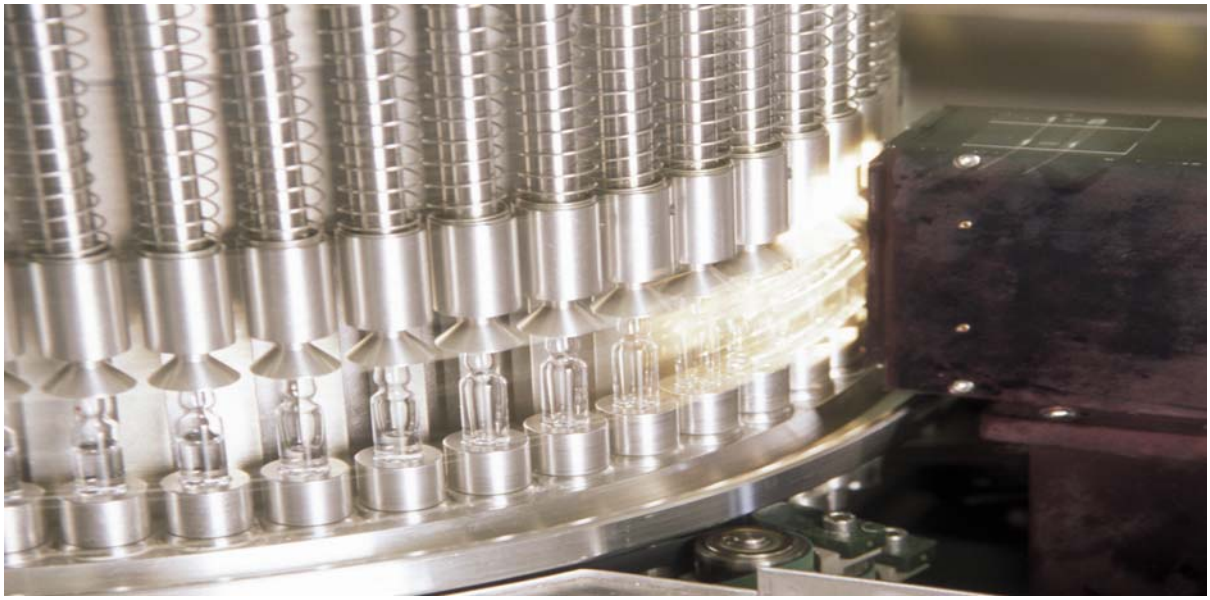
Safety of Homeopathic Injectables for Subcutaneous Administration as Used in Homeopathic and Anthroposophic Medicine



A documentation of the experience of prescribing practitioners

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SUMMARY OF THE ESSENTIALS

This survey gathered data from 1693 doctors experienced in the use of homeopathic injectables for subcutaneous use.

The data is based on over 36 million patient contacts.

All homeopathic medicinal products for subcutaneous use have been considered (low, high dilutions).

1594 of the 1693 doctors (94.2 %) choose the subcutaneous administration due to its therapeutic effect.

96.4 % of the doctors never, very rarely or rarely observe any adverse reactions due to the subcutaneous way of application.

The reported adverse reactions are mostly harmless (local redness, haematoma, local pain).

98.1 % of the doctors never, very rarely or rarely observe any adverse reactions due to the specific homeopathic medicinal product used.

The study shows, that homeopathic injectables have a very low risk profile.

A very small number of *severe* adverse reactions has been reported with products with lower degrees of dilution. Art. 14 of Directive 2001/83 excludes from the simplified registration homeopathic medicinal products which may have some risk profile due to the degree of dilution.

99.5 % of the doctors desire homeopathic injectables for subcutaneous use to stay on the market.

89 % of the doctors would severely or very severely be limited in their profession, if homeopathic injectables should disappear.

The very low risk profile of homeopathic injectables for subcutaneous use justifies the possibility for applicants to choose the simplified registration procedure.

CONTENTS

1. BACKGROUND AND FORMULATION OF THE PROBLEM

European and national authorities and legislative bodies ask for a "*Positive Risk-Benefit-Ratio*" when a medicinal product is assessed. This argument was one of the reasons why in 1992 the Directive 92/73/EC on homeopathic medicinal products restricted the simplified registration procedure to "oral or external use". Without basing this claim on facts, it was assumed that injections would bear a safety risk and therefore should be assessed by the full marketing authorisation procedure in the future.

In the meantime, this decision has been questioned not only by manufacturers and doctors, who fear to lose an important element of their therapeutic system, but also by the legislative bodies themselves. Following an expert report of 1996, the European Commission advised in an official Report to the European Parliament and the Council in 1997 the following: *"Article 7 paragraph 1 of Directive 92/73 could be amended in order to increase the scope of products subject to a simplified registration procedure. In particular this could involve the explicit inclusion of other routes of administration and modifications/clarification concerning registerable dilutions."*[1]

When the terms "risk" and "safety" are used, it is necessary to bear in mind that the simplified procedure for homeopathic medicinal products[2] does not neglect tests on these fields. Of the three criteria of medicinal products, which are "Quality", "Safety" and "Efficacy", only the assessment of the third is reduced. Up to now a plausible proof that homeopathic injectables for subcutaneous use represent severe safety problems has not been provided.

The Review of the European pharmaceutical legislation, a project which is ongoing since 2001 and entering Second Reading in 2003 brings this point once again on the agenda. Therefore, it now seems to be the right time to end speculations about risk or non-risk, by presenting reliable data that is able to answer the question whether or not subcutaneous use of homeopathic injectables implies severe safety problems.

A result of the injectables having to be assessed by the full marketing authorisation procedure could be that these products disappear from the market;: costly efficacy studies and high registration fees are mostly not covered by the turnover of the concerned medicinal products.

This is the context in which a study was designed with a twofold aim. On the one hand the experiences of prescribing practitioners with regard to safety issues would be charted. On the other hand, offering a clear view on the implications of the claim mentioned above, the extent in which practitioners who prescribe homeopathic injectables, would feel restricted in case subcutaneously administered homeopathics are banned, was studied as well.

[1] ***COM (97) 362 final***
[2] ***Article 14 of Directive 2001/83/EC***

2. RESEARCH QUESTIONS

1. In the experience of prescribing practitioners, what are the risks of the subcutaneous form of administration of homeopathic medicinal products and how great are these actual risks?

2. To what extent would prescribing practitioners, in their own opinion, be limited in their professional practice if the subcutaneous form of administration of homeopathic medicinal products were banned?

3. RESEARCH METHODS

3.1 Survey

A survey was performed in order to chart the experience of practitioners with the use of subcutaneous injections of homeopathic medicinal products, the associated risks and the extent of limitation in providing optimum treatment for patients in case these preparations would be no longer available. A questionnaire (Appendix 4) was designed to measure:

1. The years of experience as a practitioner or 'Heilpraktiker' (question 1);
2. The years of experience in prescribing homeopathic and/or anthroposophic subcutaneous preparations (question 2);
3. The factors associated with the choice of ways of administration of preparations (question 3);
4. The types and numbers of adverse effects, estimated risks, numbers of temporary and permanent effects due to the subcutaneous form of administration (question 4) and the preparations (question 5);
5. The experienced disadvantages of the subcutaneous form of administration (question 6);
6. The desire of availability of homeopathic products for subcutaneous use in the future (question 7); and
7. The estimated extent of limitation in providing optimum treatment for patients in case these preparations would be no longer available (question 8).

3.2 Prescribers

In February/March 2003, ECHAMP members approached around 4000 affiliated prescribers (General Practitioners (GP), specialists, dentists and "Heilpraktiker") throughout the following countries in Europe: Austria, Belgium, Finland, France, Germany, Ireland, Italy, The Netherlands, Spain, Sweden, Switzerland, and the United Kingdom, requesting them to complete the questionnaire and return it as soon as possible.
The following criteria were used for the selection of responders:

1. Since the questionnaire was developed to assess the experience concerning the safety of homeopathic ampoules for subcutaneous use retrospectively, those practitioners from whom this kind of experience could be expected were approached.

2. A highest possible response rate was aimed at, leading to choose practitioners perceived to have an active interest in the medicinal products of the outsending company.

3. Each company subsequently analysed its own address data-base. Analysis criteria were quite different, for example: doctors that had ordered preparations for subcutaneous use within the last years in order to test them, doctors visiting company seminaries in the last years, and doctors that were known to a company from other surveys within the range of Regulatory Affairs, for example surveys on dosage of homeopathic medicinal products in children.

No reward was given to any participating practitioner in return for completing the questionnaire.

3.3 Data management

All returned questionnaires were managed by the Louis Bolk Institute in the Netherlands and were entered into a database for data processing, using SPSS Data Entry Builder (version 3.0). The data processing itself was done using SPSS version 11.0.

All fully completed questionnaires were entered directly into the database. All incomplete or incorrectly completed questionnaires were discussed with the project leader. The following criteria were used to decide whether or not to include the questionnaires in the evaluation:

1. All the entered data were checked for the logical structure of the information provided. In case of the occurrence of illogical entries, these are mentioned in the results.
2. If an answer was clearly selected and then crossed out, and a second answer clearly selected in its place, the clearly indicated second answer to the question was entered into the database.
3. If two answers were given to a question requiring a single answer, these answers were not entered in the database. In the case of scaled questions the least favourable answer was entered.
4. All hand-written comments were entered separately and processed separately in the evaluation.
5. Only whole numbers could be entered into the database (all fractured numbers were rounded up) and before the data analysis was done, all answers were converted to the same time unit.

Data related to non-homeopathic products were excluded from the analysis.

3.4 Analysis

Various descriptive statistics were applied to the data.

4. RESULTS

The results will be described in three subchapters: descriptives (4.1), safety (4.2) and impact of theoretical banning of products for practitioners (4.3).

4.1 Descriptives

4.1.1 Response to the survey

2564 of an estimated 4000 (64.1%) prescribers approached, returned the questionnaire. Of the 2564 returned questionnaires, a total of 400 questionnaires could not be used for the analyses due to the following reasons: (a) 239 of the returned questionnaires were non-users and (b) 161 for various reasons. The various reasons were the following:

- Prescribers were sent the incorrect questionnaire (134x);
- An incorrect questionnaire was sent to the Louis Bolk Institute (5x);
- The Louis Bolk Institute received an original and a copy of the same questionnaire from the same responder (8x);
- An inappropriate group of professionals was approached (e.g. pharmacist, person had passed away)(6x);
- Prescribers had retired and therefore did not complete the questionnaire (5x); and
- The questionnaire was completely empty, thus reason unknown (3x).

- **The analyses of this report are based on the 2164 questionnaires of prescribers with experience in the use of homeopathic medicinal products: 1693 doctors and 471 'Heilpraktiker'.**

- **The main analyses are based on the response of the 1693 doctors (Chapters 4.1.3 through 4.1.6, Chapter 4.2 and 4.3). A summary of the results of the analyses of the 'Heilpraktiker' response is compared to the doctors and the total results in Appendix 1.**

4.1.2 Responders

Responses were received from 12 different countries: Austria, Belgium, Finland, France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom. Some countries had less than five responders therefore the data from these countries was added to the data of another country on the basis of their demographic relationship. Therefore, the data from Finland (23 responders) and Sweden (3); the data from Austria (65) and Switzerland (3) and the data from Ireland (2) and the United Kingdom (44) were combined (**Table 1**).

Table 1. Distribution of responses per country (with and without the 'Heilpraktiker')				
Country	Number with - without		Percentage with - without	
Austria (A) (Austria and Switzerland)	68	68	3.1	4.0
Belgium (B)	32	32	1.5	1.9
Germany (D)	1436	965	66.4	57.0
Spain (E)	163	163	7.5	9.6
France (F)	144	144	6.7	8.5
Great Britain (GB) (United Kingdom and Ireland)	46	46	2.1	2.7
Italy (I)	154	154	7.1	9.1
Netherlands (NL)	95	95	4.4	5.6
Scandinavia (Scand) (Finland and Sweden)	26	26	1.2	1.6
Total	2164	1693	100%	100%

The responders without address information (provided by the participating practitioner at the end of the questionnaire) (total 57) were added to the corresponding language group (32 German questionnaires, 25 French questionnaires).

The 1436 German responders could be divided into two groups: 962 practitioners (GP, specialist or dentist) and 471 "Heilpraktiker" (a therapeutic profession established and recognized in Germany, particularly trained in the use of natural therapies).

4.1.3 Demographics

The first questions in the questionnaire concerned the demographic data of the responders. The responders have been in practice for an average of 20.7 years (95% CI: 20.2 – 21.2; ± 10.3 SD; range: 1 - 64). They have an average of 17.0 years' experience in homeopathic/anthroposophic practice (95% CI: 16.6 – 17.5; ± 10.0 SD; range: 1 - 64), and an average of 16.3 years' experience of treating patients with subcutaneous injections (95% CI: 15.8 – 16.7; ± 10.1 SD; range: 1 - 64).

Of the 1693 responders 1125 are GPs (66.5%), 359 are specialists (21.2%), and 146 are dentists (8.6%), whereas 63 responders did not answer this question (3.7%). All 1693 practitioners used subcutaneous injections with homeopathically produced remedies.

The next questions in the questionnaire were added to achieve an estimation of the numbers of patients seen and treated within the practice of the responder. On average practitioners treated 113 patients per week (95% CI: 108.0 – 118.6; ± 109.4 SD, range: 0-800), 31 patients (95% CI: 28.6 – 33.6; ± 51.1 SD, range: 0-700) received one or more subcutaneous injections a week, thus 27% of the patients were treated with injections.

The range of 0-800 was revised by the researchers: in fact the upper limit of a maximum of 300 patients per week was seen as realistic maximum. The number of 300 was chosen based on the following calculation: 300/5 days a week = 60 patients a day; 8 working hours in a day, would mean 7,5 patients per hour or 8 minutes per patient. If 300 patients were used as an upper limit 86 out of 1693 cases were omitted. Revised results: on average 95 patients (95% CI: 91.3 – 98.9; ± 76.3 SD, range: 0-300) were treated weekly by the practitioners, 29 patients (95% CI: 26.9 – 30.7; ± 38.5 SD, range: 0-300) received at least one injection a week, thus 31% of the patients were treated with injections weekly.

In a small number of cases the responder noted that a larger amount of patients was treated per week with subcutaneous injections compared with the information supplied by the practitioners. This is attributable to the fact that e.g. in the practice of a GP, the assistant also administered injections to the patients.

4.1.4 Estimation of number of patient contacts on which the results are based

The following calculation was used to estimate the total number of patient contacts during which the patients were treated with subcutaneous injections by the sample of practitioners. The average number of patient contacts, during which the patients received an injection, per week (the least favourable number was used, resulting from the use of the cut-off point of 300, being 29) is multiplied by 45 (weeks in the year), then multiplied by the average number of years that the practitioners have been using subcutaneous injections, then by the number of participating practitioners. Hence the results are based on experience of treatment with subcutaneous injections of an estimate of 36,012,649 patient contacts (= 29 (patient contacts) x 45 (weeks/year) x 16.3 (years) x 1693 (practitioners)).

This calculation shows that the results in this report are based on the experience of practitioners with more than 36 million patient contacts with patients that have been treated with subcutaneous injections.

4.1.5 Selection of form of administration

The answers asked for in item three were aimed at the decision making process when the practitioner is making the choice between different forms of administration (**Table 2**). For 1277 of the 1693 doctors (75.4%) the choice of a form of administration was dependent on the indication. If asked whether the expected effect of administration was a determining factor to choose the form of application, 1594 of the 1693 responders (94.2%) answered positively in the case of subcutaneous administration. If asked whether a patient preference played a role in the choice, only 556 of the 1693 practitioners (32.8%) answered yes. In relation to this question it should be noted that some practitioners commented that they did not understand the question or that this was mainly the case when choosing a form of treatment for children.

Table 2. Factors affecting the selection of the form of administration

	Yes (n - %)		No (n - %)		No response (n - %)		Total	
Relationship between form of administration and treatment indication	1.277	75.4%	261	15.4%	155	9.2%	1693	100%
Effect	1.594	94.2%	46	2.7%	53	3.1%	1693	100%
Patient preference	556	32.8%	955	56.4%	182	10.8%	1693	100%

In the next question practitioners were asked to compare oral ingestion with subcutaneous injections when opting for a particular form of administration. A distinction was made between various factors, which can influence the choice of method (**Tables 3a +3b**). In general, practitioners opted for subcutaneous injections based on the following

reasons: (1) a quicker effect (1362 practitioners; 80.4%); (2) a better effect (1120 practitioners; 66.2%); (3) if oral ingestion was not possible (1478 practitioners; 87.3%) (4) easier to dose (532 practitioners; 31.4%); (5) exact location of administration (1511 practitioners; 89.2%); (6) a combination with other therapies (690 practitioners; 40.9%) and (7) a better compliance (1006 practitioners; 59.4%). There was no preference for either oral ingestion or subcutaneous injection when considering tolerability (1026 of the 1693; 60.6%). Opinions were more divided when considering ease of dosage, combining of therapies and patient preference.

Table 3a. Factors affecting the decision on the form of administration (numbers)

	Injection	Oral	Same	Not applicable	No response	Total
Quicker effect	1362	6	141	112	72	1693
Better effect	1120	6	305	170	92	1693
Easier to dose	532	165	593	300	103	1693
Exact location of administration	1511	6	40	68	68	1693
Can be combined with other therapies	690	21	725	140	117	1693
Better compliance	1006	39	390	158	100	1693
Better tolerability	195	127	1026	251	94	1693
Patient preference	99	518	586	394	96	1693
If oral administration is not possible	1478	1	28	109	77	1693

Table 3b. Factors affecting the decision on the form of administration (percentages)

	Injection	Oral	Same	Not applicable	No response	Total
Quicker effect	80.4	0.4	8.3	6.6	4.3	100
Better effect	66.2	0.4	18.0	10.0	5.4	100
Easier to dose	31.4	9.7	35.0	17.7	6.1	100
Exact location of administration	89.2	0.4	2.4	4.0	4.0	100
Can be combined with other therapies	40.9	1.2	42.8	8.3	6.9	100
Better compliance	59.4	2.3	23.0	9.3	5.9	100
Better tolerability	11.5	7.5	60.6	14.8	5.6	100
Patient preference	5.8	30.6	34.6	23.3	5.7	100
If oral administration is not possible	87.3	0.1	1.7	6.4	4.5	100

4.1.6 Summary of descriptives

The results of this study are based on the response of 1693 practitioners from 12 European countries, covering the experience of treatment with subcutaneous injections of an estimation of more than 36 million patient contacts. Both the subcutaneous form of administration in connection with the treatment indication as well as the effects related to this form of administration were positive factors in choosing the subcutaneous form of administration, compared to other forms. In general, practitioners opted for subcutaneous

injections for the following reasons: (1) quicker effect, (2) better effect, (3) if oral ingestion was not possible, (4) easier to dose, (5) exact location of administration, (6) combination with other therapies, and (7) better compliance.

4.2 Safety

The safety of the subcutaneous form of administration of homeopathic preparations was studied by investigating the adverse effects experienced by the practitioners, the gravity of the reported adverse effects, the type and number of temporary and permanent effects, and the related risk/benefit ratio. The adverse effects due to the way of administration and the adverse effects due to the specific medicinal product were studied separately.

4.2.1 Adverse effects due to the form of administration

The practitioners were asked to indicate how often they had observed adverse effects as a result of the specific subcutaneous form of administration per se, irrespective the preparation used (**Table 4**). In total 90.1% of the practitioners responded that they had never (57.4%) or very rarely (32.6%) observed adverse effects directly due to the injections. 9.9% of the practitioners indicated that they had rarely (6.4%) or only occasionally (3.5%) observed adverse effects due directly to a subcutaneous injection. The question was not answered by 41 (2.4%) practitioners.

Table 4. Adverse effects due to the form of administration (subcutaneous injection)

	Explanation	Number of doctors	Percentage	Valid percentage	Cumulative percentage
Never	Never	949	56.1	57.4	57.4
Very rarely	1 or less than 1 out of 10.000 treated patients	539	31.8	32.6	90.1
Rarely	more than 1 out of 10.000 treated patients	105	6.2	6.4	96.4
Occasionally	more than 1 out of 1000 treated patients	57	3.4	3.5	99.9
Frequently	more than 1 out of 100 treated patients	1	0.1	0.1	99.9
Very frequently	more than 1 out of 10 treated patients	1	0.1	0.1	100
No response		41	2.4		
Total		1693	100%	100%	

To determine the scale of the problem of the number of adverse effects two comparable questions were asked: (a) to give an estimation of the total number of patients they had observed in their whole career with an adverse reaction as a result of subcutaneous injections; and (b) to give an estimation of the total number of patients they have observed on average over a certain period with an adverse reaction due to subcutaneous injections.

The results of numbers of adverse effects observed throughout the whole career of a practitioner are comparable to the results observed in the former question with the scaled option: 57.4% see no adverse effects versus 56%. The number of adverse effects observed in a year were, as to be expected, lower than the number of adverse effects observed throughout the whole career: 27% versus 44% (**Tables 5a & 5b**).

Table 5a. Number of doctors reporting adverse effects found *throughout all the practising years* due to the form of administration (subcutaneous injection)				
	Number of doctors	Percentage	Valid number of doctors	Valid percentage
No adverse effects	809	47.8	809	56
Adverse effects	635	37.5	635	44
No response	249	14.7		
Total	1693	100%	1444	100%

Table 5b. Number of doctors reporting adverse effects found *in one year* due to the form of administration (subcutaneous injection)				
	Number of doctors	Percentage	Valid number of doctors	Valid percentage
No adverse effects	974	57.5	974	72.9
Adverse effects	360	21.3	360	27.1
No response	359	21.2		
Total	1693	100%	1465	100%

On average each practitioner observed 8.5 ± 65.5 SD (95% CI: 5.1 – 11.8; range: 0-2000) adverse reactions to subcutaneous injections during his entire professional practice. In a single year each practitioner would observe about 1.7 ± 16.6 SD (95% CI: 0.8 – 2.5; range: 0-520) cases with adverse reactions. The analysed mean number of patients with effects observed in a year is too high (1.7), compared to the results in the question with the scaled options ("never" through "very frequently") and the question during the whole career. This is due to the fact that only whole numbers could be entered in the database and many entries were lower than 1.

In total there were 32 types of adverse effects reported due to a subcutaneous injection (**Table 6**). For each report the practitioners were asked to assess the associated risk on a scale of 1 to 5 (1= none, 2= little, 3=some, 4= high, 5= very high). Of these 32 types, 29 are harmless and, only three reactions were reported with a mean risk higher than 'little': anaphylactic reaction (2.33), feverish symptoms (2.67), and aversion/anxiety against injections (2.50). Only one reaction was reported with a risk greater than 'high': asthma (4,00).

Table 6. Types of adverse effects and associated mean risks due the subcutaneous form of administration		
Adverse effects	**Practitioners (n)**	**Mean risk + (n)**
	974	
Local redness	182	1,56 (163)
Haematoma	155	1,52 (146)
Local pain	123	1,47 (115)
Allergic reaction	86	1,83 (82)
Local infection	70	1,70 (62)
Local skin reaction	64	1,72 (63)
Vasovagal reaction	61	1,62 (58)
Local swelling	53	1,68 (47)
Itching	41	1,80 (34)
Local burning	22	1,85 (20)
Orthostatic reaction	20	1,91 (11)
Short aggravation of symptoms	13	1,67 (12)
Nausea	13	1,5 (12)
Oedema	12	1,36 (11)
Abscess	8	1,83 (6)
Headache	8	1,57 (7)
Aversion/anxiety against injections	7	2,20 (5)
Feverish symptoms	6	2,67 (6)
Total malaise	4	2,00 (3)
Granuloma	4	1,50 (4)
Anaphylactic reaction	4	2,33 (3)
Gastro-intestinal problems	3	2,00 (3)
Depression	2	2,00 (2)
Nerve pain	2	1,50 (2)
Sleep disturbances	2	1,50 (2)
Myalgia	2	1,00 (2)
Herpes	2	1,00 (2)
Asthma	1	4,00 (1)
Psychological problems	1	2,00 (1)
Muscle contractions	1	2,00 (1)
Chilliness	1	2,00 (1)
Fatigue	1	2,00 (1)

- mean risks higher than 2 up to and including 3 are printed in blue
- mean risks higher than 3 are printed in red

4.2.2 Adverse effects due to the specific medicinal product used

The practitioners were asked to indicate how often they had observed adverse effects due to the preparation used (**Table 7**). In total 95.2% of the practitioners had very rarely (22.6%) to never (72.6%) observed adverse reactions as a result of the preparation used. 4.7% of the practitioners indicated that they had rarely (2.9%) or only occasionally (1.8%) observed adverse reactions as a result of the preparation used in a subcutaneous injection.

Table 7. Adverse effects due to the specific medicinal product used					
	Explanation	Number	Percentage	Valid percentage	Cumulative percentage
Never	Never	1120	66.2	72.6	72.6
Very rarely	1 or less than 1 out of 10.000 treated patients	349	20.6	22.6	95.2
Rarely	more than 1 out of 10.000 treated patients	44	2.6	2.9	98.1
Occasionally	more than 1 out of 1000 treated patients	28	1.7	1.8	99.9
Frequently	more than 1 out of 100 treated patients	2	0.1	0.1	100
Very frequently	more than 1 out of 10 treated patients	0	0	0	
No response		150	8.9		
Total		1693	100%	100%	

Again, to determine the scale of the number of adverse effects the practitioners were asked to answer two comparable questions: (a) to give an estimation of the total number of patients they had observed in their career with an adverse reaction as a result of the used preparation; and (b) to give an estimation of the total number of patients that they have observed on average over a certain period with an adverse reaction due to the used preparation.

The numbers of adverse effects observed throughout the whole career of a practitioner were comparable with the results found in the former question with the scaled option, 72.6% have observed no adverse effects versus 68.3%. The number of adverse effects found in a year were, as to be expected, lower, 20.9% versus 31.7% throughout the whole career (**Tables 8a & 8b**).

Table 8a. Number of responders reporting adverse effects observed ***throughout all the practising years*** due to the specific medicinal product used				
	Number of responders	Percentage	Valid number of responders	Valid percentage
No adverse effects	963	56.9	963	68.3
Adverse effects	446	26.3	446	31.7
No response	284	16.8		
Total	1693	100%	1409	100%

Table 8b. Number of responders reporting adverse effects observed ***in one year*** due to the specific medicinal product used				
	Number of Responders	Percentage	Valid number of responders	Valid percentage
No adverse effects	1038	61.3	1038	79.1
Adverse effects	274	16.2	274	20.9
No response	381	22.5		
Total	1693	100%	1312	100%

On average a practitioner observed 4.5 ± 22.1 SD (95% CI: 3.3 – 5.7; range: 0-500) adverse reactions due directly to the preparation during his total career. Per year a practitioner would observe about 1.4 ± 0.7 SD (95% CI: 1.3 – 1.4; range: 0-208) cases of

adverse reactions due to the preparation. The mean number of patients showing an effect in a year was too high (1.4) compared to the results in the question with the scaled options ("never" through "very frequently") and the question during the whole career. This was due to the fact that only whole numbers could be entered in the database and many entries were lower than 1.

In total the practitioners reported 91 preparations, that in their experience had caused in total 212 times adverse effects when given by subcutaneous injection. For 35 of these preparations more than one adverse effect was reported (**Table 9a**) and 55 had only one adverse effect (**Table 9b**). **Table 9c** shows reported adverse effects without a preparation mentioned. For each preparation the practitioners were asked to assess the associated risk on a scale of 1 to 5 (1= none, 2= little, 3=some, 4= high, 5= very high). The practitioners were also asked to evaluate the relationship between the possible risks and benefits of injections using preparations that had been observed to produce adverse reactions. The following options were given: benefit outweighs risk = 1, benefit equals risk = 2, risk outweighs benefit = 3.

In **Table 9a** 17 cases with a mean associated risk higher than 'little' (2) were reported (of which 5 were higher than "some" (3), being:
- B with adverse effect 'dyspnoea'
- D with adverse effect 'anaphylactic reaction'
- O with adverse effect 'oedema'
- T with adverse effect 'pain', and
- Z with adverse effect 'local burning'.

In **Table 9a** four cases with a ratio risk/benefit higher than 2 (meaning that the risk is higher than the benefit) were reported. These cases were:
- B with adverse effect 'dyspnoea'
- D with adverse effects 'anaphylactic reaction'
- D with adverse effect 'haematoma' and
- I with adverse effect 'palpitations'.

Table 9a. Adverse effects due to preparations, mean risk and mean risk/benefit (preparations reported by more than 1 responder)

	Number of responders (n)	Mean risk + (n)	Mean risk/benefit + (n)
A (12 Adverse effects (AE))	104		
Allergic reaction	25	1,77 (22)	1,30 (23)
Local redness	25	1,70 (23)	1,08 (24)
Local skin reaction	14	1,93 (13)	1,08 (14)
Local swelling	8	1,63 (8)	1,00 (7)
Local burning	6	1,00 (6)	1,00 (6)
Pain	6	1,83 (6)	1,00 (5)
Itching	5	1,75 (4)	1,00 (4)
Inflammation	4	1,75 (4)	1,50 (4)
Orthostatic reaction	4	2,50 (4)	1,50 (4)
Oedema	3	1,67 (3)	1,00 (3)
Anaphylactic reaction	2	3,00 (2)	2,00 (2)
Haematoma	2	1,00 (1)	1,00 (2)

B (15 AE)	56		
Allergic reaction	14	1,82 (22)	1,43 (21)
Local redness	13	1,58 (12)	1,17 (12)
Local skin reaction	7	2,14 (7)	1,00 (7)
Itching	5	2,40 (5)	1,40 (5)
Haematoma	3	1,67 (3)	1,33 (3)
Pain	3	1,33 (3)	1,00 (3)
Orthostatic reaction	2	2,00 (2)	1,50 (2)
Swelling	2	2,00 (2)	1,00 (2)
Dyspnoea	1	5,00 (1)	3,00 (1)
Inflammation	1	1,00 (1)	1,00 (1)
Local burning	1	1,00 (1)	1,00 (1)
Local infection	1	2,00 (1)	1,00 (1)
Oedema	1	3,00 (1)	1,00 (1)
Psychological problems	1		1,00 (1)
Short aggravation of symptoms	1	2,00 (1)	1,00 (1)
C (10 AE)	33		
Allergic reaction	8	2,14 (7)	1,29 (7)
Local redness	7	1,57 (7)	1,14 (7)
Pain	5	1,80 (5)	1,00 (5)
Local burning	3	1,00 (3)	1,00 (3)
Local skin reaction	3	1,25 (4)	1,25 (4)
Itching	2	1,50 (2)	1,00 (2)
Local swelling	2	1,50 (2)	1,50 (2)
Dizziness	1	1,00 (1)	1,00 (1)
Inflammation	1	2,00 (1)	1,00 (1)
Vasovagal reaction	1	2,00 (1)	1,00 (1)
D (9AE)	21		
Allergic reaction	6	2,00 (6)	1,80 (5)
Inflammation	4	1,50 (4)	1,67 (3)
Local redness	4	1,25 (4)	1,00 (1)
Itching	2	1,00 (2)	1,00 (2)
Local swelling	2	1,50 (2)	2,00 (1)
Anaphylactic reaction	1	5,00 (1)	3,00 (1)
Haematoma	1	3,00 (1)	3,00 (1)
Pain	1	2,00 (1)	2,00 (2)
Local skin reaction	0	2,00 (1)	1,00 (1)
E (6AE)	13		
Local skin reaction	4	1,75 (4)	1,25 (4)
Local redness	3	1,00 (2)	1,00 (2)
Allergic reaction	2	1,50 (2)	1,00 (2)
Pain	2	1,50 (2)	1,00 (2)
Parasthesias	1	2,00 (1)	1,00 (1)
Short aggravation of symptoms	1	m.v.	m.v.
F (5AE)	10		
Pain	4	2,00 (3)	1,00 (4)
Local redness	2	1,50 (2)	1,00 (2)
Oedema	2	2,50 (2)	1,00 (2)
Haematoma	1	1,00 (1)	1,00 (1)
Itching	1	1,00 (1)	1,00 (1)

G (6AE)	9		
Local redness	3	1,67 (3)	1,00 (3)
Allergic reaction	2	2,00 (2)	1,00 (20
Feverish symptoms	1	2,00 (1)	1,00 (1)
Inflammation	1	2,00 (1)	1,00 (1)
Itching	1	1,00 (1)	1,00 (1)
Local swelling	1	2,00 (1)	1,00 (1)
H (6AE)	8		
Local redness	2	2,00 (2)	1,00 (2)
Local skin reaction	2	1,00 (2)	1,50 (2)
Allergic reaction	1	2,00 (1)	1,00 (1)
Haematoma	1	2,00 (1)	1,00 (1)
Itching	1	2,00 (1)	
Total malaise	1	2,00 (1)	1,00 (1)
I (6AE)	7		
Local redness	2	1,00 (2)	1,00 (2)
Allergic reaction	1	2,00 (1)	1,00 (1)
Local burning	1	3,00 (1)	1,00 (1)
Local swelling	1	1,00 (1)	1,00 (1)
Orthostatic reaction	1	2,00 (1)	1,00 (1)
Palpitations	1	2,00 (1)	3,00 (1)
J (5AE)	6		
Local redness	2	2,00 (2)	1,00 (2)
Allergic reaction	1	2,00 (1)	1,00 (1)
Feverish symptoms	1	2,00 (1)	1,00 (1)
Headache	1	2,00 (1)	1,00 (1)
Swelling	1	2,00 (1)	1,00 (1)
K (5AE)	6		
Local redness	2	1,50 (2)	1,50 (2)
Allergic reaction	1	2,00 (1)	2,00 (1)
Inflammation	1		1,00 (1)
Intolerance	1	1,00 (1)	1,00 (1)
Pain	1	2,00 (1)	2,00 (1)
L (5AE)	6		
Gastro-intestinal problems	2	1,50 (2)	1,00 (2)
Allergic reaction	1	1,00 (1)	1,00 (1)
Local burning	1	1,00 (1)	1,00 (1)
Short aggravation of symptoms	1	1,00 (1)	1,00 (1)
Sweating	1	1,00 (1)	1,00 (1)
M (4AE)	6		
Allergic reaction	2	1,50 (2)	1,00 (2)
Local skin reaction	2	2,00 (2)	1,50 (2)
Haematoma	1	2,00 (1)	1,00 (1)
Itching	1	1,00 (1)	1,00 (1)
N (3AE)	5		
Allergic reaction	3	1,33 (3)	1,00 (3)
Local burning	1	3,00 (1)	1,00 (1)
Local redness	1	1,00 (1)	1,00 (1)

Q (2AE)	5		
Allergic reaction	4	2,00 (3)	1,33 (3)
Oedema	1	4,00 (1)	2,00 (1)
P (2AE)	4		
Local redness	2	2,00 (2)	1,00 (2)
Local swelling	2	2,00 (2)	1,00 (2)
Q (4AE)	4		
Feverish symptoms	1	1,00 (1)	1,00 (1)
Itching	1	1,00 (1)	1,00 (1)
Local redness	1	1,00 (1)	1,00 (1)
Short aggravation of symptoms	1	1,00 (1)	1,00 (1)
R (4AE)	4		
Allergic reaction	1	1,00 (1)	1,00 (1)
Itching	1	1,00 (1)	1,00 (1)
Local redness	1	1,00 (1)	1,00 (1)
Local skin reaction	1	2,00 (1)	1,00 (1)
S (2AE)	3		
Allergic reaction	2	3.00 (1)	1,00 (1)
Local redness	1	1,00 (1)	1,00 (1)
T	3		
Pain	3	3,33 (3)	1,00 (3)
U	3		
Allergic reaction	3	2,00 (3)	1,33 (3)
V (2AE)	3		
Allergic reaction	2	1,00 (2)	1,00 (2)
Local skin reaction	1	1,00 (1)	1,00 (1)
W	3		
Local burning	3	1,00 (3)	1,00 (2)
X (3AE)	3		
Dizziness	1	1,00 (1)	1,00 (1)
Nausea	1	1,00 (1)	
Orthostatic reaction	1	1,00 (1)	1,00 (1)
Y (3AE)	3		
Itching	1	2,00 (1)	1,00 (1)
Local burning	1	1,00 (1)	1,00 (1)
Oedema	1	1,00 (1)	1,00 (1)
Z (2AE)	2		
Local burning	1	4,00 (1)	1,00 (1)
Local skin reaction	1	1,00 (1)	
AA (2AE)	2		
Allergic reaction	1		1,00 (1)
Vasovagal reaction	1	3,00 (1)	1,00 (1)

AB (2AE)	2		
Local skin reaction	1	2,00 (1)	1,00 (1)
Oedema	1	1,00 (1)	1,00 (1)
AC (2AE)	2		
Local redness	1	2,00 (1)	1,00 (1)
Local skin reaction	1	2,00 (1)	2,00 (1)
AD (2AE)	2		
Local burning	1	1,00 (1)	1,00 (1)
Myalgia	1	2,00 (1)	1,00 (1)
AE (2AE)	2		
Local redness	1	2,00 (1)	1,00 (1)
Pain	1	1,00 (1)	1,00 (1)
AF (2AE)	2		
Depression	1	m.v.	1,00 (1)
Local skin reaction	1	2,00 (1)	2,00 (1)
AG (2AE)	2		
Anaphylactic reaction	1	2,00 (1)	1,00 (1)
Locale skin reaction	1	2,00 (1)	1,00 (1)
AH (2 AE)	3		
Allergic reaction	2	1,00 (2)	1,00 (2)
Local burning	1	2.00 (1)	1.00 (1)
AI (2AE)	2		
Local redness	1	2,00 (1)	1,00 (1)
Pain	1	2,00 (1)	1,00 (1)

- m.v. = missing value(s)
- mean risks higher than 2 up to and including 3 are printed in blue
- mean risks higher than 3 are printed in red
- mean ratios risk/benefit higher than 2 (meaning that the risk is higher than the benefit) are printed in red

In **Table 9b** 7 cases with a mean associated mean risk higher than 'little' (2) are reported (of which 2 higher than "some" (3), being:
- BO with adverse effect 'pain'; and
- CX with adverse effect 'local skin reaction'.

In **Table 9b** eight cases are reported with a mean risk/benefit ratio higher than 2, being:
- BT with adverse effect 'orthostatic reaction';
- BX with adverse effect 'allergic reaction';
- CL with adverse effect 'allergic reaction';
- CM with adverse effect 'vasovagal reaction';
- CX with adverse effect 'local skin reaction';
- DA with adverse effect 'allergic reaction';
- DB with adverse effect 'allergic reaction' and
- DC with adverse effect 'orthostatic reaction'.

