Table of Contents

	e	V XIII	4	Different products and their supply chain	3!
1	The history of cannabis	1	4.1		35
-	-	-	4.1.1		35
1.1	Cannabis in ancient times	1	4.1.2		
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
1.5	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	4.1.6		40
1.3.3	Cannabis becomes established	5	4.1.7	•	41
1.3.4	First peak in the 19th century	6	4.1.8	Comparison of cultivation systems	43
1.			4.2	Quality standards	46
1.4	Cannabis as a medicinal substance in the	-	4.2.1		
1.4.1	20th century The end of an era	7		•	46
1.4.1	The Renaissance	7	4.2.2		49
1.4.3	From Opium Law to Cannabis Law in	7	4.2.3	Quality requirements for cannabis flowers	55
1.7.5	Germany	8	4.2.4	Quality requirements for preparations from	
	-	O			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		•	68
2.1	Systematics and Taxonomy	10	4.2.6	Quality requirements for cannabis-based medicinal products	71
2.1		10	4.2.7		72
2.2	General botanical characteristics	11	4.2.8	-	73
2.2.1	Habitus, sprout and sex distribution	11			
2.2.2	Inflorescences and flowers	13	4.3		75
2.2.3	Fruits	15	4.3.1	Pre- and post-treatment during extraction .	75
2.3	Cannabis breeding and current cultivars	16	4.3.2		76
3	Biosynthetic pathways of the			-	76
,	cannabinoids	18		'	76 77
		10			78
3.1	Cannabinoids	18			79
3.1.1	Cannabinoids as chemotaxonomic markers	18	7.5.1	·	1 -
3.1.2	Cannabinoid biosynthesis	18	4.4	Special considerations for clinical	
3.1.3	Artificial enzymatic production of			investigational medicinal products	80
241	cannabinoids	23	4.5	Biotechnological production of	
3.1.4	Chemical synthesis and properties of cannabidiol (CBD)	2.6		cannabinoids	80
215	Chemical synthesis and properties of	26	4.5.1	Motivation	80
3.1.5	Δ^9 -tetrahydrocannabinol (Δ^9 -THC)	26	4.5.2	Metabolic engineering	81
3 1 6	Chemical synthesis and properties of	26	4.5.3	Challenges for the future	83
3.1.6	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	31	5.1.1	Requirements for import	87
3.4	Chemotypes of Cannabis sativa	32	5.1.2	•	88
J.+	chemotypes of cumuuis suuvu	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	
5.2.2	Quality-related requirements for the		7.5.1	Spasticity and paraplegia	
	cultivation of medical cannabis in Germany	93	7.5.2	Spasticity in multiple sclerosis	
6	Pharmacological basis of cannabinoid		7.5.3	Huntington's chorea	
	action	94	7.5.4	Epilepsy	
6.1	The endocannabinoid system	94	7.5.5 7.5.6	Dystonia	
6.1.1	What is the endocannabinoid system?	94			
6.1.2	Physiology	94	7.6	Ophthalmological diseases	
6.1.3	Disorders of the endocannabinoid system	97	7.6.1	Glaucoma	
6.1.4	Cannabinoid (CB) receptors	98	7.6.2	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		7.7.1	Dementia	
	of THC and CBD	110		Gilles de la Tourette syndrome	
6.2.1	THC	110		ADHD	
6.2.2	Cannabidiol (CBD)	113		Obsessive compulsive disorder	
6.3	Entourage offect	115		Anxiety disorders	
6.3 6.3.1	Entourage effect in the ECS			Affective disorders	
6.3.2	Entourage effect due to secondary cannabis	113	7.7.7	Post-traumatic stress disorder Psychosis	
0.5.2	ingredients	116	7.7.8	Autism spectrum disorder	
7	Medical applications and their				
•	evidence	120	7.8 7.8.1	Skin disorders Endocannabinoid system of the skin	
		120	7.8.2	Wound treatment	
7.1	General information on dosage and dose		7.8.3	Modulation of the skin barrier	
	finding		7.8.4	Atopic dermatitis	
7.1.1	Start of treatment			Pruritus	
7.1.2	Type of use			Allergic contact dermatitis (ACD)	
7.1.3	Dosage titration	122		Acne vulgaris	
7.1.4	Application frequency and distribution			Epidermolysis bullosa (EB)	
	throughout the day	122	7.8.9		
7.2	Chronic pain	123	7.8.10	Psoriasis	
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	0	Cannabis as a stimulant	4.05
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	8.1.1	Application from Berlin	
7.3.2	Hypothesis of mechanism of action for		8.1.2	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	187
7.3.5	Conclusion	134	8.2.2	Abuse, dependence, concomitant use,	
7.4	Gastroenterological diseases	135		scene entry	
7.4.1	Inflammatory bowel disease (Crohn's disease			Other cannabis-related disorders	190
	and ulcerative colitis)	135	8.2.4	Trigger factors and consequences of	
7.4.2	Irritable Bowel Syndrome	137		legalization	193

