Court File No.: T-2030-13

FEDERAL COURT

BETWEEN:

NEIL ALLARD
TANYA BEEMISH
DAVID HEBERT
SHAWN DAVEY

Plaintiffs

and

HER MAJESTY THE QUEEN IN RIGHT OF CANADA

Defendant

AFFIDAVIT OF CATHERINE SANDVOS

I, Catherine Sandvos, Legal Counsel and Deputy Manager at the Office of Medical Cannabis, Postbus 16114, 2500 BC Den Haag, the Netherlands, SWEAR THAT:

1. I am Legal Counsel at the Office of Medical Cannabis (Bureau voor Medicinale Cannabis ("BMC")) and Deputy Manager of Cluster Farma at the BMC in The Hague, the Netherlands. I have personal knowledge of the matters hereinafter deposed to by me, except where same are stated to be based on information and belief and where so stated I verily believe them to be true.

2. I have worked for the BMC since May 2007. In my role as BMC's legal counsel, I am responsible for BMC's contracting processes, including: overseeing its contracts for the cultivation and packaging of medical cannabis, carrying out the European tender process when necessary, evaluating the BMC's contracts, and ensuring compliance with contract rules and related laws. I also deal with incoming media requests and monitor policy developments regarding medical cannabis in the Netherlands and the rest of the world.

3. I have been asked by the Attorney General of Canada to address the topics set out in bold font below.

A. The purpose of the Netherlands' Bureau of Medical Cannabis and what it does

4. The Netherlands first developed a policy on medical cannabis in 1998, which had the objective of cultivating cannabis to meet pharmaceutical quality standards and to make that cannabis available for research and product development as an authorized medical product. In 2001, the Netherlands changed its policy on medical cannabis so as to also make medical cannabis available to patients in possession of a prescription.

5. This change in policy resulted from political and societal pressures. In particular, patients seeking to use cannabis for medical purposes were purchasing cannabis from so-called 'coffee shops'. Although coffee shops are tolerated in the Netherlands for selling very limited amounts of cannabis for recreational use, they are prohibited from selling cannabis as medicine. This is because the cannabis sold by coffee shops is not subject to any quality control. Moreover, patients who purchase cannabis from coffee shops for medical use have likely not received any medical counselling in respect of cannabis use. Therefore, the Netherlands believed that making a cannabis product available that met pharmaceutical quality requirements and standards and that could only be obtained by patients with a prescription, would result in - at least to some degree, it was assumed - fewer risks to health.

6. According to the Single Convention on Narcotic Drugs, 1961 (and amended in 1972), governments are permitted to make cannabis for medical purposes available upon meeting certain conditions. One such condition is that a national bureau must be established to act as a wholesaler and to commission third parties to cultivate cannabis, perform quality control and packaging, and carry out other logistical tasks.

7. To meet this requirement, the Netherlands created the BMC in 2000, which has acted as the national bureau since January 2001. On September 1, 2003, the BMC started delivering medical grade cannabis to patients for medical use through pharmacies

8. The responsibilities of the BMC are set out as follows:

   (a) To ensure the production of a consistent quality of medical cannabis which meets pharmaceutical standards;

   (b) To establish an effective procedure for distribution of medical cannabis;

   (c) To prevent diversion to the criminal circuit, for example by implementing procedures for tracking and recordkeeping; and

   (d) To ensure the availability of medical cannabis.

B. How the Netherlands' medical cannabis program was developed, including the policy rationales for the program and for any rules that govern:

(i) Restrictions, if any, on the forms of medical cannabis that may be consumed;

(ii) Restrictions, if any, on the medical conditions for which the consumption of medical cannabis may be authorized;

(iii) Whether the production of medical cannabis in residences is permitted and, if not, how medical cannabis is supplied to users; and

(iv) The amount of medical cannabis an individual user is permitted to possess and/or consume and how those amounts are determined

9. In 2001, around the time the BMC became operational as a national agency, a guidance committee with internal and external members from different disciplines was established in the Netherlands. The purpose of this committee was to assist and advise the BMC on various issues, including making amendments to the Netherlands' *Opium Act* and contacting pharmaceutical and other companies as well as patient organizations.

(Under the *Opium Act*, cannabis was scheduled as a category I drug and therefore could not be prescribed for medical use. In order to permit medical cannabis to be prescribed, the *Act* had to be amended to, among other things, re-schedule cannabis as a category II drug.)

10. When the BMC first started making medical cannabis available to patients through pharmacies in 2003, patients and growers in the illegal circuit raised complaints about and lobbied against BMC's products. In the first few years, the image of the BMC and its products was very negative and there were barely 600 patients enrolled in the program, despite the BMC's research showing the number of potential patients to be about 10,000.

11. However, this negative image changed over time as doctors gained more knowledge about medical cannabis and patients tried the product, which many were willing to do because it was available like other medications (i.e. by way of prescription from a doctor and dispensed by pharmacies).

12. Nonetheless, the fact that cannabis is available in coffee shops (even though the quality of coffee shop cannabis is different than and incomparable to the quality of medical cannabis) means it is easier for some patients to buy cannabis in coffee shops rather than through pharmacies. This is because patients buying coffee shop cannabis do not need to speak with a doctor in order to do so and, if a patient's medical cannabis is not covered by his/her health care plan, the cost of medical cannabis and coffee shop cannabis is comparable. (In particular, the cost of medical cannabis has decreased and the cost of coffee shop cannabis has increased since 2006 when the article 'An evaluation of the quality of medicinal grade cannabis in the Netherlands' by Hazekamp, A. was published. A copy of this article is attached to this affidavit and marked as **Exhibit "A"**.)

(i) Restrictions, if any, on the forms of medical cannabis that may be consumed

13. At this time, it is only permitted to prescribe medical cannabis in the form of dried inflorescences (i.e. dried flowers). The BMC is preparing to amend the Netherlands' *Opium Act* so that it will be possible in the future to prescribe cannabis oil, which will be prepared in a standardized manner for patients by pharmacies. Scientists and pharmacists in the Netherlands are currently working on a good method to safely and consistently produce cannabis oil.

14. Once patients receive their medicinal cannabis (in the form of dried inflorescences) from the pharmacy, they are free to use any method to ingest the cannabis as long as they do not make the cannabis available to someone else, which is illegal.

(ii) Restrictions, if any, on the medical conditions for which the consumption of medical cannabis may be authorized

15. Every doctor in the Netherlands is permitted to prescribe medical cannabis, and for any medical condition.

16. The BMC is not involved in prescribing or dispensing medical cannabis to patients. As such, the BMC does not have records concerning the conditions for which medical cannabis is prescribed.

17. The BMC has issued a leaflet for health care professionals concerning medical cannabis, in which the BMC has identified those conditions for which it believes there is adequate information showing medical cannabis can be effective in easing symptoms, which include the following:

- disorders that involve spasticity with pain, such as multiple sclerosis and spinal cord injuries;

- nausea and vomiting, for example resulting from chemotherapy, radiotherapy, HIV, and Hepatitis C;
- chronic pain and, in particular, neurogenic pain;
- Tourette syndrome;
- palliative treatment of cancer and AIDS, especially to stimulate the appetite so as to avoid weight loss and to decrease pain and nausea; and
- therapy resistant glaucoma.

A copy of the BMC's leaflet titled 'Medical Cannabis; Information for Health Care Professionals' dated October 2013 is attached to this affidavit and marked as **Exhibit "B".**

18. The BMC's leaflet also recommends that prescribing medical cannabis should only be considered in those cases where medical treatment with registered pharmaceutical products is inadequate, or if regular use of those products causes too many side-effects.

(iii) Whether the production of medical cannabis in residences is permitted and, if not, how medical cannabis is supplied to users

19. The Netherlands' *Opium Act* prohibits growing cannabis unless an exemption has been provided. While exemptions have been provided to, among others, companies, exemptions have not been provided to patients or recreational users. As such, the production of medical cannabis by patients or recreational users in residences is not permitted.

20. Furthermore, the Netherlands' policy on medical cannabis does not include as a goal providing exemptions to patients or recreational users to grow cannabis. Therefore, exemptions will not be provided to patients or recreational users.

21. It should be noted that the Netherlands' prosecution policies prioritize the prosecution of professional growers. If an individual is caught with five or fewer cannabis plants, it is generally assumed not to be a case of professional growing and, as a result, the individual will not face prosecution. Instead, the individual's plants and products will be destroyed.

22. Medical cannabis is supplied to patients in the Netherlands through pharmacies.

(iv) The amount of medical cannabis an individual user is permitted to possess and/or consume and how those amounts are determined

23. The amount of medical cannabis a patient is permitted to possess is exactly the same as other opiates: the first time the patient obtains medical cannabis or any other opiate, he/she is permitted to receive up to a two-week supply; after that, the patient is permitted to receive up to a three-month supply. There is no legislated maximum daily dosage of medical cannabis. A patient's daily dosage of medical cannabis is to be determined by his/her doctor.

24. The BMC is not involved in prescribing or dispensing medical cannabis to patients. As such, the BMC does not have exact figures about the number of patients who use medical cannabis, or the amounts of medical cannabis used daily.

25. Nonetheless, the BMC estimates that, on average, the total number of patients in the Netherlands authorized to use medical cannabis is about 1200, and that the average daily use is about 0,68 grams per patient. The BMC's estimates were confirmed by the article titled 'The prevalence and incidence of medicinal cannabis on prescription in The Netherlands' by Arno Hazekamp, et al., which showed an average daily use of 0,70

grams per patient. A copy of the article is attached to this affidavit and marked as **Exhibit "C".**

C. The number of cannabis strains available through the Netherlands' medical cannabis program and the reason(s) why

26. There are currently five varieties of medical cannabis (the dried inflorescences) available for patients in the Netherlands, the specifics of which are set out in the following chart:

Variety	Dronabinol (THC)	Cannabidiol (CBD)
Bedrocan	approximately 22%	less than1%
Bedrobinol	approximately 13.5%	less than 1%
Bediol (granulate)	approximately 6.3%	approximately 8%
Bedica	approximately 14%	less than 1%
Bedrolite	less than 1%	approximately 9%

27. Although the BMC only makes a small number of cannabis varieties available for medical use, each variety has a particular character in that each has different THC and CBD contents and one variety (Bedica) is from the Indica plant. The reasons the BMC makes available only a small number of varieties are set out as follows:

(a) The BMC assumes that patient preference for a particular variety is a matter of 'taste' and not related to efficacy. The BMC's assumption is based on information it has received from patients; the BMC's assumption is not based on scientific research;

(b) Practicality: As the BMC works with only one grower, it is not possible to grow numerous varieties as each variety needs its own growing cell and treatment, in terms of lighting, watering, etc.; and

(c) Cost: Growing large batches of a few varieties is more cost efficient than growing smaller batches of numerous varieties, which makes it possible to keep the cost of medical cannabis low.

D. The cost of medical cannabis in the Netherlands and how the cost is determined

28. The cost for patients to purchase 5 grams of medical cannabis is 38 €, not including taxes (VAT) or pharmacy costs.

29. The cost of 38 € is determined by calculating the costs to make medical cannabis available to patients. These costs include the costs of the BMC, the cost to purchase cannabis, the costs to analyze, package, and distribute medical cannabis, and the costs of invoicing. The BMC's costs make up about 15% of the cost of medical cannabis; the remaining 85% is comprised of the other above-noted costs.

E. The dosages of medical cannabis prescribed and/or used by patients in the Netherlands

30. Under the Netherlands' legislation, there is no maximum amount of medical cannabis that can be prescribed or that can be provided by a pharmacy.

31. Furthermore, there are no standard guidelines on dosages available. The appropriate dosage differs per patient and will depend on, among other things, the medical condition, the severity of the condition, the patient's physical condition and metabolic activity which differs per patient, the method of administration, etc. As stated above, the BMC estimates that the average daily dosage is about 0,68 grams per patient.

32. The BMC does not have records concerning the modes of administration of medical cannabis.

F. Any safety and/or quality controls applied to medical cannabis in the Netherlands

33. The BMC has set up a production and distribution chain for medical cannabis, which is described below.

(i) Growing medical cannabis

34. The BMC has contracted with a grower to grow medical cannabis.

35. Because the BMC is a public authority, in order to contract with the grower, it had to engage in the European tender process. In doing so, the BMC required that tenders be advanced only by companies that: were financially healthy, had no criminal background, had educated staff, could grow cannabis according to the current European directives for herbal medicines, could grow cannabis varieties within certain fixed THC-CBD contents, and could deliver a standardized product that met the BMC's pharmaceutical quality requirements.

36. To ensure that patients consistently receive medical cannabis that is of the same quality and composition over time, and to ensure the safety of the medical cannabis, the BMC created guidelines by revising the Good Agricultural Practice of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency so as to apply it to the production of cannabis for medical purposes. The grower contracted by the BMC to grow medical cannabis is required to grow the cannabis according to these guidelines. A copy of the guidelines titled 'Guidelines for cultivating cannabis for medicinal purposes' dated December 2002 is attached to this affidavit and marked as **Exhibit "D"**.

37. The above-referenced guidelines (Exhibit D) are to be read in conjunction with the European Good Manufacturing Practice guidelines for active pharmaceutical products, a copy of which is attached to this affidavit and marked as **Exhibit "E"**.

38. The above-referenced guidelines (Exhibit D) is annexed to the Regulation of the Netherlands' Minister of Health, Welfare and Sport of January 9, 2003, GMT/BMC 2340685, containing the policy guidelines applicable to rendering decisions on applications for *Opium Act* exemptions. A copy of this Regulation in English is currently not available. As such, a copy of the November 2002 version (unsigned), which is nearly identical to the January 2003 version, is attached to this affidavit and marked as **Exhibit "F".**

39. The Netherlands' Health Inspectorate, which promotes public health through effective enforcement of the quality of health services, prevention measures, and medical products, regularly inspects the grower's building security (e.g. systems, safes, access, etc.) and their processes to ensure compliance with the above-noted guidelines and Regulation as well as the BMC's contract with the grower.

40. Furthermore, in order for a grower to carry on business in a city, it is required to have the requisite licenses from the city, which requirements differ from city to city.

41. The production of cannabis comprises a number of steps, including harvesting, drying, processing, and packaging, some of which are described in the above-noted guidelines and Regulation. After harvesting, the plants are dried for several days in a separate room before further processing takes place. The small leaves are then removed from the flowers in a special clean room. Next, the flowers are either cut to a specific size or they are granulated (i.e. finely ground), depending on the type of medical cannabis. The medical cannabis is then put into 250 gram bags for transportation to the packaging company.

42. After each harvest, a BMC employee visits the grower for sampling and collection. In particular, the employee weighs the harvest, checks the harvest for appearance, and prepares a sample for inspection by the laboratory and a sample for contra examination, if necessary. Only after the laboratory results are received and approved by the BMC

pharmacist will the harvest be purchased by the BMC. (If the harvest is not approved by the BMC, it will be destroyed.)

(ii) Laboratory testing and irradiation

43. In order to determine that all quality requirements have been met, the medical cannabis is tested by an independent laboratory that is Good Laboratory Practices certified.

44. The quality requirements for medical cannabis were established by the BMC and are set out in an analytical monograph that complies with international standards and a specification sheet, copies of which are attached to this affidavit and collectively marked as **Exhibit "G"**.

45. As a result, the medical cannabis is tested to determine the amounts of active ingredients (e.g. THC, CBD, etc.) and the presence of unwanted substances, such as heavy metals, pesticides, and/or micro-organisms. The medical cannabis is also tested for moisture content.

46. The testing results are compiled in an analysis certificate and are later incorporated into a release certificate by the BMC. The release certificate is eventually posted on the BMC's website and can be requested by doctors and pharmacists. A copy of a sample release certificate, pertaining to the Bedrocan strain approved by the BMC in October 2014, is attached to this affidavit and marked as **Exhibit "H"**.

47. To date, almost all batches of medical cannabis produced by the grower have contained the range of the THC-CBD content levels required by the BMC.

48. Once the laboratory has approved the medical cannabis, it is sent to an irradiation company where it is irradiated with gamma radiation in the same way fruits and vegetables are irradiated. The irradiation is necessary to ensure that the cannabis is free

of microbiological contamination based on Total Aerobic Microbial Count and Total Combined Yeast and Mould Count.

(iii) Pharmaceutical packaging and distributing

49. The medical cannabis is then sent to the packaging and distribution company.

50. At the packaging and distribution company the medical cannabis is manually packed in 5 gram amounts by specialized employees in clean rooms, which meet the standards of the European Good Manufacturing Practice guidelines, a copy of which is attached to this affidavit as Exhibit E.

51. The packaging and distribution company is responsible for delivering the medical cannabis to pharmacies within 24 hours of ordering, and also does the invoicing for the BMC.

G. The differences, if any, between the medical cannabis available through the Netherlands' medical cannabis program and the cannabis available for purchase in so-called 'coffee shops'

52. The Netherlands developed its medical cannabis program to ensure there was a cannabis product available to patients under doctor guidance and by way of a pharmacy that was of pharmaceutical quality and without contamination. As a result, the medical cannabis made available by the BMC is subject to the above-noted quality controls and production practices. This is in contrast to the cannabis available through so-called 'coffee shops', which is not subject to such quality controls and production practices and the availability of which is not limited to those with a prescription.

53. In the article 'An evaluation of the quality of medicinal grade cannabis in the Netherlands' by Hazekamp, A., a copy of which is attached to this affidavit as Exhibit A, the price, THC content, and microbiology of medical cannabis from the BMC and cannabis from coffee shops are compared. The study showed the microbiological quality of the BMC cannabis was much better than that of the coffee shop cannabis. In particular, the samples of the coffee shop cannabis contained microbiological contamination, including in one sample pathogenic mould and bacteria. There was almost no difference between the BMC cannabis and coffee shop cannabis in terms of THC and moisture content.

SWORN before me at The Hague, the Netherlands, this 20 day of January, 2015.

Catherine Sandvos

Consular officer

Name: Liesbet Corriveau
Consular Officer / Agente Consulaire

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Original Article

An evaluation of the quality of medicinal grade cannabis in the Netherlands

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Abstract

Since 2003 medicinal grade cannabis is provided in the Netherlands on prescription through pharmacies. Growing, processing and packaging of the plant material are performed according to pharmaceutical standards and are supervised by the official Office of Medicinal Cannabis (OMC). The quality is guaranteed through regular testing by certified laboratories. However, in the Netherlands a tolerated illicit cannabis market exists in the form of so-called 'coffeeshops', which offers a wide variety of cannabis to the general public as well as to medicinal users of cannabis. Since cannabis has been available in the pharmacies, many patients have started to compare the price and quality of OMC and coffeeshop cannabis. As a result, the public debate on the success and necessity of the OMC program has been based more on personal experiences, rather than scientific data. The general opinion of consumers is that OMC cannabis is more expensive, without any clear difference in the quality.

This study was performed in order to show any differences in quality that might exist between the official and illicit sources of cannabis for medicinal use. Cannabis samples obtained from randomly selected coffeeshops were compared to medicinal grade cannabis obtained from the OMC in a variety of validated tests. Many coffeeshop samples were found to contain less weight than expected, and all were contaminated with bacteria and fungi. No obvious differences were found in either cannabinoid- or water-content of the samples. The obtained results show that medicinal cannabis offered through the pharmacies is more reliable and safer for the health of medical users of cannabis.