Table 9b. Adverse effects due to preparations, mean risk and mean risk/benefit ratio(preparations reported by 1 responder only)		
Product name	**Mean risk + (n)**	**Mean risk/benefit ratio + (n)**
BA		
Pain	2.00 (1)	1.00 (1)
BB		
Allergic reaction	m.v.	1.00 (1)
BC		
Pain	1.00 (1)	1.00 (1)
BD		
Allergic reaction	1.00 (1)	1.00 (1)
BE		
Local redness	1.00 (1)	1.00 (1)
BF		
Local skin reaction	1.00 (1)	1.00 (1)
BG		
Tiredness	1.00 (1)	1.00 (1)
BH		
Local redness	2.00 (1)	1.00 (1)
BI		
Local skin reaction	m.v.	m.v.
BJ		
Local skin reaction	1.00 (1)	1.00 (1)
BK		
Local skin reaction	1.00 (1)	1.00 (1)
BL		
Pain	3.00 (1)	1.00 (1)
BM		
Itching	1.00 (1)	1.00 (1)
BN		
Allergic reaction	2.00 (1)	1.00 (1)
BO		
Pain	4.00 (1)	1.00 (1)
BP		
Allergic reaction	3.00 (1)	2.00 (1)
BQ		
Muscle contractions	m.v.	m.v.
BR		
Local redness	1.00 (1)	1.00 (1)
BS		
Muscle contractions	2.00 (1)	1.00 (1)
BT		
Orthostatic reaction	1.00 (1)	3.00 (1)
BU		
Local redness	1.00 (1)	1.00 (1)
BV		
Dizziness	3.00 (1)	1.00 (1)
BW		
Haematoma	1.00 (1)	1.00 (1)
BX		
Allergic reaction	1.00 (1)	3.00 (1)
BY		
Local redness	1.00 (1)	2.00 (1)

BZ Pain	1.00 (1)	1.00 (1)
CA Local redness	1.00 (1)	1.00 (1)
CB Local burning	1.00 (1)	1.00 (1)
CC Local swelling	1.00 (1)	m.v.
CD Local burning	2.00 (1)	1.00 (1)
CE Local swelling	1.00 (1)	1.00 (1)
CF Nausea	2.00 (1)	1.00 (1)
CG Allergic reaction	2.00 (1)	1.00 (1)
CH Allergic reaction	2.00 (1)	1.00 (1)
CI Dizziness	1.00 (1)	m.v.
CJ Local redness	1.00 (1)	1.00 (1)
CK Local skin reaction	2.00 (1)	1.00 (1)
CL Allergic reaction	2.00 (1)	3.00 (1)
CM Vasovagal reaction	3.00 (1)	3.00 (1)
CN Pain	1.00 (1)	1.00 (1)
CO Headache	1.00 (1)	1.00 (1)
CP Allergic reaction	1.00 (1)	2.00 (1)
CQ Pain	1.00 (1)	2.00 (1)
CR Local skin reaction	1.00 (1)	1.00 (1)
CS Local redness	2.00 (1)	1.00 (1)
CT Local redness	1.00 (1)	1.00 (1)
CU Local redness	1.00 (1)	1.00 (1)
CV Nausea	2.00 (1)	1.00 (1)
CW Local skin reaction	2.00 91)	1.00 (1)
CX Local skin reaction	5.00 (1)	3.00 (1)
CY Pain		
DA Allergic reaction	1.00 (1)	3.00 (1)
DB Allergic reaction	2.00 (1)	3.00 (1)

DC		
Orthostatic reaction	3.00 (1)	3.00 (1)
DD		
Local skin reaction	2.00 (1)	1.00 (1)

- m.v. = missing value(s)
- mean risks higher than 2 up to and including 3 are printed in blue
- mean risks higher than 3 are printed in red
- mean risk/benefit ratios higher than 2 (meaning that the risk is higher than the benefit) are printed in red

Table 9c shows one adverse reaction with a mean risk above "little" and no effects above "some". No risk/benefits ratios above 2 were reported.

Table 9c. Adverse effects due to unknown preparations, mean risk and mean risk/benefit ratio

Adverse effect	Number of respondents	Mean risk + (n)	Mean risk/benefit ratio + (n)
Local redness	21	1,40 (15)	1,27 (15)
Local burning	11	1,67 (9)	1,00 (7)
Allergic reaction	10	1,43 (7)	1,00 (5)
Local skin reaction	10	1,36 (11)	1,00 (7)
Fatigue	2	m.v	1,00 (1)
Itching	2	1,50 (2)	1,50 (2)
Dizziness	2	2,00 (2)	1,00 (2)
Haematoma	2	1,00 (1)	1,00 (1)
Orthostatic reaction	1	0	0
Gastro-intestinal problems	1	1,00 (1)	0
Nausea	1	0	0
Local swelling	1	1,00 (1)	1,00 (1)
Feverish symptoms	1	1,00 (1)	1,00 (1)
Aggravation of symptoms	0	3,00 (1)	2,00 (1)

- m.v. = missing value(s)
- mean risks higher than 2 up to and including 3 are printed in blue
- mean risks higher than 3 are printed in red
- mean risk/benefit ratios higher than 2 (meaning that the risk is higher than the benefit) are printed in red

4.2.3 High risks, temporary and permanent effects

All responses to the question about permanent effects were divided into two groups depending on the adverse effect described: recurrent effects and permanent effects. Recurrent effects are those which always occur after use of the medicinal product concerned, but also disappear completely after a certain period of time (for example fever and haematoma). Permanent effects are those which occur and never disappear again. In the study only recurrent effects were reported.

14 responders (**Table 10a & 10 b**) have observed adverse effects with a high (n = 10; **Table 10a**) and a very high (n=4; **Table 10b**) risk due to the form of administration (subcutaneous injection). In 3 of these 14 cases a recurrent effect was observed: bleeding, itching and haematoma.

Table 10a. Risk 4: Adverse effects (risk = 4) with temporary and/or recurrent effect due to the form of administration (subcutaneous injection)			
Adverse effects with risk 4	**Responders (n)**	**Temporary effect (mean number of patients/year)**	**Recurrent effect (mean number of patients/year)**
	10		
Bleeding	2	2.5	1 (+ m.v.)
Itching	1	5	1
Local skin reaction	1	8	0
Pain	1	4	0
Vasovagal reaction	1	m.v.	m.v.
Haematoma	1	m.v.	m.v.
Asthma	1	3	m.v.
Abscess	1	0	0
Local burning	1	m.v.	m.v.

m.v. = missing value

Table 10b. Risk 5: Adverse effects (risk = 5) with temporary and/or recurrent effect due to the form of administration (subcutaneous injection)			
Adverse effects with risk 5	**Responders (n)**	**Temporary effect (mean number of patients/year)**	**Recurrent effect (mean number of patients/year)**
	4		
Feverish symptoms	1	m.v.	m.v.
Itching	1	3	m.v.
Anaphylactic reaction	1	m.v.	0
Haematoma	1	2	1

m.v. = missing value

Table 10c. Relationship between adverse effects with a risk with temporary and/or recurrent effect due to the homeopathic preparation					
Products and side-effects	**Frequency**	**Risk**	**Risk/benefit**	**Temporary effect**	**Recurrent effect**
M					
Local skin reaction	1	3	2	m.v.	m.v.
D					
Short aggravation of symptoms	1	3	2	m.v.	m.v.
W					
Vasovagal reaction	1	3	2	m.v.	m.v.
B					
Haematoma	1	3	2	1	1

B					
Allergic reaction	2	3	3	1/1	m.v. /0
A					
Local vesicle formation	1	3	3	0	0
D					
Haematoma	1	3	3	4	0
720					
Local skin reaction	1	3	2	1	0
B					
Orthostatic reaction	1	4	3	1	0
A					
Allergic reaction	1	4	3	m.v.	m.v.
Asthma	1	5	3	1	m.v.
B					
Allergic reaction	1	5	2	1	0
D					
Anaphylactic reaction	1	5	3	0	0
CY					
Local skin reaction	1	5	3	0	0

mean risk/benefit ratios higher than 2 (meaning that the risk is higher than the benefit) are printed in red
m.v. = missing value

4.2.4 Other disadvantages

Practitioners were asked to indicate whether there were other disadvantages associated with subcutaneous injections which had not been covered in previous questions. 1362 (93.3%) of the 1693 practitioners responded, 114 did not answer the question. 1362 of the responding practitioners (86.3%) did not consider that there were any other disadvantages associated with the use of subcutaneous injections. 217 practitioners (13.7%) did think there were 12 other disadvantages to using subcutaneous injections (**Table 11**).

Table 11. Other disadvantages of the subcutaneous form of administration as experienced by practitioners

Disadvantages	Number of respondents
1. Pain/local skin reactions and infections, in which the practitioner-patient interaction is disturbed	34
2. Due to (psychological) fear it is hard to administer subcutaneous injections to children, in which the practitioner-patient interaction is disturbed	25
3. Needle phobia and fear	21
4. High costs and slow delivery by the pharmacy associated with the homeopathic medicinal products	20
5. When patients cannot inject themselves, they have to visit the practitioner often	18
6. Slow pharmacological effect	3
7. The acknowledgement of homeopathic medicinal products is not optimal	2
8. The amount of injectables in one supply is not sufficient	2
9. Local burning in especially very skinny individuals	2
10. Habituation due to recurrent administration	1
11. Hard to administer to the elderly, due to gastro-intestinal problems and thin skin	1
12. Total malaise after injections	1

4.2.5 Summary of safety

57.4% of the practitioners has never observed adverse effects due to the way of administration by subcutaneous injection per se, throughout the whole career. Another 37.0% of the practitioners had (very) rarely observed an adverse reaction, 3.5% had occasionally, 0.1% had frequently and 0.1% had very frequently observed an adverse reaction due to the way of administration by subcutaneous injection per se throughout the whole career. On average, 8.5 patients with adverse effects were observed per practice throughout the whole career and per year approximately 1.7 patients are observed. 32 types of adverse reactions due to subcutaneous injections were reported. 29 of these 32 types of reactions are harmless (mean score of 'little risk' or lower). Only three reactions were reported with a mean risk between 'little risk' and 'some risk': anaphylactic reactions, feverish symptoms and aversion/ anxiety against injections. Only once one single reaction with a high risk was observed and reported: asthma.

72.6% of the practitioners reported no (adverse) effects that could be related to the specific homeopathic product used throughout the whole career. 25.5% of the practitioners had (very) rarely observed an adverse reaction due to a product. 1.8% had occasionally, 0.1% had frequently and 0% had very frequently observed an adverse reaction due to the product per se throughout the whole career. On average, 4.5 patients per practice throughout the whole career are observed with effects due to the preparation used, per year it is an average of 1.4 patient. In total the practitioners reported 91 preparations, which in their experience had caused in total 212 adverse effects when given by subcutaneous injection. 35 preparations had more than one adverse effects and 55 had only one adverse effect. In total 16 adverse reactions with a mean risk between 'little' (2) and 'some' (3) were reported, and 7 with a mean risk higher than 'some' (3). All other reported adverse effects had been judged with a mean risk lower than 'little' (2). 12 adverse reactions had a mean risk/benefit ratio higher than 2, indicating that the risk of these adverse reactions are considered higher than the benefit of the treatment with this product. From the adverse effects with a 'high' and 'very high' mean risk, only an average of 2 and respectively 1 patient per year with a recurrent effect were reported. These three adverse effects were: bleeding, itching and haematoma.

Next to the adverse effects reported as a direct result of the subcutaneous injection itself and the specific products used, 86.3% of the practitioners are of the opinion that there are no other disadvantages that are related to the subcutaneous form of administration. 13.7% did think there were 12 other disadvantages to using subcutaneous injections.

4.3 Impact of theoretical disappearing of homeopathic injectables on practitioners

The extent in which practitioners, who prescribe homeopathic injectables, would feel restricted in case subcutaneously administered homeopathics disappear, was also studied.

When asked whether the respondents would like to have continued access to the option of preparations intended for administration by subcutaneous injection, 99.5% of the practitioners answered in the affirmative (**Table 12**).

Table 12. Desire of availability of the homeopathic medicinal products for subcutaneous use in the future?

	Number of responders	Percentage	Valid percentage
Yes	1661	98.1%	99.5%
No	9	0.5%	0.5%
No response	23	1.4%	
Total	1693	100%	100%

The practitioners were also asked to what extent they would be limited in providing optimum treatment for patients if these preparations were no longer available (**Table 13**). 89.0% of practitioners indicated that in that situation they would feel severely (28.2%) to very severely (60.8%) limited.

Table 13. Extent of limitation for the practitioner

	Number of Responders	Percentage	Valid percentage	Cumulative percentage
Very severely	1016	60.0	60.8	60.8
Severely	471	27.8	28.2	89.0
Moderately	149	8.8	8.9	97.9
A little	30	1.8	1.8	99.7
None	4	0.2	0.2	100
No response	23	1.4		
Total	1693	100%	100%	

Some practitioners spontaneously wrote down some remarks with regard to the impact of theoretical disappearing of homeopathic injectables on practitioners' practices (**Table 14**).

Table 14. Remaining remarks	N
"The treatment of my patients will be virtually impossible if no subcutaneous injections will be available in the future, as there are more advantages compared to orally taken medication"	1
"All homeopathic medicinal products, and especially injectables are all very reliable and all risks are kept to the minimum"	1
"Almost all patients using homeopathic injectables have chronic symptoms and it would be unthinkable what would happen to these patients if subcutaneous injections were to be banned!"	1
"When injectables would be banned, I would have to discard various treatment methods	1
"A lot of patients will be disadvantaged if subcutaneous injections are banned as a treatment method"	1
"Who is to take the blame, when a lot of patients are disadvantaged in the future?"	1

5. SUMMARY, CONCLUSIONS AND DISCUSSION

5.1 Summary

European and national authorities and legislative bodies ask for a "*Positive Risk-Benefit-Ratio*" when a medicinal product is assessed. This argument was one of the reasons why in 1992 the Directive 92/73/EC on homeopathic medicinal products restricted the simplified registration procedure to "oral or external use". Without basing this claim on facts, it was assumed that injections would bear a safety risk and therefore should be assessed by the full marketing authorisation procedure in the future. A result of the injectables being assessed by the full marketing authorisation procedure could be that these products disappear from the market: costly efficacy studies and high registration fees are mostly not covered by the turnover of the concerned medicinal products. This would potentially restrict practitioners.

This study was done in order to present reliable data that are able to answer the question whether or not subcutaneous use of homeopathic injectables implies severe safety problems and to what extent practitioners would be limited in case these preparations would be disappear from the market. Two questions were answered by means of a survey among subcutaneously administered homeopathic injectables prescribing practitioners in 12 European countries:

1. In the experience of prescribing practitioners, what are the risks of the subcutaneous form of administration of homeopathic medicinal products and how great are these risks?

2. To what extent would prescribing practitioners, in their own opinion, be limited in their professional practice if the subcutaneous form of administration of homeopathic medicinal products medicines were banned?

Both the relative and the absolute response were high: 2164 responders (61%); 1693 doctors and 471 'Heilpraktiker'. The main analyses are based on the response of the 1693 doctors. The average number of years of experience in practice was 20.7, with an average of 16.3 years experience in the use of subcutaneous administration of homeopathic medicinal products. Per week the average number of patients observed by a practitioner is 95 of which 29 (31%) are treated with subcutaneous injections. The results presented in this report are based on an estimate of experience with more than 36 million patient contacts.

57.4% of the practitioners has never observed adverse effects due to the way of administration by subcutaneous injection per se throughout the whole career. Another 39.0% of the practitioners has very rarely or rarely observed an adverse reaction, 3.5% has occasionally, 0.1% has frequently and 0.1% has very frequently observed an adverse reaction due to the way of administration by subcutaneous injection per se, throughout the whole career. On average, 8.5 patients with adverse effects are observed per practice throughout the whole career and per year approximately 1.7 patients are observed. 32 types of adverse reactions due to subcutaneous injections are reported. Of these 32 types of reactions 29 were harmless ('little risk' or lower), only three adverse reactions are reported with a mean risk between 'little risk' and 'some risk': anaphylactic reaction, feverish

symptoms and aversion/anxiety against injections. Only one reaction with a high risk is reported: asthma.

72.6% of the practitioners reported no adverse effects that could be related to the specific homeopathic product used throughout the whole career. 25.5% of the practitioners has very rarely or rarely observed an adverse reaction due to a product. 1.8% have occasionally, 0.1% have frequently and 0% have very frequently observed an adverse reaction due to the particular product throughout the whole career. On average, 4.5 patients per practice throughout the whole career are observed with effects due to the preparation used, per year this is an average of 1.4 patient. In total the practitioners reported 91 preparations, which in their experience had caused in total 212 times adverse effects when given by subcutaneous injection. 35 of these preparations have more than one adverse effect and 55 have only one adverse effect. In total 16 adverse reactions with a mean risk between 'little' and 'some' were reported, and 7 with a mean risk higher than 'some'. 12 adverse reactions have a mean risk/benefit ratio higher than 2, indicating that the risk of these adverse reactions was considered higher than the benefit of the treatment with this product. From the adverse effects with a 'high' and 'very high' mean risk, only an average of 2 and respectively 1 patient per year with a recurrent effect were reported. These three adverse effects were: bleeding, itching and haematoma.

Next to the adverse effects reported as a direct result of the subcutaneous injection itself and the products used, 86,3% of the practitioners are of the opinion that there are no other disadvantages that are related to the subcutaneous form of administration. The other 13.7% of the practitioners reported 12 other disadvantages. Almost all (99.5%) of the responders would like to have the homeopathic medicinal products available for subcutaneous use and 89.0% would feel (very) severely limited if they disappeared.

5.2 Conclusions

On the basis of an estimation of more than 36 million patient contacts with patients treated with subcutaneous injected homeopathic preparations, by 1693 practitioners with an average of 16.3 years experience in prescribing and using subcutaneous administration of homeopathic preparations, we can conclude that *in their experience* the safety risks, quantitatively (number of adverse effects) and qualitatively (grade of adverse effects), are very small.

The number of observed adverse effects due to the way of administration by subcutaneous injection per se with a mean risk between 'little risk' and 'some risk' was only three: anaphylactic reaction, feverish symptoms and aversion/anxiety against injections. Only one reaction with a 'high risk' was reported: asthma. All other adverse effects were reported as 'little risk' or lower. The anaphylactic reaction reported due to the subcutaneous injection per se can hardly be explained scientifically. Possibly the reporting doctors should have marked this adverse reaction under those related to a particular medicinal product.

The number of observed adverse effects due to a homeopathic product per se with a mean risk between 'little' and 'some' was 16, and 7 with a mean risk higher than 'some'. All other mean risks of adverse effects were lower than 'little'. 12 adverse reactions had a mean risk/benefit ratio higher than 2, indicating that the risk of these adverse reactions is considered higher than the benefit of the treatment with this product. From these adverse effects with a 'high' and 'very high' mean risk, only on average 2 and respectively 1 patient per year with a recurrent effect were reported. These three adverse effects were: bleeding, itching and haematoma.

Some remarks with regard to the CTC grades can be made, although the study as a whole was not conceived to cope with CTC grades. Only 3 responders reported that they had each observed one case with an anaphylactic reaction (CTC grade 4) and one responder 2 during their whole career. This means that in only 5 out of more than 36 million patient contacts with patients treated with subcutaneous injected homeopathic preparations an anaphylactic reaction was observed. As is generally known, adverse reactions belonging to the allergy/ hypersensitivity area can occur with lower dilutions (e.g. injection containing 1:10 000 of mother tincture or more). Homeopathic injections with higher dilutions are very unlikely to produce allergic reactions. These facts have been confirmed by the adverse reaction reports in this study, since (except for one medicinal product in which the dilution was not reported) all observed and reported anaphylactic reactions were due to medicinal products with lower dilutions. Besides that, most reported observed effects, like for example 'local redness', 'haematoma', 'local pain', 'local skin reaction', 'local swelling', 'itching', 'local burning', can be recognized as 'mild' adverse effects (CTC grade 1) (Appendix 3).

The second research question, examining the extent in which practitioners would feel limited when homeopathic medicinal products for subcutaneous use would be banned, can be answered in only one way. The results show that 89.0% of the participating practitioners (1693) would feel (very) severely limited and 97.5% would feel moderately to very severely limited. 99.5% would like to have the homeopathic injectables for subcutaneous use available in future. When compared to oral ingestion of medicinal products, practitioners opt for subcutaneous injections for the following clinical reasons: exact location of administration, when oral ingestion is not possible, quicker effect, better effect and better compliance. On the basis of these results the conclusion can be drawn that practitioners, according to their own judgement, would be severely limited in performing their professional practice when homeopathic medicinal products for subcutaneous use would be banned.

5.3 Discussion

This study presents the first reliable, experience based, empirical data with regard to the safety risks of subcutaneous use of homeopathic injectables. It shows that, to the experience of practitioners, the safety risks both quantitatively (number of adverse effects) and qualitatively (grade of adverse effects) are very small. These results offer a first empirical support for the standpoint that homeopathic injectables should not be excluded from the simplified registration procedure.

6. REFERENCES

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7. APPENDICES

APPENDIX 1. Results of the 'Heilpraktiker', compared to practitioners and total results

Table 15. Results of the 'Heilpraktiker', compared to practitioners and total results

	'Heilpraktiker' (n=471/ 22%)	Practitioners (n=1693/ 78%)	Total (n=2164/ 100%)
Demographics			
Estimate of number of patients on which the results are based	9,736,475 (21%)	36,012,649 (79%)	45,749,124 (100%)
Years in practice (mean)	16.6 (SD: 8.25; Range: 0-48)	20.7	19.8
Years experience in homeopathic/ anthroposophic practice (mean)	16.3 (SD: 8.28; Range: 1-48)	17.0	16.9
Years experience of treating patients with subcutaneous injections (mean)	16.2 (SD: 8.4; Range: 1-48)	16.3	16.2
Estimated number of patients treated in total/week (mean)	43.2 (SD: 41.2; Range: 0-500)	87.0	83
Estimated number of patients treated with subcutaneous injections/week (mean)	32.8 (SD: 47.9; Range: 1-400)	29.0	31.6
Factors that influence the decision for administration form (percentage)			
Quicker effect (injection)	87	80.4	81.9
Better effect (injection)	68.8	66.2	66.7
Easier to dose (injection)	42.3	31.4 (same was highest: 35)	33.8
Exact location of administration (injection)	92.4	89.2	89.9
Can be combined with other therapies (injection)	55.2	40.9 (same was highest: 42.8)	43.9
Better compliance (injection)	80.3	59.4	64.0
Better tolerability (same)	52.2	60.6	58.8
Patient preference (same)	46.5	34.6	37.2
If oral administration is not possible (injection)	87.0	87.3	87.2
Occurrence of adverse effects due to way of administration (Valid percentage)			
Never	74.5	57.4	61.0
Very rarely	22.8	32.6	30.6
Rarely	2.3	6.4	5.5
Occasionally	0.5	3.5	2.8
Frequently	0	0.1	0.05
Very Frequently	0	0.1	0.05
No response			
Number of responders reporting adverse effects observed *throughout all the practising years* due to the form of administration (s.c. injection) (Valid percentage)			

No adverse effects	72.9	56	59.7
Adverse effects	27.1	44	40.3
Number of responders reporting adverse effects observed *in one year* due to the form of administration (s.c. injection) (Valid percentage)			
No adverse effects	88.5	72.9	74.4
Adverse effects	11.5	27.1	25.6
Number of cases with mean estimated risk > 3 (s.c. injection)	0	14	14
Number of cases with adverse effect risk > 2 and recurrent effect (s.c. injection)	0	1	1
Occurrence of adverse effects due to preparation (Valid percentage)			
Never	79.0	72.6	74.0
Very rarely	18.7	22.6	21.8
Rarely	1.8	2.9	2.6
Occasionally	0.5	1.8	1.5
Frequently	0.0	0.1	0.1
Very Frequently	0.0	0.0	0.0
No response			
Number of responders reporting adverse effects observed *throughout all the practising years* due to the form of administration (s.c. injection) (Valid percentage)			
No adverse effects	74.4	68.3	69.7
Adverse effects	25.6	31.7	30.3
Number of responders reporting adverse effects observed *in one year* due to the form of administration (s.c. injection) (Valid percentage)			
No adverse effects	88.9	79.1	81.2
Adverse effects	11.1	20.9	18.8
Number of cases with mean estimated risk > 3	3	6	9
Number of cases with adverse effect risk > 3 and recurrent effect (preparation)	0	3	3
Desire of availability of the homeopathic medicinal products for subcutaneous use in the future? (Valid percentage)			
Yes	99.8	99.5	99.5
No	0.2	0.5	0.5
Extent of limitation for the practitioner (Valid percentage)			
Very severely	79.7	60.8	64.0
Severely	15.9	28.2	25.5
Moderately	3.4	8.9	7.7

A little	0.9	1.8	1.6
None	0.0	0.2	0.2
No response			

APPENDIX 2. Main results per country

Table 16. Demographics, percentages per country

Explanation	A	B	D	E	F	GB	I	NL	Scan	Total
General practitioner	82.4	87.5	41.3	67.5	80.6	63.0	58.4	88.4	76.9	52.0
Specialist	13.2	6.3	14.7	22.7	9.7	37.0	35.1	8.4	23.1	16.6
Dentist	4.4	3.1	8.5	1.2	7.6	0	5.2	1.1	0	6.7
'Heilpraktiker'	0	0	32.6	0	0	0	0	0	0	21.8
No response	0	3.1	2.8	8.6	2.1	0	1.3	2.1	0	2.9
Average number of years qualified	17.1	22.7	20.0	17.1	21.5	26.3	18.8	18.8	18.4	19.8
Average number of years homeopathic medicine	13.0	17.2	17.9	10.6	16.8	21.5	14.5	16.9	17.4	16.9
Average number of years use of injections	12.9	14.4	17.5	9.7	14.4	19.9	13.2	16.4	17.0	16.2

Table 17. Occurrence of undesirable effects due to way of administration, percentages per country

	Explanation	A	B	D	E	F	GB	I	NL	Scan	Total
Never	Never	67.6	40.6	61.6	50.3	55.6	39.1	68.2	34.7	61.5	59.0
Very rarely	1 or less than 1 out of 10.000 treated patients	25.0	43.8	29.7	26.4	25.7	37.0	21.4	45.3	26.9	29.5
Rarely	more than 1 out of 10.000 treated patients	4.4	6.3	4.0	8.6	4.2	17.4	5.8	12.6	11.5	5.3
Occasionally	more than 1 out of 1000 treated patients	1.5	9.4	0.8	12.3	9.7	0	2.6	5.3	0	2.7
Frequently	more than 1 out of 100 treated patients	0	0	0.1	0	0	0	0	0	0	0
Very frequently	more than 1 out of 10 treated patients	0	0	0	0.6	0	0	0	0	0	0
No response		1.5	0	3.8	1.8	4.9	6.5	1.9	2.1	0	3.4
Total		100	100	100	100	100	100	100	100	100	100

Table 19. Occurrence of undesirable effects due to the preparation used, percentages per country

	Explanation	A	B	D	E	F	GB	I	NL	Scand	Total
Never	Never	70.6	56.3	69.6	65.0	67.4	71.7	63.6	57.9	57.7	67.9
Very rarely	1 or less than 1 out of 10.000 treated patients	16.2	34.4	19.9	23.9	16.7	10.9	13.6	29.5	26.9	20.0
Rarely	more than 1 out of 10.000 treated patients	0	0	2.1	1.2	2.8	6.5	3.9	5.3	7.7	2.4
Occasionally	more than 1 out of 1000 treated patients	0	0	1.0	2.5	2.1	4.3	3.2	2.1	0	1.4
Frequently	more than 1 out of 100 treated patients	0	0	0	0	0	0	0.6	0	3.8	0.1

Very frequently	more than 1 out of 10 treated patients	0	0	0	0	0	0	0	0	0	0
No response		13.2	9.4	7.4	7.4	11.1	6.5	14.9	5.3	3.8	8.2
Total		100	100	100	100	100	100	100	100	100	100

Table 20. Availability of the preparations for s.c. injections in the future? Percentages per country

Explanation	A	B	D	E	F	GB	I	NL	Scan	Total
Yes	98.5	100	98.7	97.5	97.9	93.5	96.1	94.7	100	98.2
No	1.5	0	0.3	0.6	0	0	1.9	1.1	0	0.5
No response	0	0	1.0	1.8	2.1	6.5	1.9	4.2	0	1.4
Total	100	100	100	100	100	100	100	100	100	100

Table 21. Extent of limitation for the doctor per country (percentages)

Explanation	A	B	D	E	F	GB	I	NL	Scan	Total
Very severely	47.1	37.5	74.3	25.2	49.3	47.8	48.1	51.6	65.4	64.0
Severely	42.6	37.5	18.5	41.7	36.8	23.9	41.6	36.8	30.8	25.2
Moderately	5.9	21.9	4.9	25.8	11.1	19.6	5.8	7.4	0	7.6
A little	2.9	3.1	1.1	5.5	0	4.3	1.9	1.1	3.8	1.6
None	1.5	0	0.1	0.6	0	0	0	0	0	0.2
No response	0	0	1.0	1.2	2.8	4.3	2.6	3.2	0	1.4
Total	100	100	100	100	100	100	100	100	100	100

Table 22. Factors affecting the decision for form of administration form (preference per country)

Explanation	A	B	D	E	F	GB	I	NL	Scan	Total
Quicker effect	inj	inj	inj	inj	inj	inj	Inj	inj	inj	82% Inj.
Better effect	inj	inj	inj	inj	Inj	inj	Inj	inj	inj	67% inj
Easier to dose	inj	same	ND	ND	ND	same	ND	same	ND	ND
Exact location of administration	inj	inj	inj	inj	inj	inj	inj	inj	inj	90% inj
Can be combined with other therapies	same	ND	inj	same	ND	same	ND	same	same	ND
Better compliance	inj	inj	inj	ND	inj	ND	ND	ND	same	64% inj
Better tolerability	same	same	same	same	same	same	same	same	same	59% same
Patient preference	same	NAp	same	oral	NAp	ND	oral	ND	same	ND
If oral administration is not possible	inj	inj	inj	inj	inj	inj	inj	inj	inj	87% inj

Injection = inj; oral; same; not applicable = NAp; no difference = ND

APPENDIX 3. Summary out of the Common Toxicity Criteria table (grades of adverse events)

	GRADE				
Adverse event	0	1	2	3	4
General score definition	None	mild	moderate	severe	Life-threatening or disabling
ALLERGY					
Allergic reaction/ hypersensitivity	None	Transient rash, drug fever <38°C	Urticaria, drug fever ≥ 38°C, and/or asymptomatic bronchospasm		Anaphylaxis
CARDIOVASCULAR (ARRHYTHMIA)					
Palpitations	None	present	-	-	-
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
CONSTITUTIONAL SYMPTOMS					
Fatigue	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky of Lansky) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or Lansky) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10^9/L	none	38.0-39.0^0 C	39.1-40.0^0 C	>40.0^0 C for 24 hours	>40.0^0 C for 24 hours
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
DERMATOLOGY/SKIN					
Bruising (in absence of grade 3 or 4 thrombocytopeni	none	localized or in dependent area	generalized	-	-

a Number of cases					
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis.
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or tropical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
GASTROINTESTINAL					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
MUSCULOSKELETAL					
Muscle weakness (not due to	normal	asymptomatic with weakness on physical	symptomatic and interfering with function, but not	symptomatic and interfering with activities of daily	bedridden or disabling

neuropathy)		exam	interfering with activities of daily living	living	
NEUROLOGY					
Dizziness/ light headedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden of disabling
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, inractable epilepsy
Syncope (fainting)	absent	-	-	present	-
PAIN					
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely intergering with activities of daily living	disabling
PULMONARY					
Apnoea	none	-	-	present	requiring intubation

APPENDIX 4. Questionnaire (English version)

Questionnaire on the Use of Homeopathic/Anthroposophic Subcutaneous Injection Preparations in Practices

This questionnaire has been developed to assess the possible risks related to the use of subcutaneous injections. The route of administration should be considered separate from the preparation used. General demographic data is asked and data from your personal experience as practising physician.
Please take your time to read the information before you answer the questions. In the right margin you will be prompted to complete an item or circle your answer.

General demographic data:

1. How many years have you been a practising physician? ☐ years

   How many years have you been treating with anthroposophic and/or homeopathic preparations? ☐ years

   In which field are you active?
   General practitioner / Specialist / Dentist — please circle one

2. Do you prescribe homeopathic/anthroposophic subcutaneous injection preparations in your practice? Yes/No

> If no, you can stop completing this questionnaire now.

> If yes, how many years have you been treating with subcutaneous injections? ☐ years

What is the estimated mean number of patients that you see in your practice per week? ☐ # patients

What is the estimated mean number of patients that are treated with subcutaneous injections per week? ☐ # patients

(think of patients treated by assistant, long term, season related, self application, etc.)

3. When you have the choice between oral and injection administration, which factors play a role in the decision making:

   Is your decision based on the way of administration?
   (e.g. due to relationship between administration form and indication) Yes / No

   Is your decision based on the effect?
   (e.g. level of effect is related to form of administration) Yes / No

Is your decision based on patient preference? **Yes / No**

For more specification of the nature of your decision please compare injections to oral administration in the following table.

Please complete each item

Generally quicker effect	Injection / oral / same / not applicable
Generally better effect	Injection / oral / same / not applicable
Generally easier to dose	Injection / oral / same / not applicable
Possibility of exact local administration (at centre of illness)	Injection / oral / same / not applicable
Can be combined with other forms of therapy (e.g. physiotherapy, acupuncture)	Injection / oral / same / not applicable
Generally better therapy control (Compliance)	Injection / oral / same / not applicable
Generally better tolerability	Injection / oral / same / not applicable
Patient preference	Injection / oral / same / not applicable
If oral administration is not possible (e.g. heavy nausea, heavy vomiting, diarrhoea, coma)	Injection / oral / same / not applicable

In the following questions, we would like you to note all undesirable effects that you have seen in your years of practice using subcutaneous injections.
Please make a distinction between effects that you have seen due to the injection itself (question 4) and effects that are, in your opinion, the result of the preparation (question 5)

Undesirable effects:

4. **Have you experienced undesirable effects caused by the <u>the way of administration</u> during subcutaneous injections in your practice?**

   Never / Rarely / Occasionally / Frequently / Very frequently [1] Please circle one

   Estimated total number of patients seen with undesirable effects due to <u>way of administration</u> since practising? ☐ # patients

   Estimated number of patients per week/ month/ year (please circle one) **with undesirable effects due to <u>way of administration</u>?** ☐ # patients

[1] Very rarely = 1 or less than 1 out of 10 000 of those treater including individual cases; rarely = more that 1 out of 10 000 of thos threated; occasionally = more than 1 out of 1000 of those treated; frequently = more than 1 out of 100 of those treated; very frequently = more than 1 out of 10 of those treated.

Please note all observed categories of undesirable effects
(please complete the related risk and number of cases per category that you note)

Observed undesirable effect	Estimated risk * *none=1, very high=5*	*Number of cases* with temporary effect per year	*Number of cases* with permanent effect per year

* none = 1; little = 2; some = 3; high = 4; very high = 5

(Iscador and Gencydo are not homeopathical products and are therefore excluded from this survey)

5. **Have you observed undesirable effects due to the preparation during subcutaneous injections in your practice?**

   Never / Rarely / Occasionally / Frequently / Very frequently Please circle one

   Estimated total number of patients seen with undesirable effects due to preparation since practising? ☐ # patients

   Estimated number of patients per week/ month/ year (please circle) **with undesirable effects due to preparation?** ☐ # patients

Please note all observed categories of undesirable effects
(please complete each item per noted effect)

Observed undesirable effect	***Preparation*** Please define	Effect related to preparation *Yes/ No?*	Estimated risk *none=1, very high=5*	Risk/ benefit*	*Number of cases* with temporary effect p. y.	*Number of cases* with permanent effect p. y.

* benefits are greater than the risks = 1; benefits are as great as the risks = 2;
risks are greater than the benefits = 3

In these last three questions we would like to capture your personal opinion

6. Are there, in your opinion, other <u>disadvantages</u> (other than the effects that you have noted up to now) related to the use of subcutaneous injections? Yes / No

If yes, please define below.

7. Would you like to have subcutaneous forms of administration available to you in the future? Yes / No

8. To what extent would you feel limited in your ability to treat patients optimally if subcutaneous forms of preparations would be removed?

   Not/ a little / moderately/ severely/ very severely please circle one

DATE DOCTOR'S STAMP DOCTOR'S SIGNATURE

Please return to:

COMPANY STAMP

APPENDIX 5. Codes of homeopathic medicinal products/substances as used in Tables 9 and 10

Codes	Medicinal product
A	Apis
B	Arnica
C	Formica/Aconitum
D	Traumeel
E	Zeel T
F	Argentum nitricum
G	Mandragora
H	Rhus toxicodendron complex
I	Cardiodoron
J	Abnoba viscum
K	Betula
L	Nosoden complex
M	Procain
N	Berberis
O	Lachesis
P	Acidum formicicum
Q	Engystol
R	Vespa crabo
S	Belladonna
T	Citrus Cydonia
U	Echinacea
V	Hyocyamus complex
W	Oxalis D2/D3
X	Spascrupeel
Y	Succinum
Z	Camphora
AA	Phosphor
AB	Antiflammin H
AC	Levisticum
AD	Disci
AE	Taraxacum
AF	Hypericum
AG	Iscucin
AH	Aconitum
AI	Thymus
BA	Acidum Salicylicum
BB	Allium Cepa
BC	Bryonia/Stannum
BD	Bryophyllum
BE	Citrus e fructibus
BF	Colchicum
BG	CPL3 complex
BH	Cuprum metallicum
BI	Cutis suis
BJ	Derivatio

BK	Dioptas
BL	Disci comp. cum argento
BM	Dulcamara
BN	Echinacin
BO	Ijzer (Ferrum)
BP	Folsaeure
BQ	Gelsemium
BR	Gentiana Lutea
BS	Graphites
BT	Hamamelis
BU	Helleborus niger
BV	Hepar sulfuris
BW	Hirudo Complex
BX	Kalmia latifolia
BY	Kupferamalgam
BZ	Lactopurum
CA	Ledum complex
CB	Lens cristallina
CC	Lithium
CD	Lymphdiaral diverse
CE	Lymphosan
CF	Lymphomyosot
CG	Melilotus
CH	Myristica sebifera
CI	Neurofibroma
CJ	Pascotox
CK	Placenta
CL	Prunus
CM	Psorinoheel
CN	Pulmo/Ferrum
CO	Salmonella TP nos.
CP	Solum uliginosum complex
CQ	Stibium metallicum
CR	Strophantus
CS	Tellurium metallicum
CT	Thuja D3
CU	Tonico injeel
CV	Toxi loges
CX	Uro L 90 N
CY	Vena suis
DA	C356 (Argentum D30, Belladonna D3, Vespa Crabro D8)
DB	C720 (Crotalus horridus D20, Lachesis mutus D12, Naja tripudans D10, Vipera torva D30)
DC	353 (Argentum D8, Arnica pl. tota D15, Betula cortex D2, Formica D8, Sulfur D6)
DD	830 (Hepatin D8, Taraxacum Stanno cultum 1%)