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**Regulatory Scientific Advice in drug development: Does company size make a difference?**

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## **Abstract**

**Purpose** To assess whether the content of Scientific Advice (SA) questions is associated with company size. This may help to learn more about the knowledge, strategic and regulatory gaps companies face during drug development.

**Methodology** A cross-sectional analysis was performed of SA provided by the Dutch Medicines Evaluation Board (MEB) in 2006-2008. Definition of company size was based on ranking by total revenues (Scrip's Pharmaceutical Company League Tables 2008). The content of each SA question was scored according to predefined domains (Quality, Non-clinical, Clinical, Regulatory and Product Information), their subdomains e.g. efficacy, and a selection of additional content variables e.g. endpoints, choice of active comparator.

**Results** In total 201 SA documents, including 1,087 questions could be identified. Small, medium-sized and large companies asked SA 110 (54.7%), 40 (19.9%) and 51 (25.4%) times, respectively. Clinical questions were asked most often (65.9%), mainly including efficacy (33.2%) and safety questions (24.0%). The most frequently asked topics were overall efficacy and safety strategy.

Small companies asked quality and non-clinical questions more often ( $p < 0.001$ ) and clinical questions less frequently than large companies ( $p = 0.004$ ). Small companies asked significantly more clinical questions about pharmacokinetics, including bio-equivalence, than medium-sized and large companies ( $p < 0.001$ ).

## **Conclusion**

The array of topics addressed in SA provides an interesting outlook on what industry beliefs is still unresolved in drug development and is worthwhile to discuss with regulators.

Company size is associated with the content of scientific advice questions. MEB advice accommodates both innovative and non-innovative drug development.

## Introduction

Marketing authorization of a new medicinal product is a critical step in the access to innovative therapies that are needed to fill current pharmaceutical gaps and unmet medical needs. Despite the increasing number of applications for marketing authorization in Europe, the proportion of applications with a negative decision remains relatively high, around 25%-30%, and was even 40% for New Active Substances with an approval outcome in 2009. (1) (2) There is increasing concern about the obvious gap between the output of drug development and registration strategies applied by companies, and EU-regulatory expectations. (3) (4) Industry response to this development echoes that improved communication with regulatory authorities during drug development is needed. (5) Additional regulatory requirements in recent years have complicated the authorization procedure and have made innovative drug development more costly. Besides, with complex biologicals, advanced therapies and personalized medicines becoming more important, the need for more specific guidance in drug development has increased. (6) (7)

Before and during the marketing authorization procedure of a medicinal product, pharmaceutical companies have various opportunities to discuss critical issues in the drug development process with regulators. A continuous and ongoing regulatory dialogue between pharmaceutical industry and regulatory authorities has often been recommended as a strategy to support innovative drug development in an efficient and tailored way. (5) (8) (3) (9) (10) A relevant part of scientific regulatory dialogue is so-called Scientific Advice (SA), the opportunity of (early) communication between a company and a regulatory authority on quality, non-clinical and various clinical aspects (e.g. study design, choice of endpoint, indication) of drug development. In Europe an increasing proportion of market application authorizations are preceded by SA; 47% of all applications in 2007 received SA and in 2008 this percentage was 56%. (1)

An applicant for SA can be a pharmaceutical company or (a group of) scientist(s) who is developing a product. Applicants are encouraged to seek regulatory SA as many times as

necessary, but both industry and authorities are not obliged to adhere to the advice received or committed to accept any result of a SA procedure. (11) In Europe, SA can either be sought at the European Medicines Agency (EMA) or at one or more of the national regulatory agencies. National regulatory agencies provide SA either as a response to national SA requests or as an answer to European SA requests, outsourced by the EMA Scientific Advice Working Party (SAWP) to one or two of its member countries according to expertise. A recent study looking at SA provided by EMA, demonstrated that the level of industry adherence to SA and company size were both predictors of a positive outcome in a marketing authorization procedure. The study also showed that among companies submitting a marketing application to EMA, large companies asked SA most frequently and were more adherent to the advice than medium-sized and small companies. (9)

Considering that adherence to SA is associated to a positive outcome in a marketing authorization procedure, and that variability in adherence to SA exists between companies, the question arises whether company size matters when looking at the type of SA that pharmaceutical companies are seeking. Answering this question may help to learn more about the knowledge, strategic and regulatory gaps companies face during drug development and how these differentiate between the various types of enterprises.