Keywords: medicinal grade cannabis, quality control, comparison, the Netherlands, Office of Medicinal Cannabis, coffeeshops.

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Introduction

The use of cannabis as a medicine is increasingly becoming a topic of public discussion in a growing number of countries around the world. As a result of the United Nations Single Convention on Narcotic Drugs (1961), which was followed by a range of complementary treaties, international legislation has been a major obstacle for developments in this field for the last several decades. However, in recent years there have been some serious efforts to bring cannabis back into scientific and clinical research and to permit its use by medical patients. Initiatives that have been taken range from the decriminalization of medicinal cannabis use in the United Kingdom and Switzerland, to serious efforts to give patients direct access to high quality cannabis, or derivatives such as standardized extracts, like in Spain and Canada.

The Netherlands have become the world's first country to make herbal cannabis available as a prescription drug in pharmacies to treat a variety of patients. Since September 2003, pharmacies dispense medicinal cannabis to patients on prescription. Doctors practicing in the Netherlands are allowed to prescribe cannabis to treat a variety of indications (see below). As a general guideline, cannabis should be prescribed only after conventional treatments have been tried and found to

be ineffective. As such, cannabis is effectively treated as a last-resort medication.

Because of the unique, liberal situation in the Netherlands with respect to drug laws, an illicit cannabis market can essentially openly compete with pharmacies, and experienced users of medicinal cannabis naturally compare both sources in terms of quality, medicinal effect, and price. It is therefore not surprising that opinions about the quality and efficacy of the state-grown cannabis emerged in the public media. Because of the popularity of cannabis as a theme in the media, opinions about the pharmacy product quickly found their way to the general public and it became clear that a group of medical cannabis users were not satisfied with the offered type of cannabis. A group of coffeeshop (see below) owners even started a campaign to promote the quality of their own material at the expense of the pharmacy cannabis. However, such opinions and initiatives were generally based on subjective measures and judgements by a group of authoritative and experienced users. Obviously, the opinion-based nature of this debate makes it complicated to evaluate the introduction of medicinal grade cannabis in the Netherlands and it clearly shows the need to address this matter in a scientific way.

The research presented here challenges the messages in the media about the dissatisfaction of some users with the medicinal grade cannabis offered by the Office for Medicinal Cannabis. This cannabis has been variously claimed to be too weak, too potent or too dry. According to some patients the 'official' cannabis doesn't work, or it does so in a very different manner from what they are used to. Other users are wary of the treatment of medicinal grade cannabis by means of gamma-irradiation, which is routinely done in order to sterilize the material. The most common complaint, however, concerns the higher price. To address these complaints, we tested samples obtained from randomly selected coffeeshops according to the validated quantitative and microbiological analyses that are routinely used for quality control of medicinal grade cannabis in the Netherlands. The obtained data was compared with that of the simultaneously obtained pharmacy product. The tests for analysis of medicinal grade cannabis used in this study have been described in the official Dutch monography for medicinal cannabis.

The results presented in this study are intended as a contribution to the discussion about the necessity or advantage of having a policy of centrally regulated production and distribution of medicinal grade cannabis. We hope it can also help the users of medicinal cannabis to make a well-informed choice in the selection of their medicine.

The Dutch drug policy

In the current situation in the Netherlands, medicinal users of cannabis can obtain their cannabis material from two distinct sources: informally through the street market and formally through the pharmacy. To understand the choices that medicinal users in the Netherlands have to make in order to decide between these two sources, it is important to have some understanding about the Dutch drug policy concerning cannabis.

The basic principles of the Dutch drug policy were largely formulated in the mid-seventies. This policy does not moralise, but is based on the assumption that drug use is an undeniable fact and must be dealt with as practically as possible. The most important objective of this drug policy is therefore to prevent or to limit the risks and the harm associated with drug use, both to the user himself and to society. As a results of this, the Ministry of Health is responsible for co-ordinating drug policy.

The cornerstone of this policy is the law known as the Opium Act, which is based on two key principles. Firstly, it distinguishes between different types of drugs on the basis of their harmfulness (cannabis products on the one hand, and drugs that represent an "unacceptable" risk on the other). The terms 'soft-drugs' and 'hard-drugs' refer to this distinction. Secondly, the law differentiates on the basis of the nature of the offence, such as the distinction between possession of small quantities of drugs intended for personal use, and possession intended for dealing purposes. Possession of up to 30 grams of cannabis is a minor offence, while possession of more than 30 grams is a criminal offence. Drug use itself is not an offence. This approach offers the scope to pursue a balanced policy through the selective application of criminal law.

Dealing in small quantities of cannabis, through the outlets known as "coffeeshops", is tolerated (condoned) under strict conditions. There are currently about 700 such coffeeshops in the Netherlands, with the majority located in the bigger cities. Tolerance is a typically Dutch policy instrument which is based on the power of the Public Prosecutor to refrain from prosecuting offences. This principle is formulated in the law and is called the "expediency principle". The small-scale dealing carried out in the coffee shops is thus an offence from a legal viewpoint, but under certain conditions it is not prosecuted. These conditions are: no advertising, no sales of hard-drugs, no nuisance must be caused in the neighbourhood, no admittance of and sales to minors (under the age of 18), and no sales exceeding 5 grams of cannabis per transaction. The stock of the coffeeshop should not exceed 500 grams of cannabis. If these rules are violated, the coffeeshop can be closed down by the municipal authorities.

The idea behind the Netherlands' policy towards the coffee shops is that of harm reduction. This is based on the argument that if small-scale cannabis dealing and use is not prosecuted under certain conditions, the users – who are mainly young people experimenting with the drug – are not criminalised (they do not get a criminal record) and they are not forced to move in criminal circles, where the risk that they will be pressed to try more dangerous drugs such as heroin is much greater.

It is widely believed that drugs are legally available in the Netherlands, and that no effort is made to combat the supply side of the drug market. Nothing could be

further from the truth. There is continual, intensive co-operation between the drug dependence care system, the judicial authorities and the public administrators. With the exception of small-scale cannabis dealing in coffeeshops, tackling all other forms of drug dealing and production has high priority. The police and customs officials regularly seize large hauls of drugs and collaborate closely with other countries in the fight against organized crime. In 2000 alone, about 40,000 kg of cannabis and about 660,000 marihuana plants were seized and 1372 nursery gardens dismantled.

Tolerance does not mean that cannabis smokers can just light up a smoke anywhere they like outside a coffeeshop. Although no formal rules prohibit cannabis smoking in public places, such as bars, restaurants or concert halls, very few people do so. If they do, no sanctions are applied; but the person is likely to be asked by the personnel to put out the cigarette. The absence of formal regulations for the use of cannabis has opened the way for these informal norms, and their existence and effectiveness is an aspect of Dutch drug policy that is often underestimated and difficult to grasp by foreigners. For example, tourists who visit Amsterdam commonly make the mistake of thinking they can smoke cannabis 'everywhere'. It must be noted that the majority of the Dutch population, especially senior citizens, has never consumed cannabis and does not know much about cannabis regulations or habits. It's in this complex situation of written and unwritten rules that consumers of medicinal cannabis in the Netherlands have to make choices about obtaining their medicine.

Medicinal cannabis in the Netherlands

Health Minister Els Borst (1994-2002) acknowledged the fact that a considerable group of people was using cannabis obtained through coffeeshops for medicinal purposes. However, its unofficial status makes it impossible to make any guarantees on the quality, consistency, or origin of the cannabis found in coffeeshops. In order to supply these patients with a safe and reliable source of high quality cannabis, the Office of Medicinal Cannabis (OMC) was established in March 2000 and started acting as a national agency on 1 January 2001. The OMC is the organisation of the Dutch Government which is responsible for the production of cannabis for medical and scientifical purposes. It holds the monopoly in the Netherlands for the import, export, and wholesale of this cannabis and its preparations on behalf of the Minister of Health, Welfare and Sport, and is notified to the International Narcotics Control Board (INCB) in Vienna. The previously mentioned United Nations Single Convention on Narcotic Drugs obliges the Netherlands to organize its Office in this way.

After an initial preparation period, medical grade cannabis became available in Dutch pharmacies in September 2003 on prescription only. Potential users must visit a medical professional (usually their own General Practitioner), who can grant approval for using cannabis for treatment in the form of a prescription.

Based on the availability and quality of clinical data and scientific literature, a selection of indications was made by the OMC for treatment with its medicinal grade cannabis. These are: nausea and loss of appetite resulting from chemotherapy, radiotherapy or HIV-combination therapy; palliative treatment for cancer and HIV patients; spasticity and pain associated with multiple sclerosis or spinal cord injury; chronic neurogenic pain; and physical or verbal tics caused by Tourette's syndrome. However, if they find it necessary in selected cases, medical professionals are allowed to prescribe cannabis for other indications as well.

The medicinal grade cannabis comes in the form of dried and manicured flowertops of female plants and is produced by an authorized grower (Bedrocan BV, Veendam, the Netherlands). Plants are cultivated indoors according to guidelines that have been derived from the general rules for Good Agricultural Practise of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency (EMEA) [3]. The detailed specifications for medicinal grade cannabis can be found on the website of the OMC [15].

Materials and methods

Medicinal cannabis of the OMC

Currently, two different cannabis varieties are available in Dutch pharmacies: Bedrocan, mean THC content 18% (specifications: 15.5-21.0%) and Bedrobinol, mean THC content 13% (specifications: 11.0-14.8%). The product is finally packaged in sealed plastic containers in quantities of 5 grams for distribution (figure 1). For this study, two original pharmacy packages (total 10 grams) of each variety were obtained through the OMC.

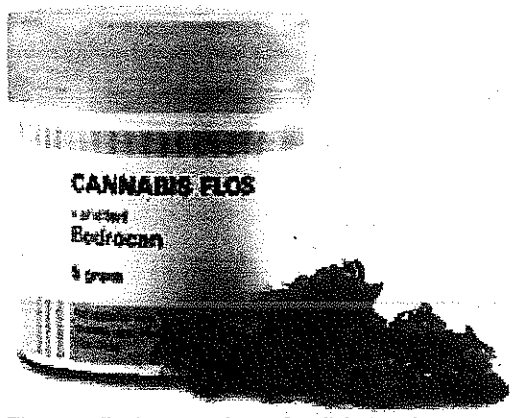

Figure 1: The 5 gram package of medicinal grade cannabis as currently available in Dutch pharmacies. There are currently 2 varieties available; the variety shown is 'Bedrocan' which has a mean THC content of 18%. (Not shown is the variety 'Bedrobinol', with a mean THC content of 13%).

Cannabis sampling

In order to conduct a statistically acceptable experiment on the quality of cannabis obtained from coffeeshops, 10 different coffeeshops were visited. These were randomly and independently selected by Intraval (Groningen/Rotterdam, The Netherlands). Furthermore, an unofficial Dutch foundation specialized in providing cannabis to medical patients was included in the study, resulting in a total of 11 locations where samples were collected. In order to guarantee that these locations remain anonymous, locations are identified by letters only (A-K). In order to limit traveling time, only coffeeshops in the West and middle of the Netherlands (the provinces of Zuid-Holland, Noord-Holland and Utrecht) were visited. About 70% of all Dutch coffeeshops are located in this most densely populated region of the Netherlands [18].

The person that visited the coffeeshops for collection of the samples pretended to be a family member of a patient suffering from multiple sclerosis, and asked what type of cannabis was recommended for this indication. The recommended cannabis was then purchased (10 grams) for performing the study.

Determination of cannabinoid composition and water content

In order to compare the potency of the samples, contents of delta-9-tetrahydrocannabinol (THC) and its acidic precursor tetrahydrocannabinolic acid (THCA) were determined by HPLC analysis. For the analysis, we used the validated HPLC-method as described in the official Dutch monography for medicinal cannabis [3]. In order to confirm the results obtained by HPLC, quantification of THC and THCA was repeated by using a recently developed quantitative ^{1}H-NMR method [6].

Although THC is known to be the major active compound in the cannabis plant, it is widely believed by researchers, as well as patients, that other components (predominantly the cannabinoids) also could play a role in the medicinal properties of cannabis [22]. The bioactivity of such compounds has been shown in a large variety of scientific studies. Examples are the cannabinoid cannabidiol (CBD) that was shown to be active in the reduction of neuropathic pain [14] and cannabinol (CBN) that acts on the immune system [8]. To include non-THC type cannabinoids in our evaluation, the total profile of cannabinoids present in each sample was measured by HPLC, as described above, and by gas chromatography (GC) [7].

Water content of the samples was determined according to the method of Karl-Fischer and was expressed as % of sample weight. Obtained values were confirmed by determining loss on drying after 24 hours heating at 40°C under vacuum.

Microbiology

Policy of the OMC prescribes that microbiological analysis of the medicinal cannabis must be performed after the plants are harvested and again after the final product is packaged. Packaged material must conform with the European Pharmacopoeia (EP), chapter 5.1.4, category 2: "microbiological quality of pharmaceutical preparations", which deals with the requirements for medicinal preparations for inhalation. To prevent the formation of microbial toxins, the product is sterilized shortly after harvest by gamma-irradiation (dose <10 kGy) and subsequently packaged under aseptic conditions. If the packaged product does not conform to the microbiological specifications of the EP, the entire batch is rejected for further medical use.

In order to determine the level of microbiological contamination of the obtained samples, microbiological analysis for the presence of potentially harmful bacteria and fungi was performed by Bactimm BV (Nijmegen, The Netherlands), the company that also performs the routine analyses of medicinal cannabis for the OMC.

Price

The most relevant way to compare prices of medicinal preparations is by expressing the price relative to the amount of active ingredient present (price per dosage). In the case of medicinal use of cannabis, it is widely assumed that the major active constituent is THC, although other cannabinoids are believed to play a role as well. Therefore, prices were corrected for the obtained weight of the samples as well as their content of THC. Corrected prices were expressed per 100 mg of THC.

Results and discussion

For completion of all the analytical tests, 10 grams of cannabis was needed, but the Dutch policy concerning the toleration of coffeeshops prohibits selling more than 5 grams per client per transaction. Therefore in most cases the sample collector had to return at a later time to obtain another 5 grams of the same cannabis. However, in 4 out of 11 visits the collector was allowed by the coffeeshop to obtain 10 grams at once. The workers in most coffeeshops were found to have experience answering questions concerning the medicinal use of cannabis and were willing to offer advice on matters such as method and frequency of use, as well as on expected results. Although the cannabis was explicitly purchased for medical use, none of the visited locations asked to see a doctor's prescription before selling the cannabis.

Obtained samples were weighed in order to divide them up in portions for performing the different tests. It was found that less than 9.50 grams were present in the obtained package(s) in 5 out of 11 cases, meaning a deficit of more than 5%. A variation of 5% in content is the tolerance that is usually accepted in trade in the EU. In one case (coffeeshop A) only 7.49 grams (-25%) were delivered. Although it was not an objective of our study, these results indicate that falsification of weight (whether intentionally or not) is not merely an incidental problem. In contrast, both samples obtained from the OMC contained almost exactly the expected

Table 1: Prices paid for each sample when '10 grams' was demanded, and amount of sample (in grams) actually obtained in the purchase. For Bedrocan and Bedrobinol, '10 grams' was obtained by combining 2 standard pharmacy packages of 5 grams each.

Cannabis sample	Price (euro)	Obtained weight (gram)
Bedrocan	€ 93.92	9.97
Bedrobinol	€ 81.94	9.90
A	€ 48.00	7.49
B	€ 50.00	9.83
C	€ 60.00	8.37
D	€ 60.00	10.79
E	€ 48.00	9.30
F	€ 60.00	9.63
G	€ 60.00	9.77
H	€ 70.00	9.61
I	€ 50.00	8.81
J	€ 60.00	9.49
K	€ 60.00	9.61

amount of 10 grams (± 0.1 gram). The prices and obtained weights of the samples are listed in table 1.

In fresh cannabis plant material, THC is predominantly present in the form of its acidic precursor THC-acid (THCA). Under the influence of heat or storage, THCA can be converted into free THC. For the recreational as well as the medicinal user, THC is the most important bio-active component, and therefore it is common practise in analytical laboratories to determine the total THC content of cannabis (THCA + THC) after heating of the plant material. However, this method is not completely reliable because a full conversion of THCA to THC is difficult to achieve. Furthermore, during the heating process degradation products of THC (such as cannabinol or delta-8-THC) can form or evaporation of THC can occur [19]. During this study these problems were prevented by determining the amount of THCA and THC individually. From these results the total THC content was then calculated. This method has only recently become available, through the development of a reliable THCA reference standard for quantification [5,16].

The THC-content of samples is shown in figure 2. For all coffeeshop samples, the THC content was found to be in the relatively narrow range of 11.7-19.1% (as percentage of dry weight plant material). The THC content of the pharmacy varieties fell also within this range: variety 'Bedrocan' (16.5% THC) was found in the middle of the range, while variety 'Bedrobinol' (12.2% THC) was at the lower end of the range.

Besides THC and THCA, other cannabinoids were taken into account as well during analysis of the cannabinoid composition of the samples. However, no major differences were observed among the coffeeshop samples when comparing the obtained GC- or HPLC-chromatograms. Likely, this is the result of decades of cross-breeding and selection for high-THC producing strains of cannabis. This process has minimized the variability between the cannabis strains, with some exception for their content of THC. Some representative HPLC chromatograms are shown in figure 3.

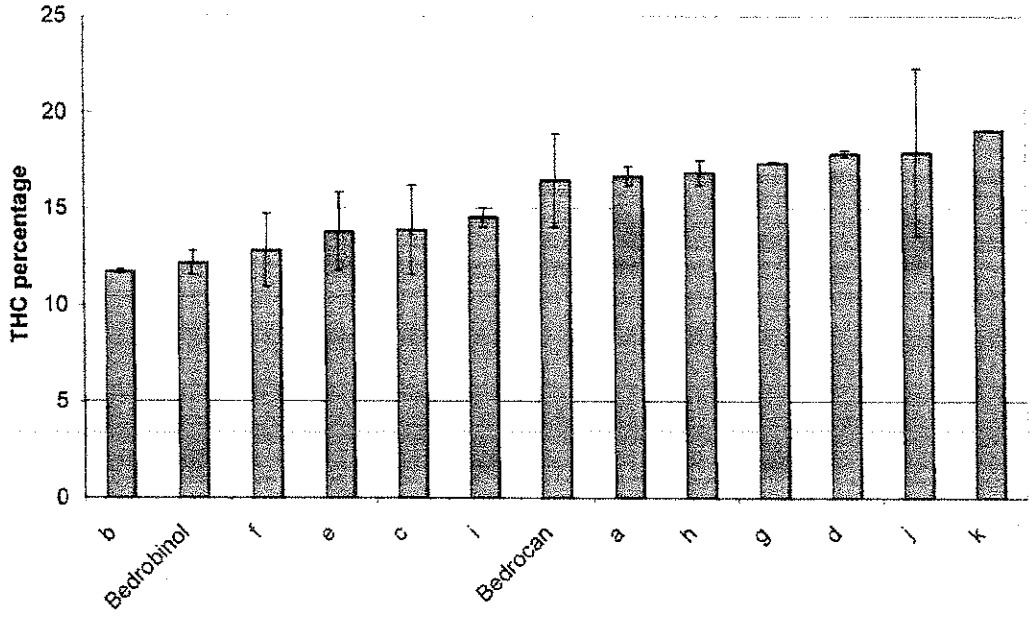

Figure 2: Content of total THC for each sample in % of sample weight. Results are shown in increasing order. Values are the mean of 2 determinations. Errorbars indicate standard error.

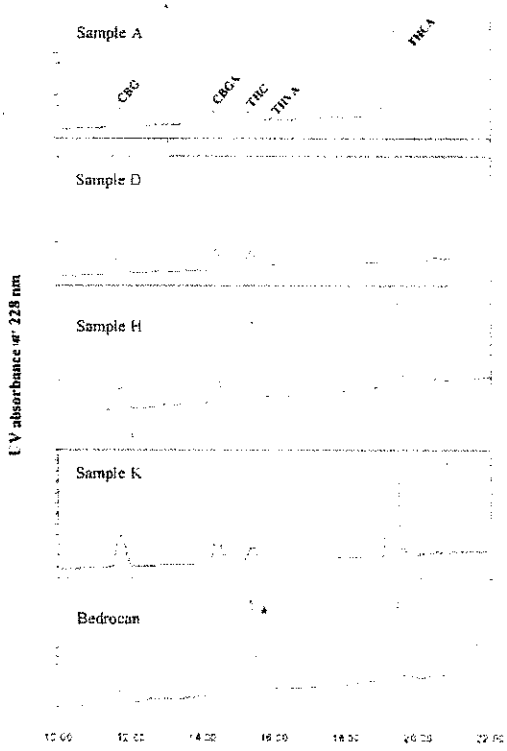

Figure 3: HPLC chromatograms (228 nm) of selected samples. No cannabinoids were observed outside the shown region of the chromatograms. Pharmacy cannabis contains a larger proportion of free THC (*). CBG: cannabigerol; CBGA: cannabigerolic acid; THVA: tetrahydrocannabivarinic acid.

When coffeeshop samples were compared to the OMC samples, only one noticeable difference was observed: the latter contains a larger proportion of free THC, and therefore a lower proportion of its carboxylic acid precursor THCA. We expect this to be the result of handling and packaging, which is likely to convert some THCA into free THC. A higher content of free THC can be beneficial when a patient consumes the cannabis in a form that has not been heated strongly or long enough, like in the case of an infusion (for cannabis tea). Under such conditions THCA will not be completely transformed into THC so a smaller amount of the active component THC will be consumed. However, when the cannabis is consumed by smoking or in the form of strongly heated products (e.g. baked products such as cookies), the transformation of THCA into THC will be virtually complete and the observed differences in initial free THC content will become irrelevant.

When water content of the samples was compared, it was found that the OMC-variety 'Bedrocan' (water content 4.7%) was not significantly different compared to the coffeeshop samples, where water contents ranged from 3.9-5.5%. For the variety 'Bedrobinol' however, a significantly higher water content of 8.0% was found. According to the OMC, this value was intentionally higher, after comments from users, in order to make the inhalation of this variety more pleasurable. According to OMC specifications the water content of the cannabis at the time of quality control (directly after packaging) must be between 5-10%.

The EP requirements with regard to microbiological purity for inhalation preparations set the following limits for sample contamination: total molds and aerobic bacteria: ≤10 colony forming units (CFU) per gram; total enterobacteria and gram-negative bacteria: ≤100 CFU per gram. The infectious bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus* must be completely absent. As shown in table 2, all samples obtained from coffeeshops carried contamination levels of bacteria and/or fungi above these limits. In contrast, both cannabis varieties from the OMC were found to be clear of such contaminations. According to the OMC, rejection of its medicinal cannabis based on microbiological contamination has never occurred to date.

The mycological laboratory of Centraal Bureau voor Schimmelcultures (CBS, Utrecht, the Netherlands) further analyzed the contaminants present in one of the samples (sample K), and identified several known pathogens, including the intestinal bacterium *Escherichia coli*, and fungi of the *Penicillium*, *Cladosporum* and *Aspergillus* types. Some of these microbes are capable of producing hazardous mycotoxins, such as aflatoxin B, ochratoxin A and B, and sterigmatocystine.

Aflatoxins, in particular, are known to be extremely potent carcinogens [17]. They are not completely destroyed by heat during smoking, and thus may be inhaled [2,10]. The presence of potentially hazardous fungi on recreationally-used cannabis has been described routinely and increasingly these fungi are being acknowledged as an underestimated source of neurological toxicity [1] or infections such as aspergillosis [4,11,20]. There are some indications that the use of anti-inflammatory steroids can increase the susceptibility to fungal infections [12] and it should be noted that a significant fraction of the population of patients that uses medicinal cannabis also uses such drugs. Moreover, medicinal cannabis is relatively commonly used by HIV/Aids patients and other types of patients that, because of their compromised immune systems, are specifically vulnerable to infections. Opportunistic lung infections with *Aspergillus* have already been suggested as a serious contribution to morbidity in this subgroup of patients [9,20].

Even for consumers who are not immunocompromised, neurological toxicity of contaminated cannabis samples is pointed out as a health risk [1]. Therefore, these combined data indicate that medicinal use of cannabis that has been purchased from uncontrolled sources could be considered as a potential health risk for the population of medicinal users, particularly for those who consume larger amounts of cannabis on a daily basis.

Table 2: Presence of bacteria and fungi (in cfu per gram) in the studied samples.
[1] CFU per gram = colony forming units present in one gram of the sample. [2] The contaminants on sample K were further identified to be the bacterium E. coli, and fungi of the types *Penicillium, Cladosporum* and *Aspergillus*.

Sample	Enterobacteria and Gram-negative bacteria (cfu/gram) [1]	Molds and aerobic bacteria (cfu/gram) [1]
OMC samples		
Bedrocan	<10	< 100
Bedrobinol	<10	< 100
Coffeeshop samples		
A	<10	480000
B	4500	900
C	<10	1000
D	70	120
E	13000	6500
F	80000	4800
G	180	350
H	27000	1300
I	350	4200
J	23000	91000
K [2]	5900	3600

The higher price of medicinal cannabis has proven to be a major drawback for medical patients in the Netherlands to obtain their cannabis from pharmacies. By expressing the price of the samples relative to the level of THC present, a fair comparison between the obtained samples is possible. Results are shown in figure 4. It is shown that the price of the pharmacy variety 'Bedrocan' (€ 5.72) is somewhat above the range of prices that were paid for coffeeshop samples (€ 3.11–5.16). The relative price of the 'Bedrobinol' variety, however, is significantly higher (€ 6.80). According to OMC, the higher costs of medicinal grade cannabis are the result of maintaining a high quality standard for the product. Included are: production according to pharmaceutical standards, aseptic packaging, distribution and costs made by pharmacies. Moreover, costs accrue as a result of constant quality controls and microbiological analyses. Finally, pharmacy cannabis includes a 6% VAT charge, while the EU VAT system does not allow that VAT is charged on the illicit (although tolerated) cannabis from coffeeshops.

Conclusion

The simple rules of supply and demand usually result in the consumer buying the product with the best quality-to-price ratio. Because of such forces, the unique situation in the Netherlands has led to a confusing situation for medicinal users of cannabis. Price comparisons and superficial inspection easily leads to favouring the cheaper material from the coffeeshops over the more expensive, but seemingly equal, pharmacy grade. The fact that only the quality of the latter is guaranteed through regular controls does not seem to impress most consumers. However, it is obvious that the standards for any medicinal preparation are high and that these can be enforced only by appropriate analytical testing. According to the OMC, another reason why the price of Cannabis available in pharmacies is currently somewhat higher than expected, is because sales are relatively low. If the number of patients would increase, this could influence the price because the fixed costs per sold unit would drop.

Because the number of coffeeshop samples that were used for this study was limited, conclusions must be drawn with some precaution and results presented here should be reported as incidental findings. Still, based on the obtained results we concluded that the price paid for medicinal cannabis distributed through the Dutch pharmacies must be considered reasonable. The cannabinoid strength and composition of the pharmacy products and the water content are not significantly different from other types of cannabis. In contrast, the pharmacy product is guaranteed to have a consistent potency, and potentially dangerous contaminations are absent. These results indicate that routine analysis of the cannabis results in a significantly safer product of high and reproducible quality. Delivery of medicinal cannabis to patients through the OMC and pharmacies results in a reliable product without the health risks commonly associated with coffeeshop cannabis.

Some patients have claimed that the official cannabis simply is not as good as their personal choice of 'mediweed'. Certainly, the possibility remains that cannabis varieties with a similar cannabinoid profile can have different strengths or effectiveness, based on the presence of other components such as terpenoids or flavonoids. Nevertheless, the current scientific consensus is that it is mainly the cannabinoids that are responsible for the bioactivity of cannabis, and testing of the samples by two different methods did not show obvious differences in cannabinoid composition. In conclusion, it seems that there remains some room for discussion on this point.

When patients choose to obtain cannabis from an uncontrolled source, they must realize that they do so with a certain risk to their health. In this test, we did not check for the presence of pesticides, fungicides or heavy metals, but there are plenty of indications that these are frequently present in cannabis samples from uncontrolled sources [13,21]. The same lack of quality control makes it impossible to determine whether products that are claimed to be grown organically, like in some coffeeshops, are really that much more trustworthy. Ultimately, it is the consumer that makes the choice. We hope that the research presented in this article may help the consumer to make an informed and safe choice.

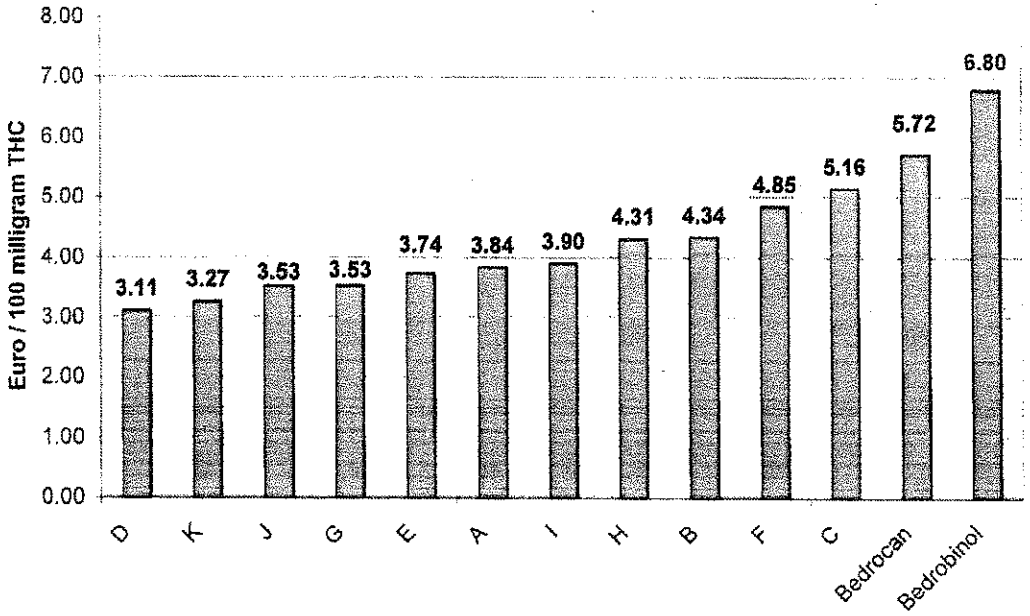

Figure 4: Price of each sample, expressed as price (in euros) paid per equivalent of 100 mg THC. Results are shown in increasing order.

Tests for the presence of heavy metals and pesticides are routinely performed for the OMC cannabis. Therefore the medicinal grade cannabis in Dutch pharmacies is guaranteed to be free (below official standard limits) of such contaminants. Unfortunately, because such tests are very costly, they could not be carried out as part of this study. Future studies should therefore include a larger number of sampled locations, and could include analysis for the presence of heavy metals, pesticides or fungicides.

Acknowledgements

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Ministry of Health, Welfare and Sports
Office of Medicinal Cannabis
P.O. Box 16144
2500 BC The Hague
The Netherlands

This is Exhibit "B" referred to in the Affidavit of Catherine Sandvos sworn before me at the City of The Hague, the Netherlands this 20 day of January, 2015.

A Consular officer

Liesbet Corriveau
Consular Officer / Agente Consulaire
28 JAN 2015
Hague

Medicinal Cannabis

Information for Health Care Professionals
Date of revision of the text: October 2013

1. Name of the medicinal product

Cannabis, dried flowers (Cannabis flos)
There are four varieties:

Variety	Dronabinol /THC	Cannabidiol/CBD
Bedrocan	approx. 22%	<1%
Bedrobinol	approx. 13.5%	<1%
Bediol (granulate)	approx. 6.3%	approx. 8%
Bedica (granulate)	approx. 14%	<1%

2. Qualitative and quantitative composition

Cannabis consists of the dried inflorescences of the female *Cannabis* sativa L. plant, and is cultivated and processed under standardised conditions in order to obtain a consistent product. Cannabis contains several constituents including substances that belong to the cannabinoids, such as dronabinol (delta-9-tetrahydrocannabinol, THC) and cannabidiol (CBD). The content of cannabinoids depends on the type of cannabis.

3. Pharmaceutical form

Dried female flowers (gamma-irradiated)

4. Clinical particulars

4.1 Therapeutic indications

There is adequate information available now, which proves medicinal cannabis can be effective in the treatment of:

- disorders that involve spasticity with pain (multiple sclerosis, spinal cord injuries)
- nausea and vomiting (resulting from chemotherapy, radiotherapy, and HIV combination therapy and medication by hepatitis C)
- chronic pain (in particular neurogenic pain)
- Tourette syndrome
- palliative treatment of cancer and AIDS especially to stimulate the appetite to decrease pain and to avoid weight loss and nausea
- therapy resistant glaucoma

If medical treatment with registered medicines is disappointing or there are too many side-effects with registered medicines, cannabis can be considered.

Experiences of patients and doctors also mention a significant number of other indications.

Medicinal Cannabis can't cure above-mentioned disorders. Cannabis can ease the symptoms of the disorders or reduce the side-effects of medicines. It is up to a doctor to decide when a patient can benefit from medicinal cannabis. The doctor isn't bound by a list of disorders.

Inhaling cannabis with a high content of dronabinol increases the risk of psychological side-effects. This can be avoided by choosing a variety with a low content of dronabinol or through oral administration (tea) when cannabis is used for the first time.

4.2 Posology and method of administration
The required amount of cannabis per day should be determined on an individual basis. The starting dosage must be low. The dosage, which is necessary to achieve the desired effects is often different/ lower than the dosage, which causes psychological side-effects (get high). If a patient benefits from a higher dose, the cannabis can be increased slowly.

Two methods of administration are recommended: oral administration or administration through inhalation. Inhaling cannabis exhibits a stronger and faster therapeutic effect.

Oral (tea): (see also 6.6)
Drink 1 cup (0.2 litre) of tea in the evening, hot or cold.
When using this method, keep in mind that it will take an average of two weeks before the maximum effect is achieved. If after roughly two weeks the result is too limited or unsatisfactory, the patient can drink one extra cup (0.2 litre) in the morning.

Inhalation (vaporizer): (see also 6.6.)
The recommended starting dose is 1-2 times a day. Inhale a few times until the desired effect is reached or until psychological side-effects occur. Wait 5-15 minutes after the first inhalation and wait between inhalations. When using the inhalation method, the strength of the cannabis must be kept in mind. Be careful about the dosage when you switch from one variety of cannabis to another, especially if you use cannabis with a higher content of dronabinol. With repeated administration of cannabis, it will take 2 weeks to get the steady-state concentrations of dronabinol. This must be kept in mind in deciding the activity of the drug.

4.3 Contra indications
Patients with a tendency to get psychotic illnesses would definitely advised not to use cannabis. Exercise great restraint to patients with underlying psychological problems.

4.4 Special warnings and precautions
Inexperienced users can be frightened by the psychological effects of cannabis. It is advised to administer cannabis for the first time in a quiet and familiar setting, and in the presence of another person who can calm down the patient if necessary.

Smoking is not recommended. Cannabis smoke contains harmful combustion products, including carcinogens and carbon monoxide. As a result, frequent use of smoked cannabis over a long period of time presumably exposes users to health risks associated with smoking. Smoking cannabis can impair pulmonary function (histopathological

changes in the mucous membranes) and reduce resistance to infection. Regular cannabis smokers can develop pharyngitis, rhinitis and COPD (Chronic Obstructive Pulmonary Disease). To limit the damage caused by combustion products, cannabis can be inhaled by a vaporizer.

Patients with heart diseases (heart arrhythmias, angina pectoris) should avoid high doses of cannabis because of the cardiovascular side-effects (in particular tachycardia). Tolerance to these effects develops within a few days to weeks. The dosage may only be increased slowly as indicated by the effects on the heart.

4.5 Interactions with other drugs and other forms of interaction
It is known that the use of cannabis at the same time with other tranquillizing substances such as alcohol, benzodiazepines and opiates cause cumulative effects. If there is a combination of cannabis with an opiate, the dose of the opiate can often be decreased. Provided that the analgetic effect improves or stays the same, the opiate can also give less side-effects. There hasn't carried out research to interactions with other drugs.

Because of the high first-pass effect in the liver, particularly in the case of oral administration of cannabis, it is possible that pharmacokinetic interactions could occur with drugs, which are broken down by the isoenzymes CYP2C9 and CYP3A4 in the cytochrome P450 system. Drugs that inhibit these isoenzymes are macrolides (in particular claritromycin and erythromycin), antimycotics (itraconazole, fluconazole, ketoconazole and miconazole), calcium antagonists (in particular diltiazem and verapamil), HIV protease inhibitors (in particular ritonavir), amiodarone and isoniazid. Simultaneous use of the enzyme inhibitors mentioned above can increase the bioavailability of dronabinol and with that, the possibility of additional side-effects.

Drugs that accelerate the breakdown of dronabinol via the isoenzymes mentioned are rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone and Saint John's Wort. If a patient stops taking one of these drugs, there can be an increase in the bioavailability of dronabinol.
Interactions are also possible with drugs which (like dronabinol) are strongly bound to plasma proteins.

4.6 Pregnancy and breastfeeding
Use of cannabis during pregnancy should be avoided. It is known that dronabinol reaches the fetus via the umbilical cord. Research indicates growth retardation when cannabis is used during pregnancy. School-aged children who were exposed to cannabis while in utero have a normal overall IQ but score lower on certain aspects (in particular, in their ability for abstract-visual reasoning, memory function, and the executive function, which is the ability to demonstrate flexible, purposeful behaviour). Hyperactivity, concentration problems and impulsivity are also reported in 10-year olds. Dronabinol is detected in breast milk. Therefore, the use of cannabis while breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines
The use of cannabis can reduce the ability to react and can cause a lower concentration. This may create problems in carrying out everyday activities. Participating in traffic and operating machines are not recommended.

4.8 Side-effects
The psychological side-effects of cannabis can vary widely, and depend on several factors: the amount of cannabis which is used, the method of administration, the patient's experience with cannabis and personal constitution, such as the person's state of mind at the time of use and how impressionable the user is to experiencing the effects. A person can become "high" after using cannabis. This is a feeling of euphoria that slowly changes into a pleasant sensation of calmness and tranquility. Users can also experience other effects while they are "high", such as sedation, cheerfulness with fits of laughter, hunger, a heightened sensitivity to perceptions of colour and music, a disrupted sense of time and space, and lethargy. This altered perception can give rise to a sense of anxiety, panic and confusion. Restlessness and insomnia are also reported. Cannabis can sometimes provoke a psychotic reaction, characterized by delusions and hallucinations. A genetic relationship between cannabis use and schizophrenia has been established, although it is not clear whether the relationshop is causal.

Physical side-effects of cannabis are:
- tachycardia
- orthostatic hypotension
- headache
- dizzyness
- sense of hot or cold in hands and feet
- red burning eyes
- muscle weakness
- dry mouth
- in cannabis smokers (and after inhaling): irritation of the bronchial tubes

These effects are temporary and disappear a few hours after use. Long term and intensive use of cannabis is presumed to have an effect on cognition, but this is reversible. In some cases, cannabis use can result in cannabis dependence and cannabis excess. Chronic users who use high doses can experience physical withdrawal symptoms such as mild forms of restlessness, irritability, insomnia and nausea if they stop.

4.9 Overdose
An overdose of cannabis may cause depression or feelings of fear, even feelings of panic and fainting are possible. In general the symptoms disappear spontaneously in a few hours. In case of overdose, benzodiazepines (diazepam IV) can be administered. Tachycardia can be treated with a beta blocker (propranolol IV).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cannabinoids act on the cannabinoid receptors. At least two different receptors (G-protein coupled receptors) are identified: CB_1 and CB_2 receptors. CB_1 receptors are found particularly in the central nervous system, while the CB_2 type occures peripheral especially in the immune system and gastrointestinal tract.

5.2 Pharmacokinetic properties

Absorption

The absorption of cannabinoids in the body is determined by the method of administration. When cannabis is *inhaled,* the cannabinoids are absorbed into the blood within minutes via the lungs and are transported to the brain. The concentration of cannabinoids in the brain reaches a maximum within 15 minutes, which coincides with the peak of the psychological and physiological effects. Absorption differs per individual and depends on various factors, including the heating of the cannabis, the number of inhalations, the waiting time between two inhalations, the inhalation time and lung capacity.

When cannabis is taken *orally,* absorption of cannabinoids in the blood is slow and more unpredictable. This results in the psychoactive effect being delayed 30 to 90 minutes with the maximum effect being experienced two or three hours later. The effect lasts four to eight hours. The result of dronabinol concentration in the blood with oral intake is 25-30% in relation to inhalation. This is partly caused by the large first-pass effect in the liver.

Distribution

After being absorbed, the cannabis constituents are distributed through-out the body. The concentration of cannabinoids rises the quickist in the tissues with large blood supply: such as brains, lungs, liver and kidneys. A substantial portion of the dronabinol is stored in fatty tissue. Dronabinol and its metabolites are strongly bound to plasma proteins. The distribution volume of dronabinol is 10 liter per kilogram of body weight.

Elimination

In the liver, isoenzymes CYP2C9 and CYP3A4 of the cytochrome P450 system initially convert dronabinol to 11-hydroxy-THC (11-OH-THC), a metabolite that is biologically active. This connection probably contributes to some of the effects of cannabis. The metabolite 11-OH-THC is further converted to 9-carboxy-THC (THC-COOH), which is biologically inactive. A range of other inactive metabolites are also formed. The elimination half-time of dronabinol and 11-OH-THC is 25-36 hours. Dronabinol metabolites can be detected in the urine up to several weeks after the last use of cannabis.

6 Pharmaceutical information

6.1 List of excipients
Not applicable.

6.2 Cases of incompatibility
Not applicable.

6.3 Shelf life
Cannabis can decompose under the influence of light and moisture. Cannabis can be stored in the original packaging until the expiry date indicated on the package.

6.4 Special precautions for storage
Store in the original package at room temperature (15-25°C).

6.5 Type and content of the packaging
Cannabis is available for pharmacies in 5-gram packages.

6.6 Instructions for use and processing
In cannabis, the cannabinoids are primarily present as pharmacologically inactive acids (for example, THC acid). Heating gives rise to free molecules through decarboxylation. Therefore, a heating step must always be carried out before administration.

Using the vaporizer
See the instructions enclosed with the device. The active ingredients of cannabis can be evaporated if the cannabis is heated. Subsequently, they can be inhaled without combustion. The right temperature has been reached when a vapour is just visible (a light mist) but no smoke has formed (thick clouds). When the vaporizer has a thermostat, the temperature must be set at 180-195 °C. It is possible to re-use the same cannabis 2-3 times in the inhaler.

Making tea
Boil half a gram of cannabis for 15 minutes in half a litre of water in a covered pan. Before using, strain the solid ingredients from the tea. Sweeten the tea as desired with honey or sugar. If you want to consume the tea, which is left, the same day, you can keep it in a thermos flask. When the tea is made for several days it is possible to store it in the refrigerator for 5 days. A fatty substance such as milkpowder must be added to the tea to keep the concentration of active ingredients in balance.

7. Particulars

In the Netherlands cannabis is mentioned in the Opiumact (list II).

Cannabis is regarded as dope by the International Olympic Committee (section III: list of forbidden drugs under special conditions)

In the Netherlands it is possible to cross the border with cannabis in the same way as other narcotic drugs:

1. If a Dutch citizen goes to a country that signed the Treaty of Schengen, the person can get a certificate at the Dutch Health Inspectorate.
2. If a Dutch citizen goes to a country outside the Schengen countries, the person has to go to the embassy of that country for a certificate.

There is always a risk of prosecution when you cross the border with cannabis without a certificate. Many countries punish severely in case of importing cannabis or using/possessing cannabis.

Cannabis is placed on the market as Cannabis flos by the Office of Medicianal Cannabis. The OMC is a department of the Ministry of Health, Welfare and Sports in the Netherlands

Import
A foreign company or pharmacy can import medicinal cannabis.

The Office of Medicinal Cannabis needs official documents for an import procedure:

- 2 original import licences
- A letter with the amount of medicinal cannabis, which is needed, and the indication of the patient.

After the OMC has received those documents it will apply for an export licence at the Dutch Health Inspectorate. The OMC draws up a contract and will send the contract with an invoice together to the applicant. If the OMC receives the signed contract and the invoice has been paid, the OMC will export the medicinal cannabis to the applicant.

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The prevalence and incidence of medicinal cannabis on prescription in The Netherlands

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Abstract

Background A growing number of countries are providing pharmaceutical grade cannabis to chronically ill patients. However, little published data is known about the extent of medicinal cannabis use and the characteristics of patients using cannabis on doctor's prescription. This study describes a retrospective database study of The Netherlands.

Methods Complete dispensing histories were obtained of all patients with at least one medicinal cannabis prescription gathered at pharmacies in The Netherlands in the period 2003–2010. Data revealed prevalence and incidence of use of prescription cannabis as well as characteristics of patients using different cannabis varieties.

Results Five thousand five hundred forty patients were identified. After an initial incidence of about 6/100,000 inhabitants/year in 2003 and 2004, the incidence remained stable at 3/100,000/year in 2005–2010. The prevalence rate ranged from 5 to 8 per 100,000 inhabitants. Virtually all patients used some form of prescription medication in the 6 months preceding start of cannabis use, most particularly psycholeptics (45.5 %), analgesics (44.3 %), anti-ulcer agents (35.9 %) and NSAIDs (30.7 %). We found no significant association between use of medication of common indications for cannabis (pain, HIV/AIDS, cancer, nausea, glaucoma) and variety of cannabis used.

Conclusions This is the first nationwide study into the extent of prescription of medicinal cannabis. Although the cannabis varieties studied are believed to possess different therapeutic effects based on their different content of tetrahydrocannabinol (THC) and cannabidiol (CBD), no differences in choice of variety was found associated with indication.

WHAT THIS PAPER ADDS

What is already known on this subject

- As clinical support for the therapeutic use of cannabis or its isolated components such as THC is mounting, several countries are now providing herbal cannabis of pharmaceutical grade to chronically ill patients.
- Many other patients obtain cannabis from illicit sources and experiment with self-medication, without the supervision of a medical professional.
- Other than surveys based on self-selected participation, not much is known about characteristics or preferences of medicinal cannabis users.

What this study adds

- This study is the first one using objective data to study national medicinal cannabis consumption patterns, providing accurate data on the incidence, prevalence and characteristics of users of prescribed medicinal cannabis in The Netherlands.
- Understanding the background and preferences of cannabis patients may help medical professionals to decide about the role of medicinal cannabis in their own practice.

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Introduction

As the medicinal properties of the cannabis plant are increasingly being unraveled, the number of countries that provide an official source of cannabis to chronically ill patients is growing. Canada (since 2001) and The Netherlands (since 2003) have had a government-run program for the last decade, supplying quality-controlled herbal cannabis grown by specialized companies [1, 2]. Several countries are now following this

example, either by setting up their own program (Israel, Czech Republic) or by importing products from The Netherlands (Italy, Finland, Germany). In the United States, the number of states that have introduced laws to permit the medical use of marijuana has now grown to 17 plus the District of Columbia (DC), even though this development is not endorsed by the US federal government [3]. In contrast to these developments, little published data is known about the extent of medicinal cannabis use and the characteristics of patients using cannabis on doctor's prescription, other than survey data relying on self-selected participation and self-reports [4–9].

The medicinal cannabis program of The Netherlands, supervised by the Office of Medicinal Cannabis (OMC) of the Dutch Health Department, provides an opportunity to study such questions. The program offers pharmaceutical grade cannabis on prescription to chronically ill patients suffering from multiple sclerosis, cancer, HIV/AIDS, chronic pain, therapy-resistant glaucoma, and Tourette's syndrome [1]. The product is cultivated by contracted company Bedrocan BV, and dispensed through pharmacies in the form of dried female flowers (Cannabis Flos) packaged in 5 g containers. Patients are advised to administer medicinal cannabis by using a cannabis vaporizer or by preparing it as a tea [10, 11]. In a growing number of cases, costs are reimbursed by health insurance companies [12].

Patients in The Netherlands typically utilise only a single pharmacy for obtaining all their prescription medicine, making it possible to track patients over time and construct complete medication histories including both GP and specialist prescriptions [13]. Therefore, using the Dutch cannabis program as a well-documented source of data, this study aims to analyse the incidence and prevalence of prescription medicinal cannabis use, as well as the demographics and characteristics of patients using cannabis on prescription.

Methods

The data collection covered the period of September 2003 (when medicinal cannabis first became officially available on prescription in The Netherlands) to the end of December 2010. Data on dispensing was collected from two sources. The main source was the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen; SFK); an independent organization collecting data from community pharmacies in The Netherlands for policy and research purposes. Medication dispensed through hospital pharmacies and nursing homes for in-house patients are not registered in the SFK database and are therefore not covered in our study. The second source of data was the only Dutch pharmacy specialized in dispensing of medicinal cannabis (Hanzeplein pharmacy, Groningen). Since 2007 this pharmacy has been active in dispensing the same medicinal cannabis for a reduced price (as a result of cheaper packaging, distribution and labour cost) through mail-order to patients located all over The Netherlands.

Data collected from both sources included date of dispensing, variety and amount of medicinal cannabis dispensed, and patient characteristics (age, gender, and geographical location by zip code). Complete comedication dispensed through the pharmacy was collected for SFK data only from 6 months preceding the first medicinal cannabis dispensing until the end of medicinal cannabis use. Comedication was coded according to the WHO ATC/DDD methodology and grouped accordingly [14]. All data were anonymized and patients were not financially or otherwise compensated.

In the period covered by this study (2003–2010), four different varieties of cannabis were available to patients, each containing a standardized amount of the known active ingredients tetrahydrocannabinol (THC) or cannabidiol (CBD) [15]. These varieties were: *Bedrocan*® (ca. 19 % THC; introduced 2003); *Bedrobinol*® (ca. 12 % THC; introduced 2005); and *Bediol*® (ca. 6 % THC, 7.5 % CBD; introduced 2007). Variety *SIMM18* (ca. 11 % THC; introduced 2003) was only available until 2006, after which it was replaced by *Bedrobinol*®.

Incident use of medicinal cannabis was defined as the first dispensing date available in the database. Since the database covers the complete period of availability of medicinal cannabis in The Netherlands, this refers to actual new users. Year-by-year prevalence was determined by counting the number of patients with at least one dispensing of a medicinal cannabis preparation in a calendar year. Total duration of cannabis use was defined as the time difference between the first and last dispensing of medicinal cannabis, supplemented with the number of days needed to consume the last dispensed amount (assuming an average daily use as shown in Table 1). Average dosage of cannabis per day per patient was calculated by dividing the total dispensed dose (in grams) of each individual, by the total duration of use (in days) calculated for that same individual.

Results

Demographics

Table 1 shows demographic data of the study population. Over the 2003–2010 study period, 5,540 individual patients were identified receiving a combined total of approximately 35,000 medicinal cannabis dispensations. The majority of patients (5,255; 94.9 %) received their product through regular community pharmacies, the remaining patients (285; 5.1 %) had their prescription filled in by the specialized cannabis pharmacy. More females (56.8 %) compared to males (42.7 %) used medicinal cannabis on prescription. The mean (median) age of the study population was 55.6 (55) years, with

Table 1 Demographics and medicinal cannabis use in the study population from 2003 to 2010

	N (%)	Average duration of use (days)	Average number of dispensations	Average daily use (grams)
Study population	5,540 (100)	251	6.43	0.68
Sex				
Male	2,366 (42.7)	244	6.70	0.71
Female	3,149 (56.8)	258	6.26	0.65
Age				
≤ 20	93 (1.7)	181	5.57	0.82
21–40	846 (15.3)	316	8.73	0.72
41–60	2,551 (46.0)	304	7.44	0.66
61–80	1,722 (31.1)	174	4.51	0.67
>80	303 (5.5)	99	3.01	0.74

a range of 14 to 93 years. The zip code information available for each patient indicated that medicinal cannabis users were fairly equally distributed, without noticeable agglomeration in specific geographical locations (data not shown).

Average cannabis use and duration

Data on cannabis use are also shown in Table 1. Patients received on average 6.4 prescriptions of medicinal cannabis with a median of 10 g dispensed per prescription. Overall, medicinal cannabis was prescribed for an average duration of 251 days. Patients had an average daily dose of 0.68 g per day dispensed. Male patients (0.71 g) were found to consume slightly more medicinal cannabis daily than female patients (0.65 g). Despite the differences in composition of active ingredients, no clear differences in average daily dose were observed between the four cannabis varieties offered (data not shown).

Incidence and prevalence

After an initial incidence of about 1,000 new users per year at the start of the cannabis program in 2003 and 2004 (equalling 6 per 100,000 persons per year), the number of new users stabilized somewhat lower around 500 per year, (3 per 100,000 per year). The number of patients receiving at least one prescription of medicinal cannabis per year ranged from 800 to 1,300 per year, which translates into a yearly prevalence rate of 5–8 per 100,000 persons as shown in more detail in Fig. 1.

Comedication and correlation with cannabis varieties

Virtually all patients used at least some form of prescription medication, other than cannabis, in the 6 months preceding the first cannabis prescription. Comedication observed most often were psycholeptics (ATC code N05; used by 45.5 % of study population), analgesics (N02; 44.3 %), anti-ulcer agents (A02B; 35.9 %) and NSAIDs (M01; 30.7 %).

Because the Dutch program provides multiple cannabis varieties, each with different content of THC and CBD, this may (tentatively) allow us to identify correlations between these pharmaceutically active components and particular symptoms under treatment, by studying the comedication used in the period before start of cannabis treatment. We therefore selected those indications that are specifically mentioned by the Office of Medicinal Cannabis, and that can be fairly unambiguously recognized by the (co)medication used. These included severe pain (as identified by use of opioid and non-opioid pain medication), cancer (oncolytics), HIV/AIDS (HIV-medication), nausea (anti-nausea medication) and glaucoma (eye drops). Other indications, such as MS or Tourette syndrome, were not investigated here because there is no specific comedication that unambiguously indicates these conditions.

As shown in Table 2 (which includes the 5,250 patients from the SFK database only), pain medication was used by 53.6 % of all cannabis users, which was further broken down into non-opioids (40.5 % of cannabis users), and weak (21.8 %) or strong opioids (21.2 %). Although cancer and HIV/AIDS are often mentioned in popular media in relation to medicinal cannabis use, oncolytics (2.7 %) and HIV medication (0.9 %) were only used by a small proportion of cannabis users. Glaucoma medication was seen in 2.2 % of users. In contrast, medication prescribed to treat nausea was used by 15.5 % of all cannabis users.

The results in Table 2 were further broken down for the different cannabis varieties available. Varieties *Bedrobinol* and *SIMM18* were combined because of their similar THC content. For ease of interpretation, only data of patients who had used one single cannabis variety is shown, which covered 4,507 (85.8 %) of all subjects. Of the remaining subjects, 682 (13.0 %) patients had used 2 different varieties, while 98 (1.9 %) had used 3 or 4 varieties. Although some minor differences between varieties are visible, there seemed to be no clear correlation between content of THC/CBD and any of the comedication we studied.

Discussion & conclusion

This first nationwide study into the extent of prescription of medicinal cannabis provides us with a characterization of patients using medicinal cannabis on prescription in The Netherlands, including demographics, average use and information on varieties and indications. A strength of this study is the virtual nationwide coverage of the data-collection, with the SFK data statistically covering about 85 % of the total Dutch population [Dutch Foundation for Pharmaceutical Statistics, personal communication]. Before conclusions may be drawn,

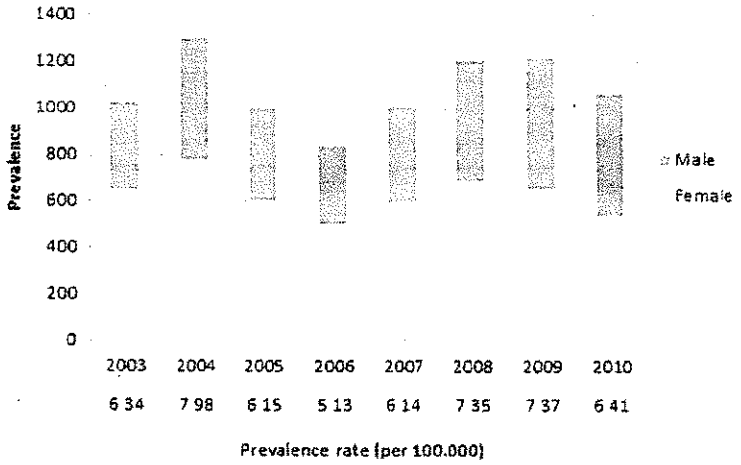

Fig. 1 Prevalence (vertical bars) and prevalence rate (secondary horizontal axis) of medicinal cannabis use in The Netherlands, 2003–2010

however, the potential limitations of the study must be clearly addressed. Our study was performed based on the assumption that Dutch patients receive all their medication from one pharmacy only. Although this is generally considered to be typical for the Dutch pharmacy system, we cannot exclude that at least a proportion of patients visited multiple pharmacies over the study period. When a patient visits a new pharmacy, the person is entered into the database under a new identifier, which in our study would have been interpreted as a new user. Also, it should be noted that obtaining cannabis from the Dutch outlets known as coffee shops remains a (pseudo-legal) option for patients [16]. A recent large-scale international survey among 953 patients performed by the International Association for Cannabinoid Medicines (AICM) indicated that the street market (including coffee shops), as well as growing your own cannabis, remain widely popular even among those patients who have access to cannabis on prescription [4].

Despite these limitations, we believe this was the first time objective data was used to study national medicinal cannabis consumption patterns, in contrast to surveys based on self-selected participation. Indeed, the differences between these two approaches can be significant. For example, the average daily use determined in our study was 0.68 g. In contrast, the international IACM survey found an average daily use ranging from 2.4 to 3.8 g per day, depending on the administration form used [4]. Unfortunately, in our current study the administration form of the cannabis was not known; although patients are advised to inhale their cannabis by using an vaporizer or to prepare tea [1], we cannot be certain they follow these instructions. We also noticed a significant difference in age of subjects between the IACM survey (mean 40.7 years) and our own study (mean 55.6 years). Other surveys have found similar results for higher daily consumption [7, 17] or younger mean age, compared to the database approach described here [18–20]. Such differences may indicate that surveys based on self-selected medicinal cannabis users, at least to some extent, inadvertently attract younger patients who have an above-average interest in herbal cannabis, and use more liberal amounts of cannabis on a daily base.

Because the SFK database did not cover the entire Dutch general population (totaling 16.6 million inhabitants in 2010),

Table 2 Use of comedication categorized per cannabis variety. Results are expressed as percentage of total users in each category

	All users[a]	Users of high THC:[b] *Bedrocan*	Users of low THC:[b] *Bedrobinol/SIMM*	Users of THC–CBD[b] *Bediol*
Total (*N*=)	5,250	2,136	1,933	438
Associated comedication (%)				
Pain medication	2,801 (53.4)	1,119 (52.4)	1,072 (55.5)	220 (50.2)
-Non-opioid	2,125 (40.5)	814 (38.1)	841 (43.5)	168 (38.4)
-Weak opioid	1,147 (21.8)	470 (22.0)	423 (21.9)	99 (22.6)
-Strong opioid	1,114 (21.2)	476 (22.3)	430 (22.2)	95 (21.7)
HIV medication	48 (0.9)	24 (1.1)	9 (0.5)	4 (0.9)
Oncolytics	139 (2.6)	66 (3.1)	50 (2.6)	9 (2.1)
Nausea medication	806 (15.4)	337 (15.8)	335 (17.3)	68 (15.5)
Glaucoma medication	116 (2.2)	49 (2.3)	40 (2.1)	10 (2.3)

[a]All users for which comedication information was available (SFK database patients only)

[b]For exact THC and CBD content, see Methods

and at least a proportion of patients is believed to consume cannabis obtained from non-official sources, our calculated prevalence rate of 5–8 per 100,000 should be considered a very conservative estimate. By comparison, prevalence rates (unofficially) reported in some other countries where medicinal cannabis use is registered by national authorities are 35 (per 100,000) for Canada and 80 for Israel, while in some US states prevalence rates of over 100 are claimed [21]. However, these numbers likely include significant numbers of pseudo-patients who, other that Dutch consumers, do not have the opportunity to obtain cannabis from legal street sources like the Dutch coffee shops. Importantly, the low average daily dose (0.68 g) found in our study points to a low potential of misuse, and a seeming absence of widespread development of tolerance. By comparison, an average Dutch cannabis cigarette used for recreational purposes contains about 0.26 g of cannabis mixed with tobacco [22]. The slightly higher daily consumption by male patients compared to females may be explained by differences in average body weight between both sexes.

By studying the comedication prescribed in the period right before first onset of cannabis use, we identified pain and nausea as common medical indications correlated with cannabis use. This may not be surprising given the fact that nausea (together with vomiting and lack of appetite) is a clinically proven indication for THC, e.g. in the form of Marinol®, while preparations containing THC and/or CBD were shown to be clinically effective for several pain indications, including severe chronic noncancer pain [23], various neuropathic pains [24], postoperative pain [25] and MS [26]. Surprisingly, the differences between varieties, in terms of average daily consumption or associated comedication, were found to be minimal. Although the cannabis varieties are believed to possess different therapeutic effects based on their different content of THC and CBD, only a minority of patients (14.9 %) had tried more than one single variety. It is unknown whether this means that the first choice of variety was already sufficiently effective in most patients, or that patients were generally not interested in trying another variety of cannabis in case the first variety failed to provide proper relief. Alternatively, doctors may have lacked sufficient information to make an informed decision, or may have refused to write another prescription after the first variety was found to be ineffective.

The Dutch program is currently unique in the world for providing a choice of standardized and quality controlled cannabis varieties to patients. Nevertheless, based on our study it should be concluded that the differences between these varieties are still insufficiently recognized. In contrast, it is important to realize that although our data accurately show *what* (how much, how often, what variety) doctors have prescribed, it cannot reveal whether the prescribed products were actually effective or not in treating the intended symptoms. Large population-based surveys, preferably among the same well-documented Dutch patient population, are needed to further describe the intentions and experiences of medicinal cannabis patients. Eventually, properly designed clinical trials are needed to provide a better understanding of the link between specific combinations of cannabinoids and medical indications. In the meantime, an increased effort to educate medical users as well as prescribers about the medicinal use of cannabis may further strengthen the Dutch model of providing pharmaceutical-grade cannabis to chronically ill patients.

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Guidelines for cultivating cannabis for medicinal purposes

Annex to the Regulation of the Minister of Health, Welfare and Sport of 9 January 2003, GMT/BMC 2340685, containing policy guidelines for the decision on applications for Opium Act exemptions (Policy guidelines Opium Act exemptions)

(authorised English translation)

This is Exhibit "D" referred to in the
Affidavit of Catherine Sandvos sworn before
me at the City of The Hague, the Netherlands
this 20 day of January, 2015.

Consular officer

20 JAN 2015

Liesbet Corriveau
Consular Officer / Agente Consulaire

Hague

1 Introduction

Under certain conditions, the Dutch government permits the cultivation of cannabis for medicinal purposes. In the case of herbal drugs, the cultivation method and primary processing of the plant determines the ultimate properties of the active pharmaceutical ingredient. Starting materials of herbal origin have a complex composition and can only be characterised to a limited extent through chemical or biological analysis. Therefore, an effective quality assurance system in the steps leading up to the production of the active pharmaceutical ingredient is needed in order to guarantee reproducible quality. These steps are cultivation, harvesting and primary processing.

The following guidelines for cultivating, harvesting and primary processing of cannabis constitute a quality assurance system that meets these requirements. The Office of Medicinal Cannabis (Bureau voor Medicinale Cannabis) will test on the basis of these requirements.

These guidelines have been derived from the general rules for Good Agricultural Practice of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency (EMEA).

This is a non-authorised translation of the official version in Dutch.

2 General

2.1 These guidelines apply to the cultivation, harvesting and primary processing of cannabis plants intended for medicinal use or the preparation of medicinal drugs. These guidelines must be read in connection with the European Good Manufacturing Practice (GMP) guidelines for active pharmaceutical products. They apply to all methods of production including organic cultivation. These guidelines also provide additional standards for the production and processing of herbal starting materials insofar as they identify the critical production steps that are needed to ensure good, reproducible quality.

2.2 The main objective of these guidelines is to increase the reliability of the medicines prepared from cannabis by establishing an appropriate quality standard for the herbal medicine cannabis. In particular, it is important that the cannabis:
- is produced hygienically to keep microbiological contamination to a minimum;
- is produced such that negative effects on the plants during cultivation, processing and storage are kept to a minimum;
- is produced under conditions that ensure that the therapeutic properties of the end product are constant and reproducible.

3 Personnel and training

3.1 Training

3.1.1 Personnel must have received adequate botanical/horticultural training before performing the tasks given to them.

3.1.2 Production personnel must be trained in the production techniques used.

3.1.3 Primary processing procedures must comply with the regulations on food hygiene.

3.2 Hygiene

3.2.1 All personnel entrusted with handling the herbal material must maintain proper personal hygiene.

3.2.2 Persons suffering from infectious diseases transmittable via food, including diarrhoea, or carriers of these diseases must be forbidden access to areas where they could come into contact with the herbal material.

3.2.3 Persons with open wounds, inflammations and skin-infections must be suspended from areas where they could come into contact with herbal material, unless they wear protective clothing or gloves until they have recovered completely.

3.2.4 Personnel must be protected from contact with toxic or potentially allergenic herbal material by means of adequate protective clothing.

4 Buildings and facilities

4.1 Rooms used in the processing of harvested crops must be clean, well ventilated and must never be used for other activities.

4.2 Buildings must be designed in a manner that protects the crops against pests and domestic animals.

4.3 The medicinal cannabis must be stored:
- in a suitable packaging
- in rooms with concrete or similar floors which are easy to clean;
- on pallets;
- at a sufficient distance from walls;
- well separated from other crops in order to prevent cross-contamination.

Organic products must be stored separately from products not grown organically.

4.4 Buildings where plant processing is carried out must have changing facilities, toilets and hand-washing facilities.

5 Equipment

5.1 Equipment used in plant cultivation and processing must be easy to clean in order to eliminate the risk of contamination.

5.2 Equipment and machinery should be mounted such that they are easily accessible. Machines used in fertiliser and pesticide application must be calibrated regularly.

5.3 The equipment must be made from materials other than wood. If wooden materials (such as pallets) are used, they must not come into direct contact with chemicals and contaminated materials, in order to prevent contamination of the herbal materials.

5.4 Equipment and machinery used for harvesting must be clean and in very good working condition. Machine parts that come into direct contact with the harvested crop must be cleaned regularly and must be free from oil and contamination, including residual plant matter.

6 Seeds and propagation material

6.1 Seeds and propagation material must be botanically identified as to species, variety, chemotype and origin. The materials used must be traceable. Starting material must be free from pests and disease as much as possible in order to guarantee healthy growth.

6.2 Cuttings of female plants must be used as propagation material for the production of cannabis.

6.3 During the entire production process (cultivation, harvest, drying, packaging), the presence of male plants and of different species, different varieties or different plant parts must be monitored. Any impurities must be removed immediately.

7 Cultivation

7.1 Soil and fertilisation

7.1.1 Cannabis for medicinal purposes must not be grown on soil contaminated with sludge, heavy metals, pesticide residues or other chemicals. Any chemicals used must therefore be kept to the minimum effective dose.

7.1.2 Manure applied should be thoroughly composted and must be devoid of human faeces. Irrigation should be controlled and according to the needs of the cannabis plant. Fertilisers should be used in such a way that leaching is reduced to a minimum.

7.2 Irrigation

7.2.1 Irrigation must be controlled and only as required by the cannabis plant.

7.2.2 Irrigation water must contain as few as possible contaminants like faeces, heavy metals, pesticides and toxicologically hazardous substances.

7.3 All tillage must be adapted to plant growth and requirements. Using herbicides and pesticides must be avoided as far as possible. Use and storage of pesticides must be in accordance with the recommendations of the manufacturer and the relevant approval authorities. Only qualified personnel are allowed to use such substances using only approved material but not in a period preceding the harvest, as indicated by the buyer or producer.

8. Harvesting

8.1 Harvesting must be done when the plants have reached the best quality for the intended use.

8.2 Damaged, and dead plants must be removed.

8.3 Harvesting must take place under the best possible conditions, avoiding wet soil or extremely high air humidity. If harvesting occurs in wet conditions, additional care needs to be taken to avoid the adverse effects of moisture.

8.4 During harvesting, care must be taken that no other species or cannabis variety gets mixed with the crop.

8.5 The harvested crop must not come into direct contact with the soil. Directly after harvesting, it must be prepared for transport in clean, dry conditions (e.g. sacks, baskets, boxes).

8.6 All containers must be clean and free from any residues from previous harvests; containers that are not in use must be kept in dry conditions; free of pests and inaccessible to domestic animals.

8.7 Mechanical damage and compacting of the herbal drug that could result in undesirable quality changes must be avoided. In this respect, take care to avoid:
- overfilling sacks/containers;
- stacking sacks/containers too high.

8.8 Freshly harvested herbal material must be delivered to the processing facility as quickly as possible in order to prevent thermal degradation.

8.9 The harvested crop must be protected from pests and domestic animals.

9 Primary processing

9.1 Primary processing includes washing, cutting before drying, freezing, distillation, drying, etc.

9.2 On arrival at the processing facility, the harvested crop must be directly unloaded and unpacked. Prior to processing, the material must not be exposed to direct sunlight (except in cases that specifically require this) and must be protected from rain.

9.3 Drying

9.3.1 Drying crops directly on the ground or under direct sunlight must be avoided.

9.3.2 Uniform drying speed and prevention of mold growth must be assured.

9.3.3 In the case that plant material is dried in the open are, it must be spread in a thin layer. To ensure good air circulation the drying racks must be placed at sufficient distance to the floor.

9.3.4 In the case plant material is not dried in the open air optimal drying circumstances like temparature and drying time must be chosen.

9.4 Waste bins must be available and must be emptied and cleaned daily. Waste must be collected in bags and/or in closable containers.

10. Packaging

10.1 Following repeated controls and removal of any material not meeting its requirements or of undesired objects, the product must be packaged in clean, dry and preferably new packaging. The label must be clear, firmly fixed and made from non-toxic material.

10.2 Reusable packaging material must be well cleaned and dried prior to use.

10.3 Packaging material must be stored in a clean, dry place that is free of pests and inaccessible to domestic animals. The packaging material must not contaminate the product.

11. Storage and distribution

11.1 Dried, packaged products and extracts must be stored in a dry, well-ventilated room in which daily temperature fluctuations are limited and good ventilation is ensured. Fresh products must be stored between 1°C and 5°C; frozen products must be kept at temperatures below -18°C (or below -20°C for long-term storage).

11.2 In the event of bulk transport, it is important to ensure dry conditions. To prevent mould formation or fermentation, it is advisable to use ventilated containers, transport vehicles and other ventilated facilities.

11.3 Decontamination of the storage area to combat pests must be carried out only where necessary and by authorised personnel only.

11.4 When frozen storage or saturated steam is used for pest control, the moisture content of the product must be controlled after treatment.

12. Special provisions for the production of cannabis intended for processing into a standardised herbal drug.

12.1 Herbs

a. In these guidelines a herbal medicine is understood to mean any medicine that contains exclusively herbal drugs or herbal preparations as active ingredients.
b. Herbal drugs are plants or parts of plants in an unprocessed state which are used for medicinal or pharmaceutical purposes. A herbal drug or a preparation is regarded as one active substance in its entirety whether or not the constituents with therapeutic activity are known.
c. Herbal drug preparations are comminuted or powdered herbal drugs, extracts, tinctures, fatty or essential oils, expressed juices, processed resins or gums, etc. prepared from herbal drugs, and preparations that are produced through fractionation, purification or concentration.
d. In departure from the above, chemically defined isolated constituents or their mixtures are not considered herbal drug preparations.
e. Herbal drug preparations may contain other components such as solvents, diluents and preservatives.

12.2 If the cannabis is intended for processing into a standardised herbal medicine, the cannabis must be cultivated under such standardised conditions that the content of the constituents is constant. Protocols of the operations committed during the cultivation must be kept available.

12.3 The content of the main constituents, which includes Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD), is determined quantitatively. For a selection of the other constituents, fingerprinting with a suitable technique, such as GC-MS, GC, HPLC or TLC will suffice.

12.4 Unless it is proven that omitting the standardisation of one of the following elements results in a constant and reproducible product, at least the following must be standardised during cultivation:

a. cultivar of the cannabis plant;
b. cultivation substrate;
c. day length;
d. light intensity;
e. colour temperature of the lighting;
f. atmospheric humidity;
g. temperature;
h. irrigation
i. ventilation;
j. plant age at the time of harvesting;
k. time of day of harvesting.

12.5 Unless it is proven that omitting the standardisation of one of the following elements results in a constant and reproducible product, at least the following must be standardised during drying:

a. atmospheric humidity;
b. temperature;
c. ventilation;
d. drying time.

13. Documentation

13.1 All processes and procedures which may affect the quality of the product must be recorded in the documentation for each batch. The following in particular must documented:
a. the location of cultivation and the name of the cultivator in charge;
b. details on crops previously grown at that location;
c. nature, origin and quantity of the herbal starting materials;
d. the chemicals and other substances used during cultivation, such as fertilisers, pesticides and herbicides;
e. standard cultivation conditions, if applicable;
f. particular circumstances which occurred during cultivation, harvesting and production which may affect the chemical composition, such as plant diseases or temporary departure from standard cultivation conditions, particularly during the harvesting period;
g. nature and quantity of the yield;
h. date or dates, and time or times of day when harvesting occurred;
i. drying conditions;
j. measures for pest control.

13.2 Analysis reports of soil analysis must be kept available in the dossier

13.3 Location

13.3.1 All batches originating from one location must be clearly labelled (e.g. with a batch number). This must be done as early on in the process as possible.

13.2.2 Batches originating from different geographic locations may only be combined if guaranteed to be the same, and that the mixture is homogenous. Mixing of batches must be documented.

13.3 It must be recorded in the documentation for each batch that the cultivation, harvest and primary processing procedures were in accordance with these requirements.

13.4 All parties involved in the production process must demand that their suppliers document all relevant stages and elements of the production process for each batch.

13.5 Audit results must be recorded in an audit report. The audit report and concomitant analysis reports and other documents must be kept for at least ten years.

14 Safeguarding the material

14.1 The buildings in which the cannabis is cultivated, processed, packaged and stored must be sufficiently secured. This means that there must be security in force and that only authorised personnel is allowed access to the buildings.

14.2 The personnel involved in the production process of cannabis must be authorised for that purpose by the employer. When concluding the supply contract, the supplier designates authorised persons and indicates how this will be verified.

14.3 There must be a balanced administration of the cannabis.

14.4 Waste must be stored in such a way that theft is impossible. If waste is collected in bags it must be stored in a lockable container (for instance a pressing container) immediately.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS Q7A

Recommended for Adoption

at Step 4 of the ICH Process

on 10 November 2000

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

This is Exhibit "E" referred to in the Affidavit of Catherine Sandvos sworn before me at the City of The Hague, the Netherlands this 20 day of January, 2015.

A Consular officer

28 JAN 2015

Liesbet Corriveau
Consular Officer / Agente Consulaire
The Hague

GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 10 November 2000, this guideline is recommended for adoption to the three regulatory parties to ICH

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GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS

1. INTRODUCTION

1.1 Objective

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this Guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This Guide is not intended to define registration/filing requirements or modify pharmacopoeial requirements. This Guide does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.

1.2 Regulatory Applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this Guide.

1.3 Scope

This Guide applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities.

This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18.

This Guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Guide.

In addition, the Guide does not apply to medical gases, bulk-packaged drug (medicinal) products, and manufacturing/control aspects specific to radiopharmaceuticals.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API Starting Material is normally introduced into the process.

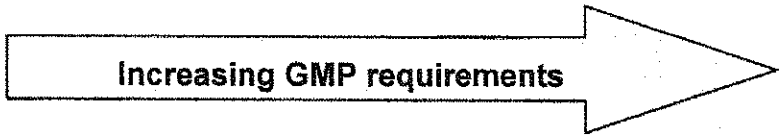
From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of this Guide.

This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material".