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		.2 Possibilities for placing on the market	
8.3.2	Nicotine (smoking)		without formal authorization	231
8.3.3	Heroin	201		231
	Comparison with cannabis	10.3	Legal basis and availability of cannabis	
0.3.4	Companson with cannabis	202	abroad (EU, non-EU)	232
9	Risks associated with the medical	10.3	.1 The Netherlands	232
	use of cannabis	205 10.3	.2 Italy	232
		10.3	.3 United Kingdom	233
9.1	Adverse drug reactions (ADRs)	205	.4 Denmark	
	THC and other CB1 agonists	205	.5 Israel	
9.1.2	CBD	209	.6 Canada	
9.1.3	Extracts and flowers	210	.7 Australia	
9.2	Interactions with cannabinoids		.8 Columbia	
9.2.1	THC and other CB1 agonists		.9 United States of America	
	_		.9 Utilled States of Affierica	235
9.2.2	CBD	10 4	Legal framework in Germany	237
9.2.3	Interactions between CBD and THC	10 4	.1 Narcotics Act (Betäubungsmittelgesetz,	
9.2.4	Extracts and flowers	214	BtMG)	237
9.2.5	Pharmacology-based guidance on the safe	10 4	.2 Narcotics Foreign Trade Ordinance (Betäubu	
	use of cannabis-based medicinal products $\ensuremath{\text{.}}$	214	mittel-Außenhandels-	182
9.3	Contraindications	215	verordnung, BtMAHV)	220
9.3.1	THC and other CB1 agonists		_	238
	_		.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 Fifth Book of the German Social Code	
9.4.2	CBD		(SGB V)	239
		10 5	Structure and function of the Cannabis	
9.5	Impairment of driving safety	218	Agency	220
9.5.1	Pharmacokinetics	10 5	.1 Legal basis	
9.5.2	Effects relevant for traffic	219	_	
9.5.3	Analytical methods for detection of		.2 Development of the Cannabis Agency	
	cannabinoids in biological material and	10.5	.3 Responsibilities and monitoring	241
	their interpretation	220 10.6	Authorization for medical use	242
9.5.4	Legal regulations		.1 (Social) medical requirements	
9.5.5	Penalty thresholds in international		.2 Documents required	
31313	comparison		.3 Course of the approval procedure	
9.5.6	Prevalence and risk identification			
			.4 Conclusion	246
9.5.7	Outlook	10.7	Companion survey/scientific project	247
10	Legal framework for the use of	11	Logal status of modisinal cannabis	
	cannabis	225	Legal status of medicinal cannabis	
40.	International action		and cannabinoids in Germany	252
	International agreements	11 1	Definitions of terms: active substance,	
	Single Convention on Narcotic Drugs, 1961	227	medicinal product, proprietary medicinal	
10.1.2	Convention on Psychotropic Substances,		product	252
	1971	228	product	232
10.1.3	United Nations Convention against Illicit	11.2	Cannabis-based proprietary medicinal	
	Traffic in Narcotic Drugs and Psychotropic		products	253
	Substances of 1988	229		
		11.3	Cannabis-based prescription drugs	254

12	Legal status of cannabis and cannabinoids in non-medicinal	256	13.8.3	Ready-to-use cannabis-based medicinal products authorized in Switzerland	293
	products	256	13.9	United Kingdom	
12.1	CBD and cannabis preparations in			Medical cannabis	
	$foodstuffs\ and\ nutritional\ supplements\$		13.9.2	CBD consumer products	297
	Food		14	Forms and methods of	
	Food supplements			administration	300
	Flavorings	262	11. 1	Dosago forms for modical uso	200
12.1.4	CBD products as medicinal products by		14.1	Dosage forms for medical use	
	function or presentation	262		Capsules	
12.2	CBD and cannabis preparations in medical			Decoctions ("tea")	
	devices	265	14.1.4	0il	304
12.3	CBD and cannabis preparations in		14.1.5	Oromucosal spray	310
	cosmetics	266	14.1.6	Inhalants	311
12.6	CDD and cannabic avaparations in		14.1.7	Suppositories	318
12.4	CBD and cannabis preparations in	267	14.1.8	Transdermal therapeutic systems and	
	smoking products	201		semi-solid dermatics	320
13	Medicinal Cannabis: Case studies		14.1.9	Parenterals	320
	from selected European countries	269		D Eyedrops	
13.1	Czech Republic	269	14.1.1	1 Edibles	322
	France		14.2	Forms of consumption in recreational use .	331
	Beginnings		14.2.1	Marijuana	335
	Main objectives		14.2.2	Solventless concentrates	336
	Experimental framework			Solvent-using concentrates	
	Patients' involvement			Cannabis tinctures	
	Category of medications offered to patients			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	
13.2.7	Selected suppliers	275		use	348
13.2.8	Approved medications	275	14.3.1	Joints, spliffs and blunts	349