## **Methods**

### *Study design and scientific advice characteristics*

A cross-sectional analysis was performed of national SA provided by the Dutch Medicines Evaluation Board (MEB) in the years 2006-2008. SA documents were retrieved from the MEB SA Database. Requests for SA, which were rejected by the MEB for reasons of lack of expertise or previously received EMA advice, were excluded. In this study was looked at individual requests for SA, so follow-up SAs for a similar medicinal product were included.

Products for which SA was given in the study period were categorized according to anatomical main group of the ATC-classification. (12) In case an ATC-classification was

missing, the anatomical main group was assessed based on the intended indication of the product. Secondly, products were categorized as new chemical substance (NCS; chemical substance not previously approved), generic (a product with identical qualitative and quantitative composition and similar pharmaceutical form as original product), biologicals (defined as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant proteins) and new application of existing drugs (previously approved chemical substances for which a new indication was sought, dosage form or other variation was being developed, in such a way that there was a need for additional efficacy and safety studies).

Company size was defined as small-, medium-sized and large, based on ranking by total revenue as reported in Scrip's Pharmaceutical Company League Tables 2008. (13)

Companies were defined large if ranked 1-20, medium-sized if ranked 21-150 and small if the company was not on the ranking list. This definition was in line with a previous study on SA. (9) For each advice we evaluated whether previous advice for the same product had been requested at the MEB, whether parallel advice had been asked for at another national regulatory agency, or both.

#### *Data collection: Characteristics of questions*

Each SA consisted of a variable number of questions asked by companies. All questions from SA given by the MEB in 2006, 2007 and 2008 were collected and analyzed in a standardized fashion. Each question, being the unit of analysis, was scored separately according to variables at three different levels: domains, subdomains and content variables (Figure 1). At the first level the question content was analyzed according to the domains "Quality, Non-clinical, Clinical, Regulatory and Product Information". Scoring more than one domain was allowed, for example when a clinical and a product information issue were discussed in the same question.

Secondly, subdomains were formulated and scored for questions in the non-clinical and clinical domains. The subdomains of the non-clinical domain were 'Pharmacodynamics', 'Pharmacokinetics' and 'Toxicology'. For domain "Clinical" a subdivision was made for questions with regard to 'Pharmacodynamics' (including Dose Finding studies), 'Pharmacokinetics' (including bio-equivalence studies), 'Efficacy' or 'Safety'. Again, scoring more than one subdomain was allowed.

Additionally, at the third and most detailed level each question was scored by a selection of content variables, e.g. primary endpoint, choice of active comparator, trial duration and overall efficacy programme. The content variables were selected based on general regulatory requirements of the drug development process and existing EMA regulatory guidelines. In this third step, a distinction was made between specific and strategic questions. Strategic questions were defined as questions in which general feedback was asked about e.g. the complete quality programme or the clinical efficacy programme. An example of a strategic question was: *"Does the MEB agree that the results of the clinical efficacy programme will be sufficient to market approval of the product in the specific indication"?* Specific questions were defined as being related to specific topics of the development plan in one single study. An example of a specific question is: *"Does the MEB agree with the chosen primary endpoints for this indication?"*

#### *Data analysis*

Associations between the type of SA questions and company size were assessed by Pearson's Chi-square analysis. P-values were calculated for each variable. Differences in average number of questions were assessed by a one way ANOVA-test.