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



2. QUALITY MANAGEMENT

2.1 Principles

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

2.14 The persons authorised to release intermediates and APIs should be specified.

2.15 All quality related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).

2.2 Responsibilities of the Quality Unit(s)

2.20 The quality unit(s) should be involved in all quality-related matters.

2.21 The quality unit(s) should review and approve all appropriate quality-related documents.

2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
4. Making sure that critical deviations are investigated and resolved;
5. Approving all specifications and master production instructions;
6. Approving all procedures impacting the quality of intermediates or APIs;
7. Making sure that internal audits (self-inspections) are performed;

8. Approving intermediate and API contract manufacturers;
9. Approving changes that potentially impact intermediate or API quality;
10. Reviewing and approving validation protocols and reports;
11. Making sure that quality related complaints are investigated and resolved;
12. Making sure that effective systems are used for maintaining and calibrating critical equipment;
13. Making sure that materials are appropriately tested and the results are reported;
14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
15. Performing product quality reviews (as defined in Section 2.5).

2.3 Responsibility for Production Activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;
2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions;
3. Reviewing all production batch records and ensuring that these are completed and signed;
4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
5. Making sure that production facilities are clean and when appropriate disinfected;
6. Making sure that the necessary calibrations are performed and records kept;
7. Making sure that the premises and equipment are maintained and records kept;
8. Making sure that validation protocols and reports are reviewed and approved;
9. Evaluating proposed changes in product, process or equipment; and
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Internal Audits (Self Inspection)

2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results;
- A review of all batches that failed to meet established specification(s);
- A review of all critical deviations or non-conformances and related investigations;
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program;
- A review of all quality-related returns, complaints and recalls; and
- A review of adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. PERSONNEL

3.1 Personnel Qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. BUILDINGS AND FACILITIES

4.1 Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- Quarantine before release or rejection of intermediates and APIs;
- Sampling of intermediates and APIs;
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction);
- Storage of released materials;
- Production operations;
- Packaging and labelling operations; and
- Laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.5 Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

4.6 Sewage and Refuse

4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and Maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.

5. PROCESS EQUIPMENT

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment;
- Cleaning schedules, including, where appropriate, sanitizing schedules;
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- Instructions for the removal or obliteration of previous batch identification;
- Instructions for the protection of clean equipment from contamination prior to use;
- Inspection of equipment for cleanliness immediately before use, if practical; and
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized Systems

5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6. DOCUMENTATION AND RECORDS

6.1 Documentation System and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2 Equipment Cleaning and Use Record

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

6.30 Records should be maintained including:

- The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
- The results of any test or examination performed and the conclusions derived from this;
- Records tracing the use of materials;
- Documentation of the examination and review of API labelling and packaging materials for conformity with established specifications; and
- The final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable;
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
- The production location and major production equipment to be used;
- Detailed production instructions, including the:
  - sequences to be followed,
  - ranges of process parameters to be used,
  - sampling instructions and in-process controls with their acceptance criteria, where appropriate,
  - time limits for completion of individual processing steps and/or the total process, where appropriate; and
  - expected yield ranges at appropriate phases of processing or time;
- Where appropriate, special notations and precautions to be followed, or cross-references to these; and

- The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 Batch Production Records (Batch Production and Control Records)

6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times;
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used;
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
- Actual results recorded for critical process parameters;
- Any sampling performed;
- Signatures of the persons performing and directly supervising or checking each critical step in the operation;
- In-process and laboratory test results;
- Actual yield at appropriate phases or times;
- Description of packaging and label for intermediate or API;
- Representative label of API or intermediate if made commercially available;
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
- Results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;
- A statement of or reference to each test method used;
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
- A statement of the test results and how they compare with established acceptance criteria;
- The signature of the person who performed each test and the date(s) the tests were performed; and
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

6.61 Complete records should also be maintained for:

- Any modifications to an established analytical method;
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- All stability testing performed on APIs; and
- Out-of-specification (OOS) investigations.

6.7 Batch Production Record Review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. MATERIALS MANAGEMENT

7.1 General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

7.2 Receipt and Quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and Testing of Incoming Production Materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material

meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4 Storage

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

7.5 Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. PRODUCTION AND IN-PROCESS CONTROLS

8.1 Production Operations

8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code;
- Receiving or control number;
- Weight or measure of material in the new container; and
- Re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time Limits

8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process Sampling and Controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 Blending Batches of Intermediates or APIs

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

- Blending of small batches to increase batch size
- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination Control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

9.1 General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.

9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2 Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label Issuance and Control

9.30 Access to the label storage areas should be limited to authorised personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

9.33 Obsolete and out-dated labels should be destroyed.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and Labelling Operations

9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

9.41 Labelling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. STORAGE AND DISTRIBUTION

10.1 Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. LABORATORY CONTROLS

11.1 General Controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.

11.15 Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2 Testing of Intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.

11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3 Validation of Analytical Procedures - see Section 12.

11.4 Certificates of Analysis

11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.

11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.

11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5 Stability Monitoring of APIs

11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist

that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.

11.6 Expiry and Retest Dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reserve/Retention Samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

11.71 Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. VALIDATION

12.1 Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes;
- Identifying process parameters that could affect the critical quality attributes of the API;

- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation Documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

12.42 Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

12.44 An exception can be made for retrospective validation for well established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

(1) Critical quality attributes and critical process parameters have been identified;

(2) Appropriate in-process acceptance criteria and controls have been established;

(3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and

(4) Impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process Validation Program

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6 Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning Validation

12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

12.8 Validation of Analytical Methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. CHANGE CONTROL

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials, and computer software.

13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. REJECTION AND RE-USE OF MATERIALS

14.1 Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and over-reacted materials.

14.3 Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4 Recovery of Materials and Solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

15. COMPLAINTS AND RECALLS

15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

- Name and address of complainant;
- Name (and, where appropriate, title) and phone number of person submitting the complaint;
- Complaint nature (including name and batch number of the API);
- Date complaint is received;
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken;
- Response provided to the originator of complaint (including date response sent); and
- Final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS

17.1 Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or intermediate.

17.11 All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this Guide.

17.2 Traceability of Distributed APIs and Intermediates

17.20 Agents, brokers, traders, distributors, repackers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

17.3 Quality Management

17.30 Agents, brokers, traders, distributors, repackers, or relabellers should establish, document and implement an effective system of managing quality, as specified in Section 2.

17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

17.6 Transfer of Information

17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

17.61 The agent, broker, trader, distributor, repacker, or relabeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)

17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.

17.7 Handling of Complaints and Recalls

17.70 Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.8 Handling of Returns

17.80 Returns should be handled as specified in Section 14.52. The agents, brokers, traders, distributors, repackers, or relabellers should maintain documentation of returned APIs and intermediates.

18. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION

18.1 General

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology.The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and

the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

18.16 In general, process controls should take into account:

- Maintenance of the Working Cell Bank (where appropriate);
- Proper inoculation and expansion of the culture;
- Control of the critical operating parameters during fermentation/cell culture;
- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
- Viral safety concerns as described in ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.*

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell Bank Maintenance and Record Keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guideline Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

18.3 Cell Culture/Fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the

established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.37 Records of contamination events should be maintained.

18.38 Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4 Harvesting, Isolation and Purification

18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

18. 44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5 Viral Removal/Inactivation steps

18.50 See the ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing

should be performed in areas that are separate from other processing activities and have separate air handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

19. APIs FOR USE IN CLINICAL TRIALS

19.1 General

19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of Raw Materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7 Changes

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8 Laboratory Controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

20. GLOSSARY

Acceptance Criteria

Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Batch (or Lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number)

A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden

The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Computer System

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized System

A process or operation integrated with a computer system.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Contract Manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical

Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination

Contamination of a material or product with another material or product.

Deviation

Departure from an approved instruction or established standard.

Drug (Medicinal) Product

The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance

See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Impurity

Any component present in the intermediate or API that is not the desired entity.

Impurity Profile

A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot

See Batch

Lot Number

See Batch Number

Manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls.

Material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

Mother Liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

Packaging Material

Any material intended to protect an intermediate or API during storage and transport.

Procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

Process Control

See In-Process Control

Production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)

The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)

Checking or testing that specifications are met.

Quality Unit(s)

An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material

A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

Retest Date

The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed)

See definition for signed

Signed (signature)

The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

Regulation of the Minister of Health, Welfare and Sport of ____ November 2002, GMT/BMC 2340685, containing policy guidelines for the decision on applications for Opium Act exemptions (Policy guidelines Opium Act exemptions)

Reference

The Hague, the Netherlands

GMT/BMC 2340685

The Minister of *Volksgezondheid, Welzijn en Sport* [Health, Welfare and Sport],

The Minister of Health, Welfare and Sport

Decrees:

Adopts the following policy guidelines:

1. The Opium Act and Opium Act exemptions

The Opium Act makes it illegal to bring into and outside the territory of the Netherlands, grow, prepare, treat, process, sell, supply, provide, transport, possess and manufacture substances falling under the regime of List I or List II of the Act (Opium Act drugs). Only pharmacists, doctors, dentists and veterinary surgeons may perform certain acts with Opium Act drugs without an exemption within the normal practice of their professions.

Under Article 5, second paragraph, of the Opium Act, some institutions (for example, those providing care for addiction) may also perform certain acts with Opium Act drugs without an exemption insofar as they have been designated by an order in council. An Opium Act exemption is necessary, however, to conduct scientific research (for example, clinical trials). Under Article 6 of the Opium Act, the Minister of Health, Welfare and Sport may grant an application for an exemption to perform one or more acts with Opium Act drugs. In the light of Article 8 of the Opium Act, these exemptions may only be granted for certain purposes and to certain persons or institutions. These policy guidelines have been drawn up with a view to deciding applications for an Opium Act exemption. They further develop the criteria mentioned in the Act which will be applied in the decision on an application for an exemption. They also indicate the restrictions and conditions which may be attached to an exemption. The fees which are associated with obtaining an exemption are also mentioned.

2. Applying for Opium Act exemptions

A distinction is made between, on the one hand, applications for an Opium Act exemption regarding cannabis, cannabis resin or the preparations thereof and, on the other hand, other applications. Applications for an Opium Act exemption regarding cannabis, cannabis resin or the preparations thereof will be handled by the *Bureau voor Medicinale Cannabis (BMC)* [Office of Medicinal Cannabis],

which, since 1 January 2001, has been acting with the authority of a government agency within the meaning of Article 28 in conjunction with Article 23 of the Single Convention on Narcotic Drugs (1961).
To apply for an Opium Act exemption regarding cannabis, cannabis resin or the preparations thereof, a fully completed application form with the requested annexes needs to be sent in. An application form may be obtained from the Ministry of Health, Welfare and Sport, Office of Medicinal Cannabis of the *directie Geneesmiddelen en Medische Technologie (GMT)* [Department of Pharmaceutical Affairs and Medical Technology], Room A-1412, Postbus 20350, 2500 EJ The Hague.
To apply for an Opium Act exemption regarding other Opium Act drugs besides cannabis, cannabis resin or the preparations thereof, an application form may be obtained from the *CIBG* [Central Health Professions Information Centre], Pharmacy Technology Department, Room M-0306, Postbus 16114, 2500 BC The Hague.
If applications are made both regarding cannabis, cannabis resin or the preparations thereof as well as regarding other Opium Act drugs, these will be considered two separate applications, to be handled separately. If granted in such a case, separate Opium Act exemptions will be issued.

3. Purposes for which an Opium Act exemption may be granted
Article 8 of the Opium Act states when an exemption may be granted. This is possible if the applicant has demonstrated:

a. that this will serve the interest of public health or that of the health of animals (article 8, first paragraph, under a);
b. that he needs the exemption to perform scientific or analytical chemical research or for instructional purposes, insofar as the interest of public health does not dictate otherwise (article 8, first paragraph, under b), or
c. that he needs the exemption to bring into or outside the territory of the Netherlands, grow, prepare, treat, process, sell, supply, provide, transport, possess and manufacture Opium Act drugs, and he has an agreement with:
   1. another person who has an exemption;
   2. a pharmacist or a doctor operating a pharmacy;
   3. a veterinary surgeon;
   4. a designated institution or person;
   5. a holder of an exemption granted in another country to import the drugs in question into that country, insofar as the interest of public health does not dictate otherwise (article 8, first paragraph, under c)

An exemption may also be granted if the applicant needs this to grow cannabis pursuant to an agreement with the Minister of Health, Welfare and Sport (see under Point 6).
Of course, the purpose indicated may never be contrary to other laws, regulations or policy guidelines.

4. Criteria attached to the aforementioned purposes
The criteria which will be applied in the decision on an application for an exemption are the following.

Re: 4, under a.
Generally speaking, Opium Act exemptions in the interest of public health or of the health of animals will fall under the general exemption for, for example, doctors, veterinary surgeons, pharmacists or special institutions. Applications for acts with Opium Act drugs may also be filed, however, which do

not fall under this exemption, but are nevertheless deemed to be in the interest of public health or that of the health of animals. In that case, an exemption may be granted under this category.

Re: 4, under b.
With regard to an application for an Opium Act exemption to perform scientific or analytical chemical research or for instructional purposes, the necessity of the permit must be demonstrated. In principle, if there are alternative options – that is, the purpose may reasonably be achieved without using Opium Act drugs -, necessity has not been demonstrated.
With regard to an application to perform scientific or analytical chemical research, the purpose must be supported in a scientific manner (for example, through a scientific research protocol for a clinical study or for improving plants).
If applicable, various quality requirements, such as GMP, GLP, GCP or GCLP, or various certification standards (for example, ISO and NEN) must be met. If these cannot be met (or not yet), this has to be supported. If experimental subjects will be involved in the research, a statement must be submitted showing that the experimental design has been reviewed favourably by a competent medical-ethical commission.
A standardised preparation (standardised, for example, regarding one or more of the substances contained) must be used. It must be indicated how the preparation will be prepared and from whom this preparation will be purchased.

The following distinction will apply to applications for instructional purposes:
1. Training dogs to detect narcotics
   Opium Act exemptions to train dogs to detect narcotics will only be granted for detection of narcotics in the Netherlands. Only the police and customs are authorised to engage in these detection activities. They train dogs internally in this regard.
2. Other instructional purposes.

Re: 4, under c.
The commercially-related purposes have been included under c. This provision pertains to, for example, natural or legal persons that trade in Opium Act drugs as a fixed business activity (such as for production or distribution) or to natural or legal persons that wish to conclude a once-only contract to supply an Opium Act drug. Under c, there is a list of those with whom such a contract may be concluded. The possibility is created under 1 to grant exemptions for mutual trade, for example, between traders and researchers. Under 5, the Convention requirement is implemented that an export exemption may only be granted if this is to supply someone in a foreign country who already has an import permit for that country.

5. Growing cannabis
An exemption is necessary under the Opium Act to grow cannabis. BMC is the institution which grants all exemptions regarding cannabis on the Minister's behalf. BMC, which, since 1 January 2001, has been acting as a government agency within the meaning of the Single Convention on Narcotic Drugs, has a monopoly with regard to the import and export of, wholesale trade in, and maintenance of stocks of cannabis and cannabis resin, and must purchase all crops and actually seize these.
BMC's task is two-fold. On the one hand, BMC must research or arrange for research regarding whether cannabis or cannabis products may be used as medicines; on the other hand, BMC must provide pharmacies in the course of 2003 with medicinal cannabis, so that patients can obtain this with a doctor's prescription.
For the first task, developing a medicine, clinical research is not only necessary, but also scientific research into the plant cannabis and into the production process. In the case of scientific research, not

only must the criteria referred to in article 8, first paragraph, under b, of the Opium Act, be met, it must also be demonstrated that the research serves a need, given the state of the art.
For the second task, supplying pharmacies, a small number of growers will be approached. In deciding on exemption applications regarding cannabis under Article 8, second paragraph, of the Opium Act, BMC will apply the following criteria. In that case, Article 8i, first paragraph, will be applicable: an exemption will only be granted if BMC concludes a contract to grow and supply cannabis. Thus, growers directly supplying the market will not be granted an exemption to grow cannabis.
In connection with administrative prevention of crime, applicants may be subjected to a security screening, which will include a request to submit administrative and financial data through annual reports with explanations and a so-called Declaration concerning the conduct of the applicant or – in the case of legal persons – of the legal person's directors and actual managers. For a proper evaluation, additional information will have to be provided on request regarding the data supplied. Once the Public Administration Probity in Decision-making Act (the BIBOB Act) has taken effect, probity screening within the meaning of that Act can constitute part of the screening.
If growers apply for an exemption, extensive screening of the applicant will be part of the procedure. In some cases, the Office of Medicinal Cannabis may decide to forego the screening if an application from an institution is involved whose trustworthiness may be assumed beforehand. If necessary, other natural or legal persons involved in the application or in growing the cannabis will be screened as well. This will enable the Office of Medicinal Cannabis to make the risk of cannabis and other Opium Act drugs disappearing to illegal markets as small as possible. The purpose of the screening is to limit the Minister's political risk as much as possible.
All applicants must meet special requirements relating to security around the cannabis, for example, regarding transport and storage. These requirements will be determined on a case-by-case basis and will be recorded contractually.
In addition, BMC will impose special requirements for prospective growers in terms of quality. Hence, the cannabis to be supplied must be produced according to the Regulations for Cultivating Cannabis for Medicinal Purposes (annex), or requirements which are equivalent in BMC's judgment. The Regulations are derived from the Points to Consider on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (EMEA/HMPWP/31/99 rev. 2) of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency (EMEA). The regulations help ensure that the product's quality is consistent. Depending on the further treatment, the product must also meet other specifications. For example, the production method must guarantee that the product contains a consistent level of active substances.
The prospective grower must also have a quality file for the product. The product characteristics must be carefully recorded in that file. It must include a description of what the growing conditions are (for example, intensity of light, temperature, dampness and fertilisation), what the specifications are of the product grown under these conditions and how there can be monitoring that the product meets these specifications. These requirements regarding composition and the possibility of monitoring are conditions for being able to develop a reproducible medicine. In addition, a prospective grower must be able to demonstrate that he is able to deliver such a standardised product within a reasonable time.
In the event that they are equally suitable, not all prospective growers will obtain an exemption. BMC will compare the growers' offers with each other, with aspects such as the degree to which the requested specifications can be met and the most favourable delivery terms and conditions being decisive, as well as the security which may be provided that none of the cannabis will end up in illegal circuits.

6. Restrictions and conditions in granting an Opium Act exemption

An exemption may be granted which is subject to restrictions. Moreover, conditions may be attached to an exemption. The restrictions and conditions will depend on the nature of the application and may

differ in each case. Each Opium Act exemption will include restrictions and conditions regarding the number and type of Opium Act drugs to which the exemption relates, the acts which may be performed, the purpose for which the exemption has been requested, adequate security regarding the Opium Act drugs present, proper records, cooperation with the Health Inspector in monitoring compliance with the exemption and the duration of the exemption.
Additional restrictions and conditions will apply to cannabis growers. For example, growers will be required to sell their entire harvest to BMC. This will be verified by comparing the size of the harvest with the size of the built-up land, the number of plants and through other monitoring measures. This will be further fleshed out in a contract that BMC will conclude with the growers concerned. Another condition that will be imposed on the exemption is that the unnecessary crops be destroyed.
The *Inspectie voor de Gezondheidszorg* [Health Care Inspectorate] will make visits to growers who have received an exemption in connection with monitoring the conditions imposed on the exemption. BMC employees will also visit companies to ensure that there is compliance with the agreed contract terms and conditions.

