



**CIBG**  
*Ministerie van Volksgezondheid,  
Welzijn en Sport*

# Medicinal Cannabis Program

Office of Medicinal Cannabis (OMC)  
Ministry of Health, Welfare and Sport  
The Netherlands

September 4<sup>th</sup> 2018

Copenhagen , Denmark



Multiple sclerosis: chronic disease with high impact on quality of life





## Reasons for a new policy

### From 1993-1998:

- Increasing pressure from society against prohibition of medical use;

### Existing practice of illegal medical use

- No quality control;
- No medical coaching of patients;
- Patients at the mercy of illicit trade.

### Health Council advised (1996):

- insufficient evidence of efficacy;
- trials done with ill-defined products.



# Microbiology: *recreational* cannabis coffee shop

(Source: A. Hazekamp et al; University of Leiden, the Netherlands)

Cannabis sample	aerobic bacteria (cfu/gram) <sup>1)</sup>	aerobic fungi (cfu/gram) <sup>1)</sup>	Identified pathogens
Bedrocan <sup>2)</sup>	<10	< 100	
Bedrobinol <sup>2)</sup>	<10	< 100	
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	5900	3600	<i>E. coli</i> <i>Penicilium</i> <i>Cladosporium</i> <i>Aspergillus</i>

1) : CFU = colony forming units

2) : limit: total areobic bacteria and fungi <100 cfu



## Foundation of OMC

- In 1998 the Dutch government decided to establish an agency as regulator for medicinal cannabis according to art. 28 of Single Convention (UN);
- Foundation of the Office of Medicinal Cannabis (OMC) (March 2000);
- Office of Medicinal Cannabis empowered as national agency (January 2001);



## National legislation

### *Amendment to the Opium Act (2002-2003)*

- With respect to hemp, hashish and hemp Our Minister is, to the exclusion of others, authorized:
  - > to bring it inside or outside the Netherlands;
  - > to sell and deliver it;
  - > to have it available, with the exception of stocks maintained by those who have a license to cultivate, work up and/or convert.

### *Amendment to the Royal Decree (2002)*

Royal Decree on prescribable and dispensable controlled substances.



## Main responsibilities of the OMC

- Ensure constant quality of medicinal cannabis produced which meets pharmaceutical standards;
- Establish an effective procedure for distribution;
- Prevent leakage to the criminal circuit (tracking procedure / recordkeeping);
- Ensure availability of medicinal cannabis.



## Organisational aspects





## Policy within the Ministry of Health

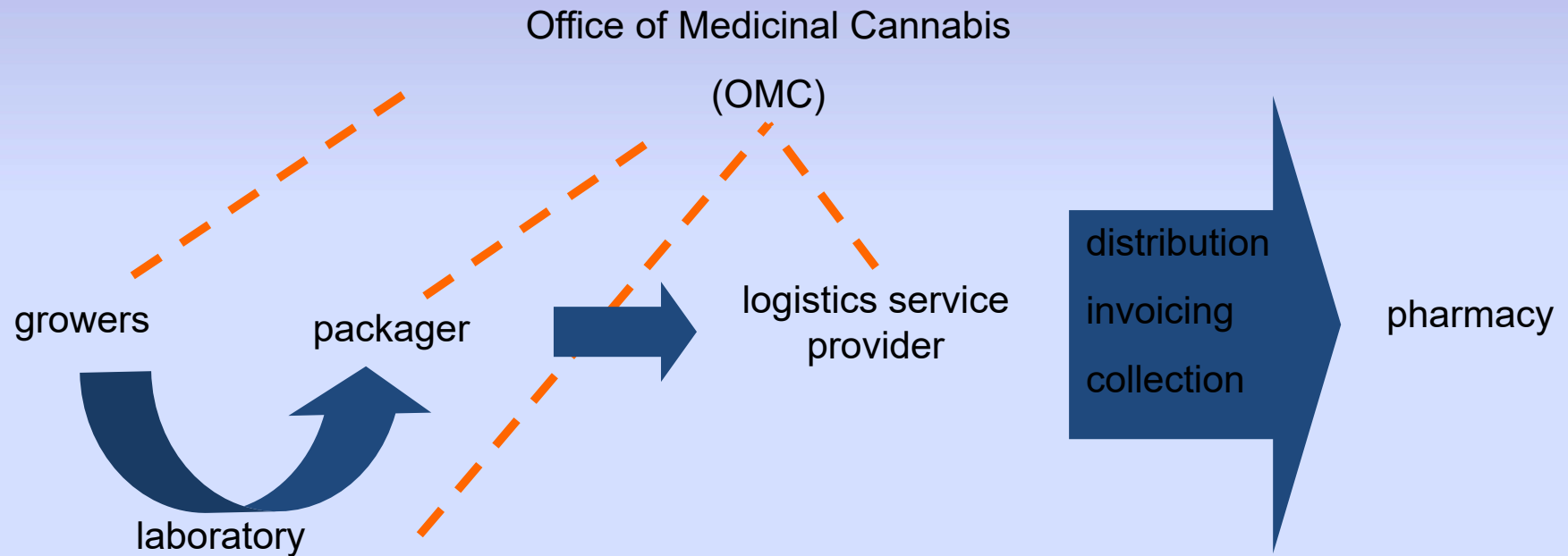
Part of pharmaceutical affairs policy

and NOT

Part of addiction care policy because:

1. Patients using cannabis as a medicine should not be stigmatised as drug abusers.
2. Cannabis as a medicine should meet all pharmaceutical requirements.

# Production and distribution model





## Contracted third parties:

**Cultivation** (Bedrocan BV)



**Quality control** (Proxy - Eurofins)



**Packaging and distribution** (Fagron BV)



**Pharmacy/Research/Product development**

Product/sample name : Bedrocan  
 Client-code : 394  
 Project-code : 0095752  
 Batch number : A1.01.89.180816  
 Analysis : Monograph OMC/Farmalyse Version 7.1/November 28, 2014  
 Version : 2

Test	Test method	Specification	Result	Complies
Appearance	Monograph	Brown green clustered flowers of 1.5 to 3 cm with a characteristic smell	Conform	Yes
Identity by microscopy	Monograph	Mainly gland hairs visible	Conform	Yes
Identity by TLC	Monograph	Must comply	Conform	Yes
Foreign material	Monograph	Stalks, insects and other vermin are absent	Conform	Yes
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	Yes
Microbiological purity	Monograph			
TAMC		Not applicable	2.4 x 10 <sup>5</sup> cfu/gram	N/A
TYMC		Not applicable	> 1.0 x 10 <sup>6</sup> cfu/gram	N/A
Pseudomonas aeruginosa		Not applicable	Absent **	N/A
Staphylococcus aureus		Not applicable	Absent	N/A
Bile tolerant gram neg bacteria		Not applicable	< 10 cfu/g	N/A
Loss on drying	Monograph	≤ 10.0%	9.8%	Yes
Assay (UPLC)	Monograph	Fingerprint must be similar Dronabinol (THC): Not applicable Dronabinol acid (THCA): Not applicable Dronabinol (THC, total eq.) ± 22 % Cannabidiol (CBD, total eq.) < 1.0 %	Conform 0.3 % 23.9 % 21 % 0.1 %	Yes N/A N/A Yes Yes
Related substances (UPLC)	Monograph	Cannabinol (CBN, total eq.) < 1.0 %	0.1 %	Yes
Absence of aflatoxines	Monograph	Aflatoxin B1: Not applicable Aflatoxin B2: Not applicable Aflatoxin G1: Not applicable Aflatoxin G2: Not applicable Sum B1, B2, G1 and G2 < 4 µg/kg	< 1.0 µg/kg < 0.2 µg/kg < 0.5 µg/kg < 0.5 µg/kg < 2.2 µg/kg	N/A N/A N/A N/A Yes
Absence of pesticides	Monograph	Ph. Eur (current ed.) 2.8.13 *	Conform	Yes
Absence of heavy metals	Monograph	Lead ≤ 20.0 ppm Mercury ≤ 0.5 ppm Cadmium ≤ 0.5 ppm Arsenic: Indicative Nickel: Indicative Zinc: Indicative	< 1 ppm < 0.1 ppm < 0.1 ppm < 2 ppm 2.1 ppm 42 ppm	Yes Yes Yes N/A N/A N/A

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Test	Test method	Specification	Result	Complies
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Remark:  
 \*) The following components are not being analyzed on using the current method:  
 Dithiocarbamate; Fenchlorophos; Methacriphos; S-421.  
 \*\*) Probable genus identification: Pseudomonas moesellii determined.

**QA-statement:**  
 This study met the criteria for a valid test and was performed in compliance with the Good control Laboratory Practice as defined in the Guide to Good Manufacturing Practice for Medicinal Products in the European Community.  
 The reported results adequately reflect the raw data of the study.

**Conclusion:**  
 The results do comply with the specifications

This certificate is approved by Manager QA on 17 January 2017

19 Jan 17  


**VISUAL INSPECTION**

No remarks

**MICROBIOLOGICAL EXAMINATION REPORT**

Bioburden, pour plate methode

Article tested	Batch	LIN*	Results cfu Total Aerobic Microbial Count / gram	Results cfu Total Yeast and Moulds Count / gram	Present / Absent <i>P. aeruginosa</i> , <i>S. aureus</i> and Bile tolerant gram neg bacteria / gram
Cannabis flos Bedrocan	13D15EY13E14	10.701	< 10	< 10	All absent

\*: LIN = Lab. Identification Number ; n.a.= not applicable

**REFERENCE METHOD(S)**

EP 2.6.12 + 2.6.13

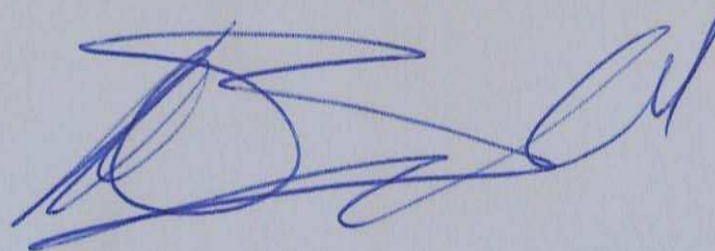
P324100917

Approved by QC Bactimm:

Date: 26 jun 2013

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Signature:





## Medicinal cannabis complies with pharmaceutical quality guidelines

- Standardized product with constant content (dronabinol, cannabidiol and other)
  - Within ranges of regulatory authorities
- Very low concentration of degradation compounds (e.g. CBN)
- Free of contamination
  - Micro-organisms
  - Pesticides
  - Heavy metals



## Products - varieties

- Cannabis flos, variety Bedrocan: 22% THC, <1% CBD
- Cannabis flos, variety Bedrobinol: 13,5% THC, <1% CBD
- Cannabis flos, variety Bedica granulated: 14% THC, <1% CBD
- Cannabis flos, variety Bediol, granulated: 6,3% THC, 8% CBD
- Cannabis flos, variety Bedrolite granulated: <1% THC, 8% CBD

*Note: all varieties are also available in 'placebo'*





## Retrospective study 2011-2016 (de Hoop et al, 2018)

	N	Average duration of use (days)	Average daily use (grams)
Study population	10,826 (100)	254	0.73
<i>Male</i>	5257	275	0,77
<i>Female</i>	5569	235	0,68
<i>Age</i>			
≤ 20	189 (1.7)	151	0.79
21-40	2006 (18,5)	323	0.82
41-60	4640 (42,9)	306	0.72
61-80	3348 (30,9)	175	0.69
> 80 <sup>17</sup>	643 (5.9)	113	0.68



## Dependency - Tolerance

- Low average daily dosage points to a low potential of misuse;
- Average daily dosage remain stable over longer period of time suggesting absence of tolerance or overconsumption;
- No signs that use of medicinal cannabis by Dutch patients may increase recreational use;



## Prescription behaviour of (Dutch) physicians

- ***Only if treatment in conformity with guidelines or protocols does not work sufficiently or gives too many side effects.***
- ***A Dutch physician is free to prescribe medicinal cannabis.***



## Supply of information in the Netherlands

- Seminars and presentations for organizations involved;
- Direct contact with patients, general practitioners and specialists;
- Website and call center OMC;
- Leaflets for physicians, pharmacists and patients;



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# Medicinale Cannabis

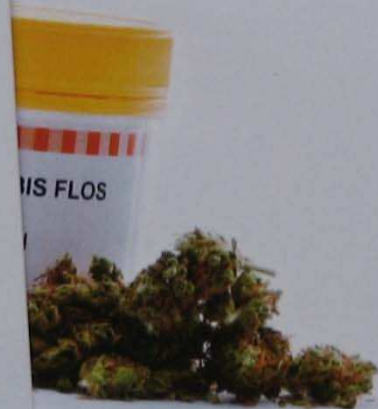
Informatiebrochure voor patiënten



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# Medicinale Cannabis

voor artsen en apothekers





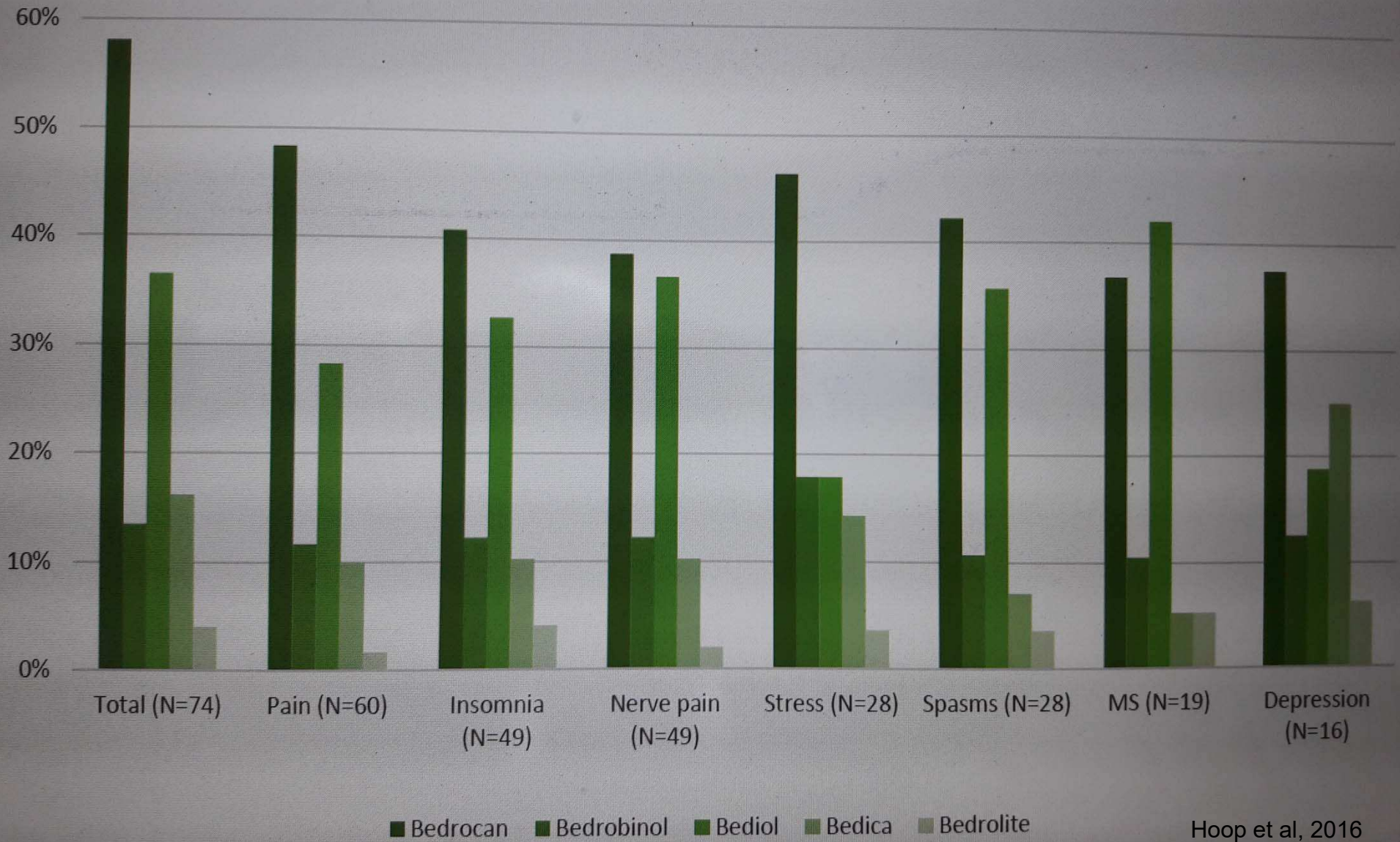
# Additional information for health care provider

*(Dutch Institute For Rational Use of Medicine in cooperation with OMC)*

- Interactive module (Pharmaco Therapeutic Consultation)  
[\(https://medicijngebruik.nl/\)](https://medicijngebruik.nl/)
  - Source of information for professionals to achieve knowledge about therapeutic use/prescription of medical cannabis
  - Education and counseling
  - General guidance
- Special issue 'Medical Cannabis' for professionals (2017)  
[\(https://medicijnbalans.nl/journaal/\)](https://medicijnbalans.nl/journaal/)
  - Quality issues and therapeutic indications
  - Available varieties
  - Route of administration

Patient characteristics	N	Percentage
Age	53,1 ^	(24-81) ^
Sex		
Mail	35	(45,5%)
Female	42	(54,5%)
<b>Therapeutic indication</b>		
Multiple Sclerose	16	(20,8%)
Chronic pain	51	(66,2%)
Nausea / vomiting	7	(9,1%)
Cancer	5	(6,5%)
Mental disorders	10	(13,0%)
Others	18	(23,4%)
<b>Therapeutic use</b>		
Spasticity	37	(48,1%)
Pain relieve	63	(81,8%)
Anxiety	8	(10,4%)
Drowsiness	42	(54,5%)
Appetite stimulation	10	(13,0)
Daily functioning	26	(33,8)
State of mind	15	(20,8%)
Others	7	(9,1%)
23		

Figure 1 Distribution graph 'Pharmacy cannabis strains for OP patients for most common indications'\*







## Overview reported (main) side effects (ATC-N02BG10)

*(source: Pharmacovigilance Centre Lareb the Netherlands )*

- Cardiac side effects: palpitations (n=2);
- Eye: dry eyes; pain in the eyes (n=4);
- Gastrointestinal tract: diarrhoea, dry mouth (n=7);
- Nervous system: depressed level of consciousness (n=1);
- Respiratory: dyspnoea; tonsillar disorder (n=2).



## Scientific evidence – reimbursement issue



Pathology	# of studies	# of patients
<b>All studies 1976 – 2012:</b>		
<b>139 studies</b>		
<b>9000 patients</b>		
Other indications:	3	86
<b>Total</b>	<b>37</b>	<b>2563</b>



## Scientific research – clinical studies

- Not the right comparator used during the study;
- Number of patients (too) small, short follow-up, subjective outcome;
- Specifications of cannabis used;
- Not placebo-controlled;
- In general: lack of therapeutic evidence;
- e.o.



## General conclusions

- Important shortcomings in evidential value of the studies;
- Only very few clinical studies performed with cannabis (products) meet modern criteria for clinical studies;



Negative advice to the Minister of Health (2016/2017);



Health insurance companies changed reimbursement:

**from 'coulance' towards 'out-of-pocket'**



## OMC and scientific / clinical research

- Members of Parliament proposed 3 resolutions (June 2018):

(1) discuss the role and/or position of the OMC in clinical research with medicinal cannabis;

(2) young children with epilepsy;

(3) individual patients who (finished) treatment /regular pharmaco-therapy insufficient;

*Resolutions were adopted*



Thank you for your attention.

**QUESTIONS?**