## **Results**

During the study period the MEB provided 214 times SA. Thirteen advice documents were missing (4 and 9 documents in 2006 and 2007, respectively). In total 201 SA documents, including 1,087 questions could be identified. SA has been provided for 187 single products,

whereas 117 single companies (80 small, 21 medium sized and 16 large companies) received SA in the study period. The general SA characteristics are given in Table 1. SA was most frequently given for nervous system drugs (24.9%), but for a variety of other therapeutic areas SA was provided as well. More than 60% of SA was given for generics and new applications of existing drugs. Small, medium-sized and large companies asked SA 110 (54.7%), 40 (19.9%) and 51 (25.4%) times respectively. More than 40% of the companies seeking for SA had previously received advice for the same drug at the MEB or another national agency.

On average five questions per SA were asked (table 2). Clinical questions were asked most frequently, 716 times (65.9%). Within the clinical subdomain, efficacy and safety questions were most frequently asked, 361 (33.2%) and 261 (24.0%) times respectively.

Small companies asked significantly lower numbers of questions per SA compared to medium and large sized companies ( $p < 0.001$ ). Large and medium sized companies asked significantly more SA questions about new chemical entities than small companies ( $p < 0.001$ ). Small companies asked 70% of SA questions about drug development of generics and new applications of existing drugs. These small companies were a diverse representation of companies; generic companies (20%), innovative pharmaceutical or biotech companies (40%) and other companies mainly consisting of medical technology companies, working on new applications of drugs and consultants. Medium-sized companies, about 85% of these were innovative pharmaceutical or biotechnology companies, most frequently asked SA questions related to the development of biologicals ( $p < 0.001$ ).

With regard to domain, the majority of questions asked by companies were about clinical development issues, while small companies were more visible on quality and non-clinical questions. One out of five SA questions was on regulatory issues, with no difference between types of companies. Within the clinical domain, small companies asked significantly more often about pharmacokinetics, including bio-equivalence, than medium-sized and large

companies. These companies less often posed efficacy questions than large companies (24.4% vs. 44.8%  $p < 0.001$ ). The proportion of safety and strategic questions was not associated with company size.

In Figure 2 the overall top ten of most frequently asked topics on the most detailed third level of variables is given, showing a strong preference for clinical topics. Overall, most frequently asked questions were questions about overall efficacy strategy (9.6%) and safety strategy (9.1%). Besides, strategy questions about the clinical pharmacokinetic programme were in the top ten. Indication, primary endpoints, dosing and study population were examples of popular specific topics. More details of the ten most frequently asked topics are given in Table 3.

## **Discussion**

One of the main findings in this study was that indeed SA, provided by a national authority is different, both quantitatively and in terms of kind of questions, when looking at company size. Our content analysis of SA demonstrates that the majority of questions raised by companies, particularly the large ones, were about clinical drug development. Small companies spent more attention to quality and nonclinical issues than large companies. The array of topics addressed in SA provides an interesting outlook, given all its limitations caused by strategic behaviour of companies and selective acceptance of SA by regulators, on what industry beliefs is still unresolved in drug development and is worthwhile to discuss with regulators.

Regnstrom et al. emphasized the importance of adherence to SA for a successful marketing approval. (9) The question arises whether our findings of companies' priorities in drug development are in line with the most often occurring major objections or factors for approval failure. A 2002 study with EMA data found that major objections raised by regulators in the marketing authorization procedure were lack of adequate randomized controlled trials to

prove clinical efficacy and the occurrence of unresolved safety issues. (3) The EMA reported in 2008 that critical issues related to study design (39%), patient population (35%), endpoint (35%) and the magnitude of an effect (48%) were important drivers of a negative application. (1) In a 2010 study with FDA data on orphan drugs Heemstra et al. found that failing to achieve primary endpoints and lack of description of appropriate target population were related to non-approval. (10) Our study also showed that topics like study design, endpoints, study population and special safety issues were all in the top ten of most frequently addressed issues in SA.

Quality documentation is a particular bottleneck for Small and Medium sized Enterprises (SMEs). The EMA Small and Medium sized Enterprise office reported that quality documentation caused 41% of the major objections in application procedures of SMEs in 2008. (14) Our results demonstrated that SMEs asked significantly more often about quality issues than large companies, the latter hardly discussed any quality issues. This implies that SMEs lack knowledge with regard to quality documentation or capacity to comply with the requirements.