7. Provisions regarding the exemption for import and export

7.1 Generally

With regard to bringing Opium Act drugs into or outside the territory of the Netherlands (Article 2, under A, and 3, under A, of the Opium Act), an import or export exemption is required. Applications for an import or export exemption will be handled by a special inspector of the Health Care Inspectorate. This inspector will have authority to act for the Minister of Health, Welfare and Sport.
In handling applications for an import and export Opium Act exemption, a distinction will be made between an application regarding an Opium Act drug from List I (Article 2 of the Opium Act) and an application regarding an Opium Act drug from List II (Article 3 of the Opium Act). An exemption will always relate to drugs from either List I or List II; a combined exemption will not be possible. This means that the fee referred to under Point 10 of these policy guidelines will be charged per exemption.
An exemption will apply solely to a particular lot or lots of Opium Act drugs as described in the application. The import or export act must be completed within six months after the exemption is granted; if this is not the case, a new exemption will have to be requested.
Applications for an exemption to bring Opium Act drugs into or outside the territory of the Netherlands must be directed to: Health Care Inspectorate, Opium Act Matters Section, Postbus16119, 2500 BC The Hague.

7.2 Data to be provided in connection with import

If the exemption is intended to bring Opium Act drugs into the territory of the Netherlands, the following data must be provided:

- for each drug to be brought into the territory of the Netherlands, the name, the quantity and its pharmaceutical form; if the drug to be imported concerns a preparation with a special name, that name must also be stated;
- for each drug to be brought into the territory of the Netherlands that comes from a country requiring an export document for the export, a copy of that document;
- name and address of the person, including legal persons, outside the Netherlands from whom the drug or drugs will be purchased;
- the time period within which the drug or drugs will be brought into the territory of the Netherlands;
- a statement of the type of transport by which the drug or drugs will be transported to the Netherlands.

7.3 Data to be provided in connection with export

If the exemption is intended to bring Opium Act drugs outside the territory of the Netherlands, the following data must be provided:

- for each drug to be brought outside the territory of the Netherlands, the name, the quantity and its pharmaceutical form; if the drug to be exported concerns a preparation with a special name, that name must also be stated;
- a document issued by the competent government agency in the country to which the drug is to be exported, to the effect that the drug may be imported there;
- name and address of the person, including legal persons, or the government agency outside the Netherlands which will purchase the drug or drugs from the applicant;
- -the statement "export to customs warehouse", in the event that storage in a customs warehouse in the country of destination has been approved, as evidenced by a declaration placed on the import document by the competent government agency in the country of destination;
- the time period within which the drug or drugs will be brought outside the territory of the Netherlands;
- a statement of the type of transport by which the drug or drugs will be brought to the country of destination.

8. Varying provisions regarding the exemption for import and export of cannabis and cannabis resin

Varying provisions will apply for the import and export of cannabis and cannabis resin (Article 3, under A). Under Article 8i, fifth paragraph, under a, only the Minister of Health, Welfare and Sport has authority to import and export. This provision means that a person wishing to import or export cannabis or cannabis resin must enter into an import or export agreement with the Office of Medicinal Cannabis, acting on the authority of the Minister. To enter into an import or export agreement with the Office of Medicinal Cannabis, the data mentioned in Section 8.2 or 8.3 must be provided. In connection with this agreement, the fee owed for the import or export (see Point 11) will be passed on. In practice, the person wishing to import or export will already have an Opium Act exemption from the prohibitions of Article 3, under B to D inclusive: preparation, processing, treatment, provision, transport, possession, manufacturing. In such cases no in-depth screening will be conducted.

9. Denial or revocation of Opium Act exemption

An exemption may be denied or revoked. The reasons for denial or revocation are listed in Articles 8b to 8e inclusive of the Opium Act.

10. Fees

Fees will be set by ministerial regulation, the Opium Act Implementation Regulations. The point of departure in calculating the fees incurred to obtain an Opium Act exemption is that the user pays. These fees will be subject to change if the costs related to granting the exemption change. At the time these policy guidelines take effect, a fee of EUR 1225 will be charged to process an application for an exemption or a modification, supplementation or extension thereof, and an annual fee of EUR 350 will be charged during the term of the exemption. In deviation from the foregoing, in the case of an exemption for bringing a drug into or outside the territory of the Netherlands, a fee of EUR 40 will be charged to process an exemption application.

11. Final provision

These policy guidelines shall be cited as: Policy guidelines Opium Act exemptions. These policy guidelines will take effect at the same time that the Act amending the Opium Act (Act of 13 July 2002, *Stb.* [Bulletin of Acts and Decrees] 2002, 520) takes effect.

12. Repeal of earlier policy guidelines

The policy guidelines of 11 May 1998, *Stcrt.* [Government Gazette] 1998, 92, amended on 18 May 2001, Stcrt. 2002, 96 and on 6 December 2001, Stcrt. 2002, 237, are repealed.

The Minister of Health, Welfare and Sport

A.J. De Geus

Annex: Regulations for Cultivating Cannabis for Medicinal Purposes

Analytical Monograph Cannabis Flos (hempflowers)

OMC / Farmalyse BV Version 7.0 / October 31, 2013

Release Testing of Cannabis Flos

Introduction

This monograph describes the release testing of Cannabis Flos (hemp flowers), specifically the varieties: Bedrocan, Bedrobinol, Bediol, Bedica, Bedrolite and Bedropuur. The test parameters are:

1. Appearance
2. Foreign Material
3. Fineness
4. Identification A: Microscopic Properties
5. Identification B: TLC
6. Microbiological Contamination
7. Aflatoxins
8. Pesticides
9. Heavy Metals
10. Loss On Drying
11. Assay and Related Substances

Sample Preparation

The ungrinded sample will be used for test numbers 1, 2, 3, 6 and 7. The remaining sample will be grinded using a simple kitchen blender until the material is about 5 mm in diameter, homogenised and subsequently used for the remaining tests. Please note that that the LOD test has to be carried out on the same day as the samples for the test Assay and Related Substances are prepared.

List of Abbreviations

Δ9-THC:	Δ9-Tetrahydrocannabinol
Δ8-THC:	Δ8-Tetrahydrocannabinol
THCA:	Tetrahydrocannabinol Acid
CBD:	Cannabidiol
CBDA:	Cannabidiol Acid
CBG:	Cannabigerol
CBN:	Cannabinol
cm:	centimeter
EP:	European Pharmacopoeia
ICP-OES:	Inductively Coupled Plasma – Optical Emission Spectroscopy
LLOQ:	Lower Limit Of Quantitation
LOD:	Loss On Drying
mg:	milligram
min.:	minute(s)
mL:	milliliter
mm:	millimeter
µL:	microliter
NLT:	Not Less Than
NMT:	Not More Than
PTFE:	Poly Tetra Fluoro Ethylene
RF:	Response Factor
rpm:	rotations per minute
RRT:	Relative Retention Time
RSD:	Relative Standard Deviation
S/N:	Signal-to-Noise ratio
SST:	System Suitability Test
TAMC:	Total Aerobic Microbial Count
TYMC:	Total Yeast and Molds Count
TBA:	2-t-Butyl-Anthraquinone
TLC:	Thin Layer Chromatography
v/v:	volume / volume

Analytical Monograph Cannabis Flos (hempflowers)

OMC / Farmalyse BV Version 7.0 / October 31, 2013

Release Testing of Cannabis Flos

1. Appearance

Bedrocan, Bedrobinol, Bedropuur:	Brown green clustered flowers of 1.5 to 3 cm length with a characteristic smell.
Bediol,Bedica and Bedrolite:	Brown green granulate of the flowers (about 5 mm) having a characteristic smell.

2. Foreign Material

Bedrocan, Bedrobinol, Bedropuur:	The sample material is free from stalks, insects and other vermin.
Bediol,Bedica and Bedrolite:	The sample material is free from insects and other vermin.

3. Fineness

Bedrocan, Bedrobinol, Bedropuur:	Macroscopic inspection of the ungrinded material does not show leaves shooting out more than 20% of the length of the flowers. Moreover, the stalks are cut away directly under the bottom flowers of the inflorescence.
Bediol,Bedica and Bedrolite:	Stalks are not longer than 2.0 cm and only 20% of the stalks is between 1.5 and 2.0 cm.

4. Identification A: Microscopic Properties

4.1 Reagents

Chloral hydrate solution: A solution of 80 grams Chloral hydrate in 20 mL Demi water.

4.2 Execution

Prepare a Chloral hydrate preparation by adding a few drops of the Chloral hydrate solution to a spatula tip of plant material and shortly cooking it on a little flame. Under the microscope gland hairs are mainly observed.

5. Identification B: TLC

5.1 Reagents

Petroleum ether (40-60 fraction)
Diethyl ether
Fast Blue B Salt (stabilised with Zinc chloride); CAS number: 14263-94-6
Ethanol (absolute)
Methanol
Bedrocan reference extract
Bedrobinol reference extract
Bediol reference extract
Bedica reference extract
Bedrolite reference extract
Bedropuur reference extract

Analytical Monograph Cannabis Flos (hempflowers)

OMC / Farmalyse BV Version 7.0 / October 31, 2013

Release Testing of Cannabis Flos

5.2 Execution

TLC-plate:	Silicagel F_{254} (Merck art. nr. 5715)
Eluent:	Petroleum ether : Diethyl ether = 40 : 10 (v/v). Saturate the TLC chamber.
Travel distance of solvent front:	10 cm.
Spray agent:	A solution of 1 gram Fast Blue B Salt in a mixture of 50% Ethanol in Demi water.

System Suitability
Use the Bediol reference extract for the SST.

Analysis
Sample solution A:
Use Sample solution 1A from the test "Assay and Related Substances" (see Section 11).

Standard solution A:
Use the reference extract that matches the variety to be analysed in the test "Assay and Related Substances" (see Section 11).

Apply 10 µL of the sample solution and standard solution to the TLC plaat in a band of max. 5 mm width. Place the plate in the TLC chamber containing eluent and let the solvent front develop about 10 cm. Dry the plate in the air, apply spraying agent and if necessary warm the plate with a laboratory heater to enhance the visibility of the spots. Observe the plate in normal light.

Assessment of the plate
Bedrocan, Bedrobinol, Bedica and Bedropuur:
The main spot in Sample solution A is coloured red (THCA) and has an RF value and intensity equal to those of the corresponding reference extract. The chromatogram of Sample solution A may show a red-violet zone corresponding to Δ^9-THC.

Bedrolite:
The main spot in Sample solution A is coloured orange (CBDA) and has an RF value and intensity equal to those of the corresponding reference extract.

Bediol:
In addition to the spots mentioned before, an orange coloured spot is observed corresponding with the spot from the reference extract of Bediol (CBDA).

Location of the spots:

Top of the plate	
Orange zone (CBD) Red-violet zone (Δ^9-THC) Red zone (THCA) Orange zone (CBDA)	 Red zone (THCA) Orange zone (CBDA)
Standard solutions	Sample solution A

6. Microbiological Contamination

These tests are executed on 10 grams ungrinded material. The material that has not undergone germ reducing treatment is tested for:

- TAMC
- TYMC
- Total combined count (TAMC + TYMC)

Release Testing of Cannabis Flos

- Enterobacteriaceae and gram negative bacteria
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*

7. Aflatoxins

This test is executed on 5.0 grams ungrinded material. The analysis is according to the current EP monograph "Determination of aflatoxins B_1, B_2, G_1 and G_2 in herbal drugs (2.8.18)". The specification is NMT 4 µg per kg.

8. Pesticides

Pesticides are tested according to EP monograph 2.8.13.

It should be noted that not all EP Pesticides are being analysed with the GC-MS method. For that reason the following text is added to the CoA: "The following components are not being analysed with the current method: Bromide inorganic, Dithiocarbamates, Fenchlorophos, Methacriphos, S-421".

9. Heavy metals

This test is executed on 5 grams grinded material using different atomic absorption and emission techniques.

Lead:	max. 20.0 ppm	(ICP-OES)
Cadmium:	max. 0.5 ppm	(ICP-OES)
Mercury:	max. 0.5 ppm	(Combustion Atomic Absorption)
Arsenic:	Indicative	(ICP-OES)
Nickel:	Indicative	(ICP-OES)
Zinc:	Indicative	(ICP-OES)

10. Loss on drying

This test is executed on 0.500 gram of the grinded sample material using EP monograph 2.3.32 method C. It is heated during 24 hours at 40°C above Phosphorous Pentoxide under vacuum. The specification is: NMT 10.0%.

11. Assay and Related Substances

11.1 Reagents

Ethanol (absolute)
Acetonitrile
Formic Acid
Milli-Q Water

11.2 Equipment

UPLC-column:	Waters Aquity C18, 1.7 µm, 2.1 x 150 mm
Column temperature:	30 °C
Tray temperature:	8 °C
Mobile phase:	0.1 % Formic Acid in Acetonitrile (A)
	0.1 % Formic Acid in Milli-Q Water (B)
Solvent / Needle wash:	A : B = 70 : 30 (v/v)
Centrifuge:	Eppendorf, Model 5810 (or equivalent)

Release Testing of Cannabis Flos

Gradient:	t (min.)	A (%)	B (%)
	0	70	30
	6.00	70	30
	10.50	100	0
	10.70	100	0
	11.00	70	30
	12.50	70	30
Flow:	0.4 mL / min.		
Injection volume:	10 µL		
Detection (UV):	228 nm		
Run time:	12.5 min.		

11.3 Execution

Sample Solutions (fresh material)

Weigh 1000 mg of the grinded sample material in a "Falcon tube" and shake (ca. 300 rpm) during 15 minutes with 40 mL Ethanol and centrifuge (3000 rpm). Transfer the clear upper layer into a 100 mL volumetric flask. Repeat this step two times with 25 mL Ethanol and make up the solution to the mark with Ethanol. Filter the Sample solution over a 0.45 µm PTFE filter. Pipet 1.0 mL of the filtrate in a volumetric flask of 10 mL and make up to volume with Solvent (*Sample Solutions 1A M1 and 1A M2*). Dilute Sample Solution 1A a factor 10 with Solvent (*Sample Solutions 1B M1 and 1B M2*).

Standard Solutions

Weigh accurately about 50 mg TBA standard in a volumetric flask of 100 mL, add 25 mL Solvent and dissolve. Make up to volume with Solvent. Dilute 1.0 mL to 50.0 mL with Solvent (S1+S2; 0.01 mg / mL).

LLOQ Solution

Dilute the Standard Solution TBA with a concentration of 0.01 mg / mL to a concentration of 0.002 mg / mL by pipetting 5.0 mL of the Standard Solution TBA in a volumetric flask of 25.0 mL and make up to volume with Solvent.

Resolution Solution

Dilute 200 µL Δ9-THC Stock Standard Solution (*i.e.* 2 mg / mL Δ9-THC in Ethanol) and 1000 µL Δ8-THC Stock Standard Solution (*i.e.* 0.0249 mg / mL Δ8-THC in Ethanol) in a volumetric flask of 10 mL and make up to volume with Solvent.

Reference Extract Solution

It should be noted that each variety has its own reference extract.
Prepare a dilution (factor 5) from the reference extract by pipetting 50 µL of the reference extract (corresponding to the sample) in a vial with insert and dilute with 200 µL Solvent.

Injection Sequence

Prepare the following injection sequence:

Release Testing of Cannabis Flos

Injection Nr	Vial content	Purpose
1	Blanc Solution	SST
2	LLOQ Solution	SST
3	Resolution Solution	SST (Resolution)
4	Standard Solution S1 – Injection 1	SST (RSD)
5	Standard Solution S1 – Injection 2	SST (RSD)
6	Standard Solution S1 – Injection 3	SST (RSD)
7	Standard Solution S1 – Injection 4	SST (RSD)
8	Standard Solution S1 – Injection 5	SST (RSD)
9	Standard Solution S1 – Injection 6	SST (RSD)
10	Standard Solution S2 – Injection 1	SST (Recovery)
11	Standard Solution S2 – Injection 2	SST (Recovery)
12	Reference Extract Solution	Check Sample against Reference
13	Sample Solution 1A M1	Assay & Related Substances
14	Sample Solution 1A M1	Assay & Related Substances
15	Sample Solution 1A M1	Assay & Related Substances
16	Sample Solution 1A M1	Assay & Related Substances
17	Standard Solution S1 – Injection 1	Check for drift of Std during analysis

11.4 System Suitability Test

- The RSD of 6 replicate injections of Standard Solution S1 (peak area TBA) is ≤ 2.0%;
- Standard Solution S2 has a Recovery of 98.0% to 102.0% when calculated against Standard Solution S1;
- The Resolution between the peaks of Δ9-THC en Δ8-THC in de Resolution Solution should be ≥ 1.2;
- The TBA peak in the LLOQ Solution has a S/N value of ≥ 10;
- The chromatographic profile of Sample Solution 1A must resemble that of the corresponding Reference Extract.

11.5 Calculation Assay THCA (and CBDA in Bediol and Bedrolite)

Sample solutions 1B M1 and 1B M2 are used to calculate the total content of THCA on dried sample material according to the formula displayed below. See Table 1 for the corresponding Response Factors. When testing the varieties Bediol and Bedrolite, also the total content of CBDA has to be calculated.

$$\text{THCA (\%)} = 100 \times \frac{\text{Am} \times \text{Vm} \times \text{Ws} \times \text{Vf}}{\text{Rf} \times \text{As} \times \text{Vs} \times \text{Wm}} \times \frac{100}{(100 - LOD)}$$

$$\text{THC total equivalents (\%)} = \%\text{THCA} \times 0.877 + \%\text{THC}$$

In which:

Am_{1B}:	Area of Sample (for Assay)
Am_{1A}:	Area of Sample (for Related Substances)
Vm:	Volume of Sample (mL)

Release Testing of Cannabis Flos	
Ws:	Weight of TBA reference standard (mg)
RF:	Response Factor against TBA (see Table 1)
As:	Area of TBA reference standard
Vs:	Volume of TBA reference standard (mL)
Wm:	Weight of Sample (mg)
Vf:	Dilution factor (10 or 100)
LOD:	Loss On Drying (see Section 10)
0.877:	Factor for the conversion of the Molecular Weights and for compensating for the loss of CO_2 as a result of decarboxylation

11.6 Calculation of Related Substances

Calculate the total of Related Substances (CBN?) from Sample Solution 1A M1 and 1A M2 on dried basis using the example calculation shown above. See Table 1 for the corresponding Response Factors.

Concentrations less than 0.05% shall be reported as NMT 0.05%.

Table 1: RRTs and RFs for UPLC.

Component	RRT	RF
CBDA	0.78	1.91
CBD	0.92	1.00
TBA	1.00	1.00
CBN	1.43	2.30
THC	1.62	0.91
CBNA	1.67	1.50
THCA	1.82	1.66

12. Literature

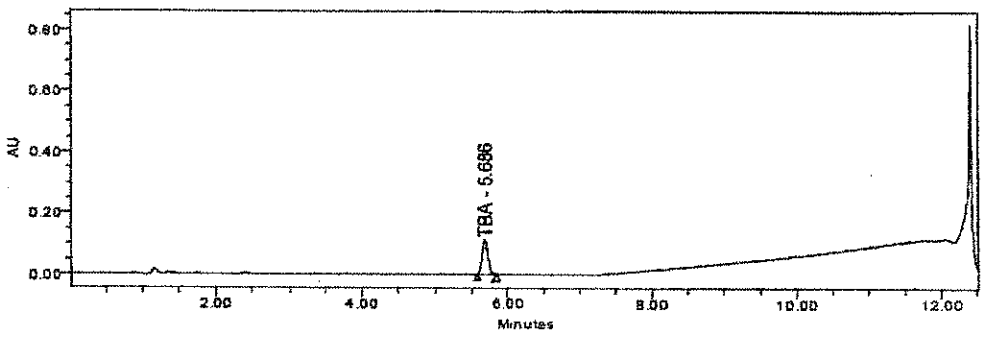
1. Monograph "BMC/Farmalyse ter vrijgiftecontrole van Cannabis Flos (Hennepbloemen); variëteiten Bedrocan, Bedrobinol en Bediol; versie 7.0." (in Dutch).
2. EP 01/2012:1433 Herbal drugs; for the tests LOD and Heavy Metals.
3. "Validatie gehaltebepaling m.b.v. UPLC uitgevoerd door Farmalyse" (rapport UPLC-0512-1); in Dutch.
4. "Pesticiden: Validatie uitgevoerd door *TNO Voeding* met als referentie ASC-2004/0941rev1-mol."; in Dutch.
5. Validation of the analytical method for the determination of the Cannabis Flos variety Bedica and the determination of the response factors of the cannabinoids Δ9-THC, CBD, CBN, THCA, CBDA and CBNA. VWS 2012-013 *version 2* April 18, 2013.
6. Determination of the Cannabis Flos varieties Bedrocan and Bedica on the Thermo (U)HPLC at Farmalyse B.V. VWS, September 2013.

Analytical Monograph Cannabis Flos (hempflowers)

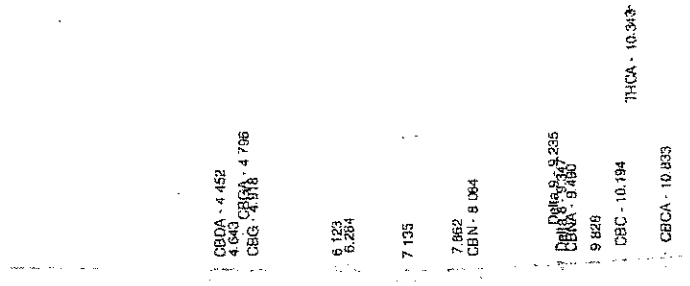
OMC / Farmalyse BV Version 7.0 / October 31, 2013

Release Testing of Cannabis Flos

Annex
This annex contains various example chromatograms.



Chromatogram of Standard Solution

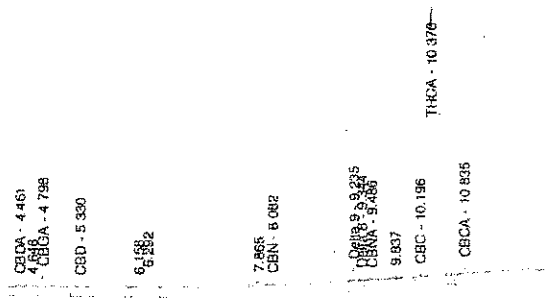


Chromatogram of Reference Extract Bedrocan

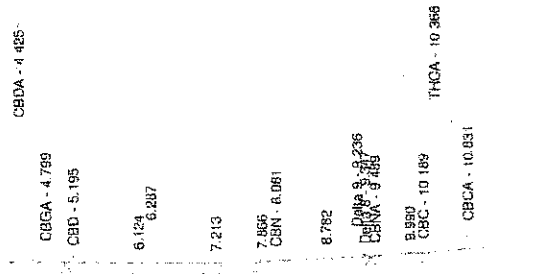
Analytical Monograph Cannabis Flos (hempflowers)

OMC / Farmalyse BV Version 7.0 / October 31, 2013

Release Testing of Cannabis Flos



Chromatogram of Reference Extract Bedrobinol



Chromatogram of Reference Extract Bediol

Specification sheet

(version: August 2014)

Product: **Cannabis flos,** ssp. sativa**, variety Bedrocan** (hemp flowers)
Market: to be sold on the pharmaceutical market
Strength: dronabinol: approx. 22% cannabidiol: <1.0%
Dosage form: flowers
Package size: 5 grams in containers, 250 grams in bags

	Method	**Specification**
Appearance	Monograph[1]	Brown green clustered flowers of 1,5 to 3 cm with a characteristic smell
Identity		
microscopy	Monograph	Mainly gland hairs visible
thin layer chromatography	Monograph	Monograph
Foreign material	Monograph	Stalks, insects and other vermin are absent
Fineness	Monograph	• no leaves shooting out more then 20% of the length of the flowers • stalks are cut away directly under the bottom flowers of the inflorescence
Absence of pesticides	Monograph	Ph. Eur (current ed.) 2.8.13
Microbiological purity	Ph. Eur (current ed.) 5.1.4.	
Total aerobic microbial count (TAMC)	5.1.4.-1.	≤ 10^2 cfu/gram
Total yeast and moulds count (TYMC)	5.1.4.-1.	≤ 10 cfu/gram

[1] Analytical monograph by BMC / Farmalyse, version 7.0 of October, 2013

	Method	Specification
P. aeruginosa, S. aureus and Bile tolerant gram neg bacteria	5.1.4.-1.	Absent
Absence of heavy metals		
lead	Ph. Eur (current ed.) "Heavy metals in herbal drugs and fatty oils" (monograph)	max. 20.0 ppm
mercury		max. 0.5 ppm
cadmium		max. 0.5 ppm
arsenic (indicative)		-
nickel (indicative)		-
zinc (indicative)		-
Absence of aflatoxines	Ph. Eur (current ed.) "Determination of aflatoxins B_1, B_2, G_1 and G_2 in herbal drugs" (2.8.18)	<4 µg/kg
Loss on drying	Ph. Eur (current ed.) "Loss on drying" meth. C (2.2.32)	≤10.0 %
Assay (UPLC)		
fingerprint	Monograph	similar
dronabinol (THC)	Monograph	approx. 22 %
cannabidiol (CBD)	Monograph	<1.0 %
Related substances (UPLC)		
cannabinol (CBN)	Monograph	<1.0 %

Specification sheet

(version: August 2014)

Product: **Cannabis flos,** ssp. sativa, **variety Bedrobinol** (hemp flowers)
Market: to be sold on the pharmaceutical market
Strength: dronabinol: approx. 13.5% cannabidiol: <1.0%
Dosage form: flowers
Package size: 5 grams in containers

	Method	**Specification**
Appearance	Monograph[2]	Brown green clustered flowers of 1,5 to 3 cm with a characteristic smell
Identity		
microscopy	Monograph	Mainly gland hairs visible
thin layer chromatography	Monograph	Monograph
Foreign material	Monograph	Stalks, insects and other vermin are absent
Fineness	Monograph	• no leaves shooting out more then 20% of the length of the flowers • stalks are cut away directly under the bottom flowers of the inflorescence
Absence of pesticides	Monograph	Ph. Eur (current ed.) 2.8.13
Microbiological purity	Ph. Eur (current ed.) 5.1.4.	
Total aerobic microbial count (TAMC)	5.1.4.-1.	≤ 10^2 cfu/gram
Total yeast and moulds count (TYMC)	5.1.4.-1.	≤ 10 cfu/gram

[2] Analytical monograph by BMC / Farmalyse, version 7.0 of October, 2013

	Method	Specification
P. aeruginosa, S. aureus and Bile tolerant gram neg bacteria	5.1.4.-1.	Absent
Absence of heavy metals		
lead	Ph. Eur (current ed.) "Heavy metals in herbal drugs and fatty oils" (monograph)	max. 20.0 ppm
mercury		max. 0.5 ppm
cadmium		max. 0.5 ppm
arsenic (indicative)		-
nickel (indicative)		-
ninc (indicative)		-
Absence of aflatoxines	Ph. Eur (current ed.) "Determination of aflatoxins B_1, B_2, G_1 and G_2 in herbal drugs" (2.8.18)	<4 µg/kg
Loss on drying	Ph. Eur (current ed.) "Loss on drying" meth. C (2.2.32)	≤10.0 %
Assay (UPLC)		
fingerprint	Monograph	Similar
dronabinol (THC)	Monograph	approx. 13.5 %
cannabidiol (CBD)	Monograph	<1.0 %
Related substances (UPLC)		
cannabinol (CBN)	Monograph	<1.0 %

Specification sheet

(version: August 2014)

Product: **Cannabis flos**, ssp. sativa, **variety Bediol** (hemp flowers)
Market: to be sold on the pharmaceutical market
Strength: dronabinol: approx. 6.3% cannabidiol: approx. 8%
Dosage form: flowers, granulated
Package size: 5 grams in containers, 50 grams in bags

	Method	**Specification**
Appearance	Monograph[3]	Brown green granulated material of the flowers (about 5 mm) with a characteristic smell
Identity		
microscopy	Monograph	Mainly gland hairs visible
thin layer chromatography	Monograph	Monograph
Foreign material	Monograph	Insects and other vermin are absent
Fineness	Monograph	Stalks are not longer than 2.0 cm Only 20% of the stalks is between 1.5 and 2.0 cm
Absence of pesticides	Monograph	Ph. Eur (current ed.) 2.8.13
Microbiological purity	Ph. Eur (current ed.) 5.1.4.	
Total aerobic microbial count (TAMC)	5.1.4.-1.	≤ 10^2 cfu/gram
Total yeast and moulds count (TYMC)	5.1.4.-1.	≤ 10 cfu/gram
P. aeruginosa, S. aureus and Bile tolerant gram neg bacteria	5.1.4.-1.	Absent

[3] Analytical monograph by BMC / Farmalyse, version 7.0 of October, 2013

	Method	Specification
Absence of heavy metals		
lead	Ph. Eur (current ed.) "Heavy metals in herbal drugs and fatty oils" (monograph)	max. 20.0 ppm
mercury		max. 0.5 ppm
cadmium		max. 0.5 ppm
arsenic (indicative)		-
nickel (indicative)		-
zinc (indicative)		-
Absence of aflatoxines	Ph. Eur (current ed.) "Determination of aflatoxins B_1, B_2, G_1 and G_2 in herbal drugs" (2.8.18)	<4 µg/kg
Loss on drying	Ph. Eur (current ed.) "Loss on drying" meth. C (2.2.32)	≤10.0 %
Assay (UPLC)		
fingerprint	Monograph	Similar
dronabinol (THC)	Monograph	approx. 6.3 %
cannabidiol (CBD)	Monograph	approx. 8 %
Related substances (UPLC)		
cannabinol (CBN)	Monograph	<1.0 %

Specification sheet

(version: August 2014)

Product: **Cannabis flos**, ssp. indica, **variety Bedica** (hemp flowers)
Market: to be sold on the pharmaceutical market
Strength: dronabinol: approx. 14% cannabidiol: <1.0%
Dosage form: flowers, granulated
Package size: 5 grams in containers

	Method	Specification
Appearance	Monograph[4]	Brown green granulated material of the flowers (about 5 mm) with a characteristic smell
Identity		
microscopy	Monograph	Mainly gland hairs visible
thin layer chromatography	Monograph	Monograph
Foreign material	Monograph	Insects and other vermin are absent
Fineness	Monograph	Stalks are not longer than 2.0 cm Only 20% of the stalks is between 1.5 and 2.0 cm
Absence of pesticides	Monograph	Ph. Eur (current ed.) 2.8.13
Microbiological purity	Ph. Eur (current ed.) 5.1.4.	
Total aerobic microbial count (TAMC)	5.1.4.-1.	≤ 10^2 cfu/gram
Total yeast and moulds count (TYMC)	5.1.4.-1.	≤ 10 cfu/gram
P. aeruginosa, S. aureus and Bile tolerant gram neg bacteria	5.1.4.-1.	Absent

[4] Analytical monograph by BMC / Farmalyse, version 7.0 of October, 2013

	Method	Specification
Absence of heavy metals		
lead	Ph. Eur (current ed.) "Heavy metals in herbal drugs and fatty oils" (monograph)	max. 20.0 ppm
mercury		max. 0.5 ppm
cadmium		max. 0.5 ppm
arsenic (indicative)		-
nickel (indicative)		-
zinc (indicative)		-
Absence of aflatoxines	Ph. Eur (current ed.) "Determination of aflatoxins B_1, B_2, G_1 and G_2 in herbal drugs" (2.8.18)	<4 µg/kg
Loss on drying	Ph. Eur (current ed.) "Loss on drying" meth. C (2.2.32)	≤10.0 %
Assay (UPLC)		
fingerprint	Monograph	similar
dronabinol (THC)	Monograph	approx. 14 %
cannabidiol (CBD)	Monograph	<1.0 %
Related substances (UPLC)		
cannabinol (CBN)	Monograph	<1.0 %

Specification sheet

(version: August 2014)

Product: **Cannabis flos,** ssp. sativa**, variety Bedrolite** (hemp flowers)
Market: to be sold on the pharmaceutical market
Strength: dronabinol: < 1.0% cannabidiol: approx. 9.0%
Dosage form: flowers, granulated
Package size: 5 grams in containers

	Method	Specification
Appearance	Monograph[5]	Brown green granulated material of the flowers (about 5 mm) with a characteristic smell
Identity		
microscopy	Monograph	Mainly gland hairs visible
thin layer chromatography	Monograph	Monograph
Foreign material	Monograph	Insects and other vermin are absent
Fineness	Monograph	Stalks are not longer than 2.0 cm Only 20% of the stalks is between 1.5 and 2.0 cm
Absence of pesticides	Monograph	Ph. Eur (current ed.) 2.8.13
Microbiological purity	Ph. Eur (current ed.) 5.1.4.	
Total aerobic microbial count (TAMC)	5.1.4.-1.	≤ 10^2 cfu/gram
Total yeast and moulds count (TYMC)	5.1.4.-1.	≤ 10 cfu/gram
P. aeruginosa, S. aureus and Bile tolerant gram neg bacteria	5.1.4.-1.	Absent

[5] Analytical monograph by BMC / Farmalyse, version 7.0 of October, 2013

	Method	Specification
Absence of heavy metals		
lead	Ph. Eur (current ed.) "Heavy metals in herbal drugs and fatty oils" (monograph)	max. 20.0 ppm
mercury		max. 0.5 ppm
cadmium		max. 0.5 ppm
arsenic (indicative)		-
nickel (indicative)		-
zinc (indicative)		-
Absence of aflatoxines	Ph. Eur (current ed.) "Determination of aflatoxins B_1, B_2, G_1 and G_2 in herbal drugs" (2.8.18)	<4 µg/kg
Loss on drying	Ph. Eur (current ed.) "Loss on drying" meth. C (2.2.32)	≤10.0 %
Assay (UPLC)		
fingerprint	Monograph	similar
dronabinol (THC)	Monograph	< 1.0 %
cannabidiol (CBD)	Monograph	approx. 9.0 %
Related substances (UPLC)		
cannabinol (CBN)	Monograph	<1.0 %

Ministry of Health, Welfare and Sport

Office of Medicinal Cannabis

This is Exhibit "H" referred to in the Affidavit of Catherine Sandvos sworn before me at the City of The Hague, the Netherlands this 20 day of January, 2015.

Consular officer

Liesbet Corriveau
Consular Officer / Agente Consulaire
20 JAN 2015

Release certificate

Product:	**Cannabis flos, variety Bedrocan (hemp flowers)**		
Country:	to be sold on the pharmaceutical market		
Strength:	dronabinol: approx. 22%	cannabidiol : <1.0%	
Dosage form:	flowers		
Package size:	5 grams in container		
Batch:	**14H04EY14I02**		
Order numbers:	containers: 297561 to 297571		
Grower/drier:	Bedrocan BV P.O. Box 2009 NL- 9640 CA Veendam	harvest date/period: 4 August 2014	
Gamma irradiation:	Synergy Health Soevereinstraat 2 NL-4879 NN Etten-Leur	date: 2 September 2014	dose: ≥ 10,0 kGy
Packager:	Fagron BV Venkelbaan 101 NL-2908 KE Capelle a/d IJssel	date: 26 September – 3 October 2014	
Part of analysis:	1.general analysis	2.microbiology of end product in container	
Laboratories:	1. Farmalyse BV Pieter Lieftinckweg 2 NL-1505 HX Zaandam	2. Bactimm BV Middenkampweg 17 NL-6545 CH Nijmegen	
Analysis number:	1. 394-1409-1158	2. 16.857	
Report date:	1. 19 September 2014	2. 6 October 2014	
Testing method:	Analytical monograph by BMC / Farmalyse, version 7.0, Oct. 31, 2013		
End check:	Office of Medicinal Cannabis	date: 17 October 2014	

	Method	Specification	Result
Appearance	monograph	brown green clustered flowers of 1,5 to 3 cm with a characteristic smell	conform
Identity			
microscopy	monograph	mainly gland hairs visible	conform
thin layer chromatography	monograph	monograph	conform
Foreign material	monograph	stalks, insects and other vermin are absent	conform
Fineness	monograph	• no leaves shooting out more than 20% of the length of the flowers • stalks are cut away directly under the bottom flowers of the inflorescence	conform

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e-mail:
info@cannabisbureau.nl

Ministry of Health, Welfare and Sport

Office of Medicinal Cannabis

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2
Our reference
14H04EY14I02

	Method	Specification	Result
Microbiological purity	Ph. Eur (current ed.) 5.1.4.		
Total aerobic microbial count (TAMC)	5.1.4.-1.	$\leq 10^2$ cfu/gram	< 10 cfu/gram
Total yeast and moulds count (TYMC)	5.1.4.-1.	≤10 cfu/gram	< 10 cfu/gram
P. aeruginosa, S.aureus and Bile tolerant gram neg bacteria	5.1.4.-1.	absent	conform
Absence of aflatoxines	Ph.Eur (current ed.) "Determination of aflatoxins B_1, B_2 G_1 and G_2 in herbal drugs" (2.8.18)	< 4 µg/kg	< 2.2 µg/kg
Absence of pesticides	monograph	Ph. Eur (current ed.) 2.8.13	conform
Absence of heavy metal			
lead	Ph. Eur (current ed.) "Heavy metals in herbal drugs and fatty oils" (monograph)	max. 20.0 ppm	< 1.0 ppm
mercury		max. 0.5 ppm	< 0.1 ppm
cadmium		max. 0.5 ppm	< 0.1 ppm
Loss on drying	Ph. Eur (current ed.) "Loss on drying" meth. C (2.2.32)	≤10.0 %	8.2 %
Assay (UPLC)			
fingerprint	monograph	similar	conform
dronabinol (THC)	monograph	approx. 22 %	21.5 %
cannabidiol (CBD)	monograph	<1.0 %	0.1 %
Related substances (UPLC)			
cannabinol (CBN)	monograph	< 1.0 %	0.1 %
Content of container	BMC-SWV 320	approx. 5 gram	± 5.04 gram
Expiry date			08 / 2015

I hereby certify that the above information is authentic and accurate. This batch of product has been cultivated and manufactured, including packaging and quality control at the above mentioned sites in full compliance with the GAP requirements as published in the Dutch State Gazette (Staatscourant) as the annex to the Regulation of the Minister of Health, Welfare and Sport of 9 January 2003, GMT/BMC 2340885, and with the specifications as stated in this document. The batch processing, packaging and analysis records were reviewed and found to be in compliance with GAP and GMP.

The Hague, the Netherlands, 17 October 2014

Dr. M.J. van de Velde
Head, Office of Medicinal Cannabis