it refused. CFI therefore issued fresh proceedings.

The main grounds for judicial review were:

a. Ground 1: the Home Office had misinterpreted the meaning of the prohibition in the licence which, properly construed, prohibited testing where the end use was cosmetic;
b. Ground 2: if the licence condition did not have this meaning, the Home Office had failed to undertake a lawful harm:benefit test under s 5B(3)(d) of ASPA in failing to impose such a limitation and complying with its own published policy about cosmetics testing (including botox). Although the department had a broad discretion when applying the test, CFI argued that causing severe suffering to tens of thousands of animals, year on year, for a purpose the Government accepted was trivial (aesthetic end-use) had on any basis to fail it: otherwise, an animal experiment could never fail. Importantly, because this was post-market testing, it was possible to differentiate between types of end-use, as indeed the Home Office accepted by imposing the licence limitation.

[8] *Cruelty Free International V Secretary of State for the Home Department* [2017] Case No: CO/4124/2016

We were granted permission for judicial review, with Mr Justice Edis recognising that there did seem to be a material change in the Home Office's position. Not untypically, the department then changed its position again and reverted to accepting that botox testing on animals was indeed not allowed for aesthetic end use (this made Ground 2 redundant). However, it then placed an interpretation on the limitation which would mean that it would hardly ever apply.

For example, it argued that the ban on animal testing only applied where it was 'clear' that the 'only' end-use of the botox batch being tested was for aesthetic purposes. This would mean 99% of the batch could be intended for aesthetic purposes, but due to the 1% intended for medicinal use, the batch could be tested on animals.

The Home Office also still maintained that all it had to do was check that there was market authorisation in place for every territory where botox animal-tested in this country was sold. Throughout all pre-hearing correspondence, the hearing itself and post-hearing submissions, the Home Office provided no credible evidence that it required any more proof from the testers as to the end use. Indeed, the head of the relevant department, Mr Will Reynolds, explicitly said in his post-hearing witness statement that everyone concerned – the department, the licence-holders and the botox companies – understood that a market authorisation was all that was required: 'This is because so far as we (and they) are concerned, a product which is covered by a marketing authorisation as a medicinal product is intended for use as a medicinal product'.

Mrs Justice Cheema- Grubb had made it clear at the hearing that that was not enough. Inexplicably given what Mr Reynolds said, however, she found that the Home Office was doing more than checking for marketing authorisations.

The judge did agree that no part of a batch destined for aesthetic end use could be tested on animals[9]and with CFI's arguments on other issues of construction. However, she said that CFI had not produced any evidence that botox tested at Wickham ended up being used for aesthetics purposes.[10] But this was to ask for the impossible – CFI did not have access to the commercially secretive botox distribution network. It had, however, provided evidence of extensive aesthetic use in UK beauty clinics of botox of the type tested at Wickham, supported by Home Office acknowledgment that over 50% of botox use was for aesthetic purposes (in fact a conservative estimate).

The judge recognised that 'there is an important public interest, consistent with government policy, in ensuring that the suffering of animals at any, but certainly the most severe level, does not occur except where necessary under a rational and enforceable regulatory scheme'[11]. Whether her decision satisfied that public interest is open to serious doubt.

As frustrating as the regulatory framework is, the good news is that alternatives to the mouse model are being developed and it is not unreasonable to assume that at some point in the not too distant future botox will no longer be tested on animals. Not capable of proof, but the likelihood is that it is undercover investigations, campaigning and use of the law which have provided the impetus, sadly previously lacking, to develop alternatives.

[9] Para 74
[10] Para 64
[11] Para 62