Some limitations of this study need to be discussed. Firstly, the scoring method of the SA, although highly standardized, may be susceptible to some subjectivity. In order to minimize this, we scored the questions according to strict definitions of content variables. These variables were derived from scientific regulatory documents and guidelines.

Secondly, our definition of company size differs from the official EU definition of SMEs. According to the official SME definition, only 15 of 201 SA requests would have been classified as an SME request. This would create a group of “large companies” which was too heterogeneous to draw any conclusions about. Therefore, we based the SME definition on ranking by total revenue as reported in Scrip’s Pharmaceutical Company League Tables 2008, which was in line with a previous study on SA with EMA data. (9)

Another limitation of our study is that we did not investigate company's reasons for asking SA. These reasons may range from a real interest in the answers to the questions raised in SA to expected positive effects on the regulatory process (and outcome) by the applicants from dialogue and alignment with regulators in general.

It should be noted that company budgets may drive the decision to ask SA. However, during a significant part of the research period the MEB provided SA free of charge. In addition, the costs that were introduced later are very limited, varying from 3500 to 8000 euro per advice. Therefore we believe it is unlikely that the costs of SA have influenced our results and we do not consider this a limitation of our study.

The fact that some SA requests at the MEB were rejected may raise the question whether results of this study are representative for national SA provided by other regulatory agencies. Advice requests were rejected when former advice was obtained from EMA, in case the complexity was expected to be better dealt with at EMA-level or when the indication of the product was outside the scope of the expertise of the MEB. Therefore the array of clinical areas represented in this study is also a reflection of national MEB expertise. Despite national expertise in e.g. central nervous system and cardiovascular products, the MEB gave SA about drug development in a broad range of therapeutic areas (Table 1). Similar broad ranges of therapeutic areas are expected for SA at other national regulatory agencies in the EU as well. In addition, when comparing the Dutch national SA with other national SA, the top ten of most frequently asked topics will probably not be influenced by differences in expertise because it consists of topics that are related to drug development in general. Therefore, we think our results give a well-balanced overview of issues in drug development.

Regulatory dialogue about challenging issues at the critical edge of drug development is seen as a key success factor for bringing new medicinal products with a positive benefit-risk

to the patient. An EMA brainstorm session held with regulators and pharmaceutical industry representatives in 2007 made clear that a special need exists for dialogue about new high risk advanced therapies and technologies and for new scientific approaches in targeted drug development, such as validation of biomarkers, choice of study endpoints or better methods to identify treatment responders. Besides, the use of more flexible and adaptive study designs was raised as a key issue to be discussed in a dialogue with regulators. (5)

According to the EMA, in particular many SMEs are active in the development of the highly innovative Advanced Therapy Medicinal Products (ATMPs). (14) SA related to such high risk advanced therapies and technologies are channeled to the EMA. In contrast, other small companies asked MEB-advice most frequently about generic applications, bio-equivalence and new application of existing drugs. One may argue that answers to these SA questions could also be found in regulatory guidelines. The need for such advice may be partly attributable to lack of experience in drug development or lack of clarity in existing guidelines.

The role of scientific advice also has bearing on the way companies formulate their questions. For all types of companies about 20% of all questions asked, were “strategic”. Further research should assess whether companies benefit more from asking specific or strategic questions. Besides, in further research national SA could be compared to European SA to assess whether strategic questions are asked on both levels and to evaluate commonalities and differences in the roles of European and national SA.

Moreover, the level of complexity of SA questions would give deeper insight information in the issues addressed. This would also enable further research on how complexity drives market authorization holders’ behaviour when it comes to SA.

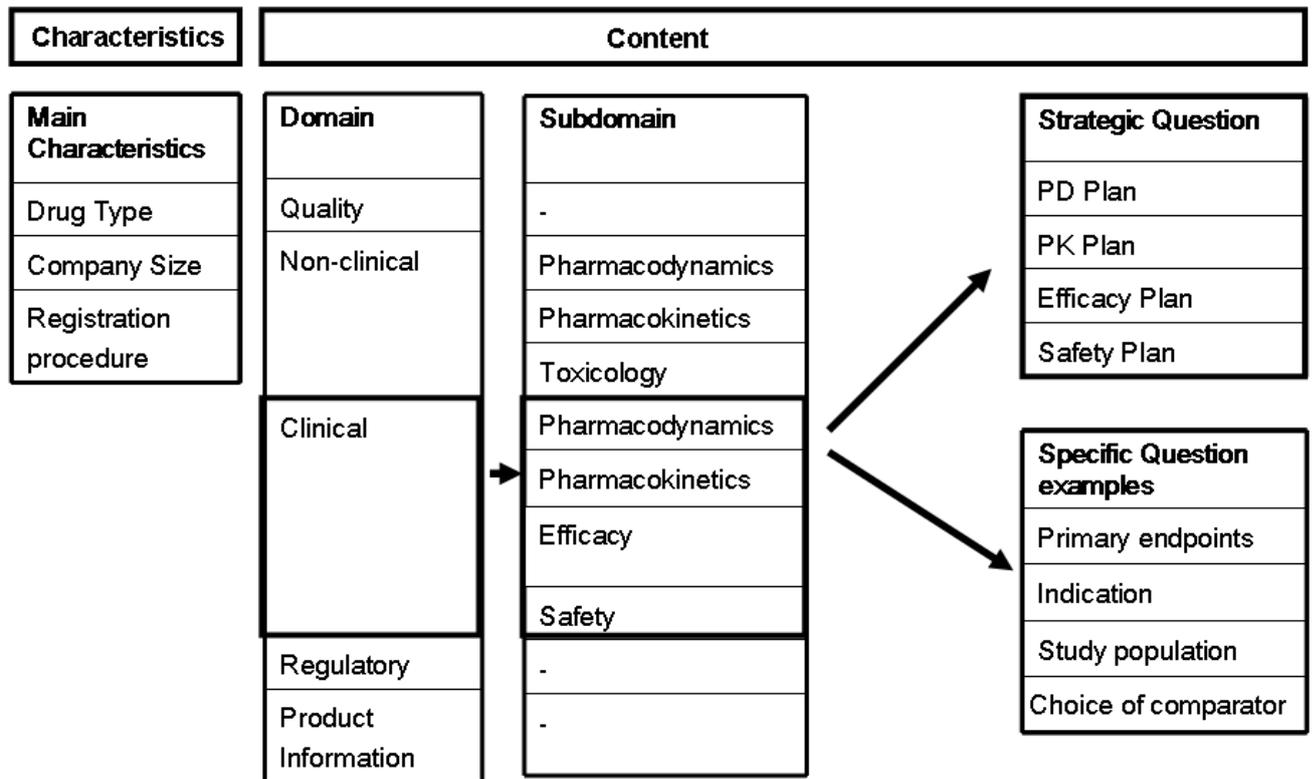
In conclusion, SA as provided by a regulatory authority provides a detailed outlook of unresolved issues in drug development. This picture is a function of industry presence in a certain country, of expertise at a national regulatory authority, but also of critical issues at the edge of regulatory decision making. Indeed, there is variability in how different companies

deal with this. The results of this study show that company size is associated with the content of SA questions and that national SA accommodates both innovative and non-innovative drug development. Clinical pharmacology topics are at the top of issues discussed in SA, a finding that asks for more analysis on how fruitful industry, regulatory and academic clinical pharmacologists interact and align in order to stimulate drug innovation.

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Figure 1: Scoring method for SA questions



**Table 1 Baseline characteristics of SA**

<b>Variables</b>	<b>Advice (N=201) (% of total no. of advice)</b>
<b>Year</b>	
2006	77 (38.3%)
2007	47 (23.4%)
2008	77 (38.3%)
Total	201(100%)
<b>ATC-Code</b>	
A/Alimentary tract & Metabolism	12 (6.0%)
B/ Blood& Blood forming organs	16 (8.0%)
C/ Cardiovascular system	34 (16.9%)
G/ Genito-Urinary system & sex hormones	15 (7.5%)
J/ Antiinfectives	13 (6.5%)
L/ Antineoplastic & Immunomodulating products	29 (14.4%)
N/ Nervous system	50 (24.9%)
Other	32 (15.9%)
<b>Product Type EMEA</b>	
NCE	43 (21.4%)
Generic	59 (29.4%)
New application of existing drug	64 (31.8%)
Biological (including biosimilars)	34 (16.9%)
Other (General advice)	1 (0.5%)
<b>Orphan drugs</b>	
Orphan drug	3 (1.5%)
Non-orphan drug	198 (98.5%)
<b>Company Size</b>	
Small	110 (54.7%)
Medium-sized	40 (19.9%)
Large	51 (25.4%)
<b>Type of Registration Procedure</b>	
Central	48 (23.9%)
Decentral	42 (20.9%)
Mutual Recognition Procedure	19 (9.5%)
National	11 (5.5%)
To be decided	75 (37.3%)
Missing	6 (3.0%)
<b>Previous/ Parallel advice</b>	
No previous	102 (50.7%)
At MEB	17 (8.5%)
At Other agencies	62 (30.8%)
At MEB & other agencies	9 (4.5%)
Missing	11 (5.5%)

**Table 2 Company size relations with characteristics and content of SA questions**

Questions N=1087	Small Pharma	Medium Pharma	Large Pharma	Total	P-values
<b>Total No. of Questions</b>	431 (39.7%)	310 (28.5%)	346 (31.8%)	1087(100%)	<0.001
<b>Average No. of Questions</b>	3.9 (1-18)	7.8 (1-27)	6.8 (1-17)	5.4 (1-27)	<0.001
<b>SD</b>	3.2	5.7	3.9	4.3	
<b>ATC-Code</b>					
A/Alimentary tract & Metabolism	29 (6.7%)	0 (0.0%)	41 (11.8%)	70 (6.4%)	<0.001
B/ Blood& Blood forming organs	26 (6.0%)	66 (21.3%)	7 (2.0%)	99 (9.1%)	<0.001
C/ Cardiovascular system	39 (9.0%)	63 (20.3%)	69 (19.9%)	171(15.7%)	<0.001
G/ Genito-Urinary system & sex hormones	6 (1.4%)	48 (15.5%)	60 (17.3%)	114(10.5%)	<0.001
J/ Antiinfectives	40 (9.3%)	15 (4.8%)	8 (2.3%)	63 (5.8%)	<0.001
L/ Antineoplastic & Immunomodulating products	58 (13.5%)	30 (9.7%)	75 (21.7%)	163 (15.0%)	<0.001
N/ Nervous system	114 (26.5%)	80 (25.9%)	58 (16.8%)	252 (23.2%)	0.003
Other	119 (27.6%)	8 (2.6%)	28 (8.1%)	155 (14.2%)	<0.001
<b>Product Type EMEA</b>					
NCE	47 (10.9%)	89 (28.7%)	173 (50.0%)	309 (28.4%)	<0.001
Generic	125 (29.0%)	17 (5.5%)	31 (9.0%)	173 (15.9%)	<0.001
New application of existing drug	178 (41.2%)	106 (34.2%)	101 (29.2%)	385 (35.4%)	0.002
Biological (incl.biosimilars)	80 (18.6%)	98 (31.6%)	41 (11.8%)	219 (20.1%)	<0.001
Other (General advice)	1 (0.2%)	0	0	1 (0.1%)	0.46
<b>Previous/parallel advice</b>					
No previous	233 (54.1%)	90 (29.0%)	98 (28.3%)	421(38.7%)	<0.001
At MEB	9 (2.1%)	38 (12.3%)	64 (18.5%)	111(10.2%)	<0.001
At Other agencies	161 (37.4%)	154 (49.7%)	134 (38.7%)	449 (41.3%)	0.002
At MEB & other agencies	6 (1.4%)	11 (3.5%)	32 (9.2%)	49 (4.5%)	<0.001
Missing	22 (5.1%)	17 (5.5%)	18 (5.2%)	57 (5.2%)	0.973
<b>Domain</b>					
Quality	43 (10.0%)	26 (8.4%)	5 (1.4%)	74 (6.8%)	<0.001
Non-Clinical	69 (16.0%)	22 (7.1%)	19 (5.5%)	110 (10.1%)	<0.001
Clinical	272 (63.1%)	192 (61.9%)	252 (72.8%)	716 (65.9%)	0.004
Regulatory	86 (20.0%)	59 (19.0%)	60 (17.3%)	205 (18.9%)	0.649
Product Information	11(2.6%)	22 (7.1%)	22 (6.4%)	55 (5.1%)	0.009
<b>Clinical Subdomain</b>					
Pharmacodynamics (incl. Dose Finding)	26 (6.0%)	13 (4.2%)	27 (7.8%)	66 (6.1%)	0.154
Pharmacokinetics (incl.BE)	123 (28.5%)	30 (9.7%)	41 (11.9%)	194(17.8%)	<0.001
Efficacy	105 (24.4%)	101 (32.6%)	155 (44.8%)	361(33.2%)	<0.001
Safety	97 (22.5%)	78 (25.2%)	86 (24.9%)	261(24.0%)	0.639
<b>Type of Questions</b>					
Strategic Questions	93 (21.6%)	64 (20.6%)	65 (18.8%)	222 (20.4%)	0.627

**Table 3 Definitions & Question examples of top ten most frequently asked topics**

<b>Topic</b>	<b>Definition</b>	<b>Question example</b>
Overall Efficacy Strategy	Complete clinical study program in order to proof efficacy of a drug.	<i>Does the MEB think the proposed efficacy programme is appropriate for a marketing authorization?</i>
Overall Safety Strategy	Complete clinical study program in order to proof safety of a drug.	<i>Does the MEB think the proposed safety programme is appropriate for a marketing authorization?</i>
Indication	The definition/wording of indication and the appropriateness of the suggested indication.	<i>Does the Agency agree that “Treatment of symptoms associated with interstitial cystitis / painful bladder syndrome including bladder pain, urinary urgency and frequency” is a registrable indication?</i>
Primary efficacy endpoints	The appropriateness of the primary endpoint selected to proof efficacy of a drug.	<i>Does MEB agree that the primary endpoint of overall survival supported by the secondary endpoints of PFS, tumour response rate and duration of response is appropriate to support registration of drug X in first line in advanced non-small cell lung cancer?</i>
Study design	Multiple methodological issues of one specific randomized clinical study.	<i>The recently initiated Phase II-III clinical trial has the following characteristics:”.....” Is this trial design acceptable for definitive confirmation of the clinical benefit and of an acceptable safety profile of drug X?</i>
Dosing	The appropriateness of the doses chosen for a clinical study.	<i>The scheme for the individual dosing is a 10 mg/kg loading dose followed by a 5 mg/kg maintenance dose. The company considers increasing the maintenance dose if no adverse effects are seen. Does the MEB agree to the proposed dosing regimen?</i>
Study population	The appropriateness of the inclusion and exclusion criteria	<i>Does the Agency concur with the definition of the patient population to be studied in the Phase 3</i>

	used for patient selection in a study.	<i>randomized trial to support regular approval in their respective proposed indications?</i>
PK Strategy	The appropriateness of the complete clinical pharmacokinetic study program	<i>Does the MEB agree with the proposed clinical pharmacokinetic programme?</i>
Validity of measurement method	The application of specific measurement methods (e.g. symptom scores) to assess clinical endpoints.	<i>The MD Anderson Symptom Inventory (MDASI) will be used in the randomized Phase 3 study to measure the patient reported outcomes of symptom severity and interference (SSI). Does the Agency concur with the use of the MDASI instrument?</i>
Special safety issues	The investigation of specific safety issues on organ system level.	<i>Are there any specific aspects on safety you would like us to pay special attention to?</i>  <i>Does the agency concur with the company's proposal to perform only ECGs in the proposed pivotal studies, given the absence of a QTc prolongation effect in a thorough QT study?</i>

**Figure 2 Top ten Most frequently asked topics**