13.2.9	Supply and distribution	276	14.3.2	Chillums, one-hitters, pipes	351
12 2	Greece	270		Hookahs and bongs	
13.3				Bucket smoking	
13.4	Italy	280		Hot knives (spots)	
13.5	Malta	281		Glass smoking or hot needles	
13.6	Poland			Vaping	
	Magistral preparations		14.3.8	Dabbing	356
	Compounding		15	Compounding of medicinal products	
	Pharmaceutical raw material			containing cannabinoids in the	
	Dosage forms of magistral preparations			pharmacy	358
	Extemporaneous medicine of medical	200	15.1	Legal framework	358
	cannabis in Poland	286		Magistral preparations (Rezepturarznei-	330
13.7	Portugal	287		mittel)	358
	_		15.1.2	Officinal medicinal product (Defektur-	250
	Legal framework			arzneimittel)	358
	Authorization procedures in Switzerland		15.2	Manufacturing documentation	360
	Fig. 1. Section of the section of th			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
15 <i>L</i>	Available starting materials and sources of		15.8.7	Imported cannabis flowers in preparations \dots	448
13.4	supply	364		Cannabis flowers from German cultivation \dots	
15 <i>l</i> ı 1	Flowers		15.8.9	Cannabis extracts in unchanged state	450
	Extracts		15.8.1	O Cannabis extracts in preparations	451
	Cannabinoids		15.8.1	1 Dronabinol in preparations	451
	Special characteristics of manufacturing	312	15.8.1	2 Cannabidiol in preparations	451
13.7.7	sets	373	16	Supply of cannabis prescriptions in	
		313		the pharmacy	458
15.5	Testing of starting materials for cannabis				
	flowers, cannabis extracts and			Legal framework	458
	cannabinoids		16.1.1	General formalities of the regulation of	
	Cannabis flowers			narcotics	458
	Extracts		16.1.2	Maximum quantities in the prescription of	
	Dronabinol			cannabis medicinal products	459
	CBD	390	16.1.3	Specific features of the prescription of	
15.5.5	Combined test systems discriminating THC			cannabis medicinal products	
	or CBD-dominant and equilibrated starting			Prescription drugs	
	materials	394		Proprietary medicinal products	
15.6	Manufacture of magistral prpeparations	399		Non-availability	
	Weighing correction			Drug substitution in cannabis preparations	468
	Plausibility check		16.1.8	Discount agreements for cannabis	
	Important processing aspects for			medicinal products	470
	standardized cannabis formulations	409	16.1.9	Obligation to check for cost coverage by	
15.6.4	Child-resistant packaging	420		statutory health insurance	471
	Baking mixtures		16.1.10	0 Individual imports in accordance with	
15.6.6	Production of flower or extract mixtures			Section 73(3) of the German Medicinal	
	with defined THC and CBD contents	424		Products Act	471
45 7	Duana untion of officiant modifical		16.2	Special features of pharmacy logistics when	1
15.7	Preparation of officinal medicinal			handling medicinal products containing	
1 - 7 1	Test instructions for officinal medicinal	431		cannabis	472
15.7.1		. 21	16.2.1	Storage	472
1 5 7 7	products Test protocol for officinal medicinal	431	16.2.2	Cannabis in mail order and courier service	473
13.7.2	products	1. 21	16.2.3	Transfer of narcotic drugs containing	
1 5 7 2	Risk-based tiered model for final analytical	431		cannabinoids between pharmacies	474
15.7.3	•	1.22	16.2.4	Returns of narcotics containing	
1	testing	432		cannabinoids	475
13.1.4	Application of the risk-based tiered model to medicinal products containing cannabis		16.2.5	Dealing with quality defects	475
	or cannabinoids	435	16.2.6	Withdrawal of narcotics containing	
	or carriabilitorus	400		cannabinoids by pharmacies	476
15.8	Price calculation	445	16.2.7	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	40	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 ⁺ 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	
	Narcotics Act	484		Traveling outside the Schengen area	506
17.3	Special features of narcotics documentation	,	18.6.3	Carrying of cannabis medicinal products	
	for prescription medicinal products	•		by physicians	509
	containing cannabis	485	18.7	Hunting license	500
17.3.1	Narcotics documentation specific to variety/		10.1	_	309
	extract	485	18.8	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
17.3.4	Weighing gain, weighing loss and overfill	492	The ed	itor	535
17.3.5	Mishaps during production	492			
			ine au	thors	230