Relationship between uncontrolled trial designs and type of European marketing authorisation application

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Major research project for Science and Business Management

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Utrecht, 12-07-2021

Content

List of abbreviations

ATMP	Advanced Therapy Medicinal Products
AEC	Authorisation under exceptional circumstances
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Conditional marketing authorisation
EMEA	European Agency for the Evaluation Medical Products
EC	European Commission
EMA	European Medicines Agency
EPARs	European public assessment reports
EU	European Union
FDA	Food and Drug Administration
FDCs	Fixed dose combinations
HTA	Health Technology Assessment
ICD-10	International Classification of Diseases and Related Health Problems
IQR	Interquartile range
KAS	Known active substance
MA	Marketing Authorisation
MAA	Marketing Authorisation Applications
MAH	Marketing authorisation holder
MoA	Mechanism of Action
NAS	New active substance
NSCLC	non-small-cell lung carcinoma
Q1	Quartile 1
Q3	Quartile 3
RCT	Randomised controlled trial
RR	Risk ratio
SA	Scientific advice
SMA	Standard marketing authorisation
SmPC	Summary of product characteristics
SOB	Specific Obligation

Summary

Background. Over the last 25 years different types of European Marketing Authorisation Applications (MAAs) were granted based on the comprehensiveness of data. When at time of MAA there was comprehensiveness of data, a standard marketing authorisation (SMA) could be granted and when there was no comprehensiveness of data (yet), authorisation under exceptional circumstances (AEC) could be granted. From 2006 onwards, also a conditional marketing authorisation (CMA) could be granted when there was no comprehensiveness of data yet. For all these type of MAAs, randomised controlled trials were the golden standard to evaluate clinical efficacy and when other study designs including uncontrolled clinical trials were used this should be justified. Prior studies already investigated the use of uncontrolled trials for Marketing Authorisation Applications (MAAs) in the United States and Europe in general. However, since none of these studies studied the differences between the types of MAAs, we aimed to get further insight in the relation between the different types of MAAs and the acceptation of MA approval based on uncontrolled trials, taking into account the time of authorisation.

Design and methods. We considered all MAAs that were approved by the EMA between 1995 and 2020 and selected marketing authorisation (MA) approvals that were based on full MAAs and for which the pivotal trial design was uncontrolled. To study the relation between the use of uncontrolled pivotal trial designs and the type of MAA, we divided our study cohort in five groups based on time of authorisation and the three types of MAA. For the time of authorisation, we separated MA approvals under Regulation No. 2309/93 from MA approvals under Regulation No. 726/2004. This led to the following five groups: SMA 2309/93, AEC 2309/93, SMA 726/2004, AEC 726/2004 and CMA 726/2004. Thereafter, two approaches were used to answer the research question. For our first approach, we extracted arguments for the acceptation of uncontrolled trials as the basis for initial MA approval from the individual European Public Assessment Reports. In addition, we visualised the arguments for the use of uncontrolled trials per group by using UpSet plots. For our second approach, we extracted treatment-, disease- and study-related characteristics from the EPARs, the European Commission community register, an internal EMA database, the table of all human and veterinary medicