## **Table of Contents**

Preface		V	4	Different products and their	
List of	f abbreviations	XIII		supply chain	3!
1	The history of cannabis	1	4.1	Cultivation and processing of the drug	35
		_	4.1.1	Cannabis physiology	35
1.1	Cannabis in ancient times	1	4.1.2	Standardized and quality assured cannabis	
1.2	Hemp in the Middle Ages	1		flowers	36
1.3	Cannabis in 19th century European		4.1.3	Plant genetic resourcesand propagation	37
1.3	mainstream medicine	4	4.1.4	Outdoor cultivation	38
1.3.1	Indian hemp arrives in Europe	4	4.1.5		39
1.3.2	A momentous study	4		Indoor cultivation	40
1.3.3	Cannabis becomes established	5		Harvest and post-harvest methods	41
1.3.4	First peak in the 19th century	6	4.1.8	Comparison of cultivation systems	43
	·	_	4.2	Quality standards	46
1.4	Cannabis as a medicinal substance in the		4.2.1	Differentiation of substances, preparations	
	20th century	7		and medicinal products	46
1.4.1	The end of an era	7	4.2.2	Quality assurance	49
1.4.2		7	4.2.3	Quality requirements for cannabis flowers	55
1.4.3	From Opium Law to Cannabis Law in Germany	8	4.2.4	Quality requirements for preparations from cannabis flowers	64
1.5	Cannabis as a treatment option in the 21st		4.2.5	Specific requirements for isolated canna-	
	century	8		binoids as active ingredients in medicinal	
2	Botanical description	10		products	68
_	•	10	4.2.6	Quality requirements for cannabis-based	
2.1	Systematics and Taxonomy	10		medicinal products	71
2.2	General botanical characteristics	11	4.2.7	Stability studies	72
2.2.1	Habitus, sprout and sex distribution	11	4.2.8	Regulatory aspects of quality control	73
2.2.2	Inflorescences and flowers	13	4.3	Production of cannabis extracts	75
2.2.3	Fruits	15	4.3.1	Pre- and post-treatment during extraction	75
2.2	Committee to the second second	46	4.3.2	Extraction with ethanol	76
2.3	Cannabis breeding and current cultivars	16	4.3.3	Extraction with hydrocarbons	76
3	Biosynthetic pathways of the		4.3.4	Extraction with supercritical carbon dioxide.	76
	cannabinoids	18	4.3.5	Isolation of pure cannabinoids	77
3.1	Cannabinoids	18	4.3.6	Development of the extraction process	78
3.1.1	Cannabinoids as chemotaxonomic markers	18	4.3.7	Validation of the extraction process	79
3.1.2	Cannabinoid biosynthesis	18	4.4	Special considerations for clinical	
3.1.3	Artificial enzymatic production of		7.7	investigational medicinal products	80
	cannabinoids	23			00
3.1.4	Chemical synthesis and properties of		4.5	Biotechnological production of	
	cannabidiol (CBD)	26		cannabinoids	80
3.1.5	Chemical synthesis and properties of		4.5.1	Motivation	80
	$\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC)	26	4.5.2	Metabolic engineering	81
3.1.6	Chemical synthesis and properties of		4.5.3	Challenges for the future	83
	nabilone	28	5	Supply of medical cannabis	87
3.2	Terpenes	30	5.1	Import from EU and non-EU countries	87
3.3	Other secondary substances	24	5.1.1	Requirements for import	87
J.J	-	31	5.1.2	Permit and documentation requirements	88
3.4	Chemotypes of Cannabis sativa	32	5.1.3	Organizational processing	90



5.2	Cultivation in Germany	92	7.5	Neurodegenerative, neuroinflammatory	
5.2.1	Prerequisites and legal framework	92		and other neurological diseases	. 144
5.2.2	Quality-related requirements for the		7.5.1	Spasticity and paraplegia	. 144
	cultivation of medical cannabis in Germany	93	7.5.2	Spasticity in multiple sclerosis	. 144
6	Pharmacological basis of cannabinoid		7.5.3	Huntington's chorea	. 144
6	Pharmacological basis of cannabinoid action	04	7.5.4	Epilepsy	. 147
	action	94	7.5.5	Dystonia	. 148
6.1	The endocannabinoid system	94		Parkinson's disease	
6.1.1	What is the endocannabinoid system?	94		Outstand and discours	
6.1.2	Physiology	94	7.6	Ophthalmological diseases	
6.1.3	Disorders of the endocannabinoid system	97		Glaucoma	
6.1.4	Cannabinoid (CB) receptors	98		Uveitis	
6.1.5	Ligands	100	7.6.3	Dry eye	. 151
6.1.6	Biological and biographical differences	105	7.7	Psychiatric disorders	
6.2	Pharmacokinetics and pharmacodynamics			Dementia	
	of THC and CBD	110		Gilles de la Tourette syndrome	
6.2.1	THC			ADHD	
6.2.2	Cannabidiol (CBD)		7.7.4	Obsessive compulsive disorder	. 160
				Anxiety disorders	
6.3	Entourage effect		7.7.6	Affective disorders	. 163
6.3.1	Entourage effect in the ECS	115		Post-traumatic stress disorder	
6.3.2	Entourage effect due to secondary cannabis		7.7.8	Psychosis	. 165
	ingredients	116	7.7.9	Autism spectrum disorder	. 166
7	Medical applications and their		7.8	Skin disorders	. 172
	evidence	120	7.8.1	Endocannabinoid system of the skin	. 173
7 1	General information on dosage and dose		7.8.2	Wound treatment	. 175
7.1	finding	120	7.8.3	Modulation of the skin barrier	. 176
7.1.1	Start of treatment		7.8.4	Atopic dermatitis	. 176
– . –	Type of use		7.8.5	Pruritus	. 178
7.1.2			7.8.6	Allergic contact dermatitis (ACD)	. 178
7.1.3	Dosage titration Application frequency and distribution	122	7.8.7	Acne vulgaris	. 179
7.1.4	throughout the day	122	7.8.8	Epidermolysis bullosa (EB)	. 179
	tilloughout the day	122	7.8.9	Pyoderma gangrenosum	. 179
7.2	Chronic pain	123	7.8.10	Psoriasis	. 180
7.2.1	Preclinical findings	123	7.8.11	Skin cancer	. 180
7.2.2	Clinical findings and evidence	124	7.8.12	Conclusion	. 181
7.2.3	Dosage	128		Cannabis as a stimulant	405
7.2.4	Tolerability and safety	129	8		
7.3	Nausea, vomiting, appetite stimulation	132	8.1	Model projects on cannabis	
7.3.1	Definitions	132		Application from Berlin	
7.3.2	Hypothesis of mechanism of action for			Application from Schleswig-Holstein	
	cannabinoids	132	8.1.3	Renewed application from Berlin	. 186
7.3.3	Nausea and vomiting	132	8.2	Consequences of cannabis use	. 187
7.3.4	Appetite stimulation and cachexia	133	8.2.1	Cannabis intoxication	
7.3.5	Conclusion		8.2.2	Abuse, dependence, concomitant use,	
7.4	Gastroenterological diseases	135		scene entry	
7.4.1	Inflammatory bowel disease (Crohn's disease		8.2.3	Other cannabis-related disorders	. 190
1.4.1	and ulcerative colitis)		8.2.4	Trigger factors and consequences of	
71. 7	•			legalization	. 193
7.4.2	Irritable Bowel Syndrome	131			

8.3	Comparison to other stimulants and		10.2	Regulatory framework at European level	230
	addictive substances (alcohol, caffeine,		10.2.1	Possibilities for placing on the market on	
	nicotine, heroin etc.)	198		the basis of a formal authorization	231
8.3.1	Alcohol	198	10.2.2	Possibilities for placing on the market	
8.3.2	Nicotine (smoking)	200		without formal authorization	231
8.3.3	Heroin				
8.3.4	Comparison with cannabis	202	10.3	Legal basis and availability of cannabis	
				abroad (EU, non-EU)	
9	Risks associated with the medical			The Netherlands	
	use of cannabis	205		Italy	
9.1	Adverse drug reactions (ADRs)	205		United Kingdom	
9.1.1	THC and other CB1 agonists			Denmark	
9.1.2	CBD			Israel	
9.1.3	Extracts and flowers			Canada	
			10.3.7	Australia	234
9.2	Interactions with cannabinoids	212	10.3.8	Columbia	235
9.2.1	THC and other CB1 agonists		10.3.9	United States of America	235
9.2.2	CBD	213	10 %	Legal framework in Germany	227
9.2.3	Interactions between CBD and THC			Narcotics Act (Betäubungsmittelgesetz,	251
9.2.4	Extracts and flowers	214	10.4.1		
9.2.5	Pharmacology-based guidance on the safe		40 / 2	BtMG)	
	use of cannabis-based medicinal products	214	10.4.2	Narcotics Foreign Trade Ordinance (Betäubun	igs-
	Controladications	245		mittel-Außenhandels-	
9.3	Contraindications			verordnung, BtMAHV)	238
9.3.1	THC and other CB1 agonists		10.4.3	Narcotics Prescription Ordinance	
9.3.2	CBD	216		(Betäubungsmittel-Verschreibungs-	
9.4	Tolerance and addiction or dependence	217		verordnung, BtMVV)	238
9.4.1	THC and other CB1 agonists		10.4.4	Fifth Book of the German Social Code	
9.4.2	CBD	218		(SGB V)	239
			10.5	Structure and function of the Cannabis	
9.5	Impairment of driving safety			Agency	239
9.5.1	Pharmacokinetics		10.5.1	Legal basis	
9.5.2	Effects relevant for traffic	219		Development of the Cannabis Agency	240
9.5.3	Analytical methods for detection of			Responsibilities and monitoring	241
	cannabinoids in biological material and		10.5.5	Responsibilities and morntoring	241
	their interpretation	220	10.6	Authorization for medical use	242
9.5.4	Legal regulations	221	10.6.1	(Social) medical requirements	242
9.5.5	Penalty thresholds in international		10.6.2	Documents required	244
	comparison	221	10.6.3	Course of the approval procedure	244
9.5.6	Prevalence and risk identification	222	10.6.4	Conclusion	246
9.5.7	Outlook	223			
10	Logal framework for the use of		10.7	Companion survey/scientific project	247
10	Legal framework for the use of		11	Legal status of medicinal cannabis	
	cannabis	225		and cannabinoids in Germany	252
10.1	International agreements	225		-	
	Single Convention on Narcotic Drugs, 1961			Definitions of terms: active substance,	
	Convention on Psychotropic Substances,			medicinal product, proprietary medicinal	
	1971	228		product	252
10.1.3	United Nations Convention against Illicit		11.2	Cannabis-based proprietary medicinal	
	Traffic in Narcotic Drugs and Psychotropic				253
	Substances of 1988	220		•	233
		443	11 2	Cannahis-hased prescription drugs	25%

12	Legal status of cannabis and		13.8.3 Ready-to-use cannabis-based medicinal	
	cannabinoids in non-medicinal		products authorized in Switzerland	293
	products	256	13.9 United Kingdom	295
12.1	CBD and cannabis preparations in		13.9.1 Medical cannabis	295
	foodstuffs and nutritional supplements	256	13.9.2 CBD consumer products	297
12.1.1	Food	256	14 Forms and methods of	
12.1.2	Food supplements	260	administration	300
12.1.3	Flavorings	262		300
12.1.4	CBD products as medicinal products by		14.1 Dosage forms for medical use	
	function or presentation	262	14.1.1 Tablets	
12.2	CBD and cannabis preparations in medical		14.1.2 Capsules	
	devices	265	14.1.3 Decoctions ("tea")	
			14.1.4 0il	
12.3	CBD and cannabis preparations in		14.1.5 Oromucosal spray	
	cosmetics	266	14.1.6 Inhalants	
12.4	CBD and cannabis preparations in		14.1.7 Suppositories	318
	smoking products	267	14.1.8 Transdermal therapeutic systems and	
12	Madicinal Counchies Consequies		semi-solid dermatics	
13	Medicinal Cannabis: Case studies from selected European countries	269 14.1.	14.1.9 Parenterals	
			14.1.10 Eyedrops	
13.1	Czech Republic	269	14.1.11 Edibles	322
13.2	France	270	14.2 Forms of consumption in recreational use	
	Beginnings		14.2.1 Marijuana	
	Main objectives		14.2.2 Solventless concentrates	
	Experimental framework		14.2.3 Solvent-using concentrates	
	Patients' involvement		14.2.4 Cannabis tinctures	
	Category of medications offered to patients		14.2.5 Foods containing cannabis	
	within the scope of the study	273	14.2.6 Synthetic cannabinoids	346
13.2.6	Call for applications		14.3 Types of administration in recreational	
	Selected suppliers		use	348
13.2.8	Approved medications	275	14.3.1 Joints, spliffs and blunts	349
	Supply and distribution		14.3.2 Chillums, one-hitters, pipes	351
400	Crange		14.3.3 Hookahs and bongs	351
13.3	Greece	279	14.3.4 Bucket smoking	353
13.4	Italy	280	14.3.5 Hot knives (spots)	354
13.5	Malta	291	14.3.6 Glass smoking or hot needles	354
13.3	Tidl W	201	14.3.7 Vaping	354
13.6	Poland		14.3.8 Dabbing	356
	Magistral preparations		15 Compounding of medicinal products	
	Compounding		containing cannabinoids in the	
	Pharmaceutical raw material		pharmacy	358
	Dosage forms of magistral preparations	285	-	
13.6.5	Extemporaneous medicine of medical		15.1 Legal framework	358
	cannabis in Poland	286	15.1.1 Magistral preparations (Rezepturarznei-	_
13.7	Portugal	287	mittel)	358
13.8	Switzerland	290	15.1.2 Officinal medicinal product (Defektur- arzneimittel)	358
	Legal framework		·	
	Authorization procedures in Switzerland		15.2 Manufacturing documentation	
	•		15.2.1 Manufacturing instructions	
			15.2.2 Manufacturing protocol	361

15.3	Starting material testing	361	15.8.2	Specifics of cannabis price calculation	445
15.3.1	Legal framework and testing obligations	361	15.8.3	Rounding rules for price calculation	447
15.3.2	Starting materials without a certificate of		15.8.4	Special PZN for magistral preparations	
	analysis	361		containing cannabinoids	447
15.3.3	Starting materials with a certificate of		15.8.5	Determining the most economical package	
	analysis	362		or package size combination	448
15.3.4	Test methods	364	15.8.6	Imported cannabis flowers in unchanged	
15.3.5	Documentation obligation	364		form	448
	Available starting materials and source of		15.8.7	Imported cannabis flowers in preparations	448
15.4	Available starting materials and sources of		15.8.8	Cannabis flowers from German cultivation	450
	supply		15.8.9	Cannabis extracts in unchanged state	450
	Flowers		15.8.1	0 Cannabis extracts in preparations	451
	Extracts			1 Dronabinol in preparations	
	Cannabinoids	372		2 Cannabidiol in preparations	
15.4.4	Special characteristics of manufacturing			·	
	sets	373	16	Supply of cannabis prescriptions in	
15.5	Testing of starting materials for cannabis			the pharmacy	458
	flowers, cannabis extracts and		16.1	Legal framework	458
	cannabinoids	374	16.1.1	General formalities of the regulation of	
15.5.1	Cannabis flowers			narcotics	458
	Extracts		16.1.2	Maximum quantities in the prescription of	
	Dronabinol			cannabis medicinal products	459
	CBD		16.1.3	Specific features of the prescription of	
	Combined test systems discriminating THC			cannabis medicinal products	459
	or CBD-dominant and equilibrated starting		1614	Prescription drugs	
	materials	304		Proprietary medicinal products	465
	THE COLUMN TO TH	334		Non-availability	468
	Manufacture of magistral prpeparations			Drug substitution in cannabis preparations	468
	Weighing correction			Discount agreements for cannabis	400
	Plausibility check	403	10.1.0	medicinal products	4.70
15.6.3	Important processing aspects for		1610	Obligation to check for cost coverage by	410
	standardized cannabis formulations	409	10.1.9	statutory health insurance	1.71
	Child-resistant packaging		16 1 10	Individual imports in accordance with	4/1
	Baking mixtures	421		Section 73(3) of the German Medicinal	
15.6.6	Production of flower or extract mixtures				1.71
	with defined THC and CBD contents	424		Products Act	4/1
15.7	Preparation of officinal medicinal		16.2	Special features of pharmacy logistics when	1
	products	<i>l</i> , 21		handling medicinal products containing	
	Test instructions for officinal medicinal	731		cannabis	472
13.1.1	products	<i>I</i> . 21	16.2.1	Storage	472
1572	Test protocol for officinal medicinal	431	16.2.2	Cannabis in mail order and courier service	473
	products	4.21	16.2.3	Transfer of narcotic drugs containing	
	Risk-based tiered model for final analytical	431		cannabinoids between pharmacies	474
	testing	422	16.2.4	Returns of narcotics containing	
		432		cannabinoids	475
	Application of the risk-based tiered model		16.2.5	Dealing with quality defects	475
	to medicinal products containing cannabis			Withdrawal of narcotics containing	
	or cannabinoids	435		cannabinoids by pharmacies	476
15.8	Price calculation	445		Destruction of narcotics containing	
15.8.1	Basic principles of price calculation for			cannabinoids	476
	compounded preparations	445			

17	Narcotics documentation	479	17.3.6	Prescription of cannabis-based proprietary	
17.1	Legal basis	479		medicinal products	493
17.2	General documentation requirements for narcotics	479	18	Important considerations for counseling cannabis patients	498
17.2.1	Import and export of narcotics (Section 11 of the Narcotics Act)	480	18.1	General instructions for use	498
17.2.2	Dispensing and acquisition of narcotics (Section 12 of the Narcotics Act)	480	18.2	Instructions for use specific to the dosage form or mode of administration	498
17.2.3	Dispensing narcotics on the basis of a		18.3	Vaporization	498
	prescription (Section 13 of the Narcotics		18.3.1	Filling dosing capsules	498
	Act)	482	18.3.2	Volcano Medic 2	500
17.2.4	Labeling according to Section 17 of the		18.3.3	Mighty Medic or Mighty <sup>+</sup> Medic	500
	Narcotics Act and Section 14 of the Ordinance on the Prescription of Narcotics	483	18.4	Dosing	501
17.2.5	Destruction of narcotics according to		18.5	Cannabis patients and driving	505
	Section 16 of the Narcotics Act	484	18.6	Traveling with cannabis	506
17.2.6	Reporting according to Section 18 of the			Traveling within the Schengen area	
17.3	Narcotics Act  Special features of narcotics documentation for prescription medicinal products			Traveling outside the Schengen area	
	containing cannabis	485	18.7	Hunting license	509
17.3.1	Narcotics documentation specific to variety/ extract	485		Recognizing abuse and dealing with	
17.3.2	Formulation production and			suspected misuse	509
	documentation	487	Photo	credits	513
17.3.3	Excess consumption	489	Subjec	t index	517
	Weighing gain, weighing loss and overfill		The ed	itor	535
17.3.5	Mishaps during production	492	The au	thors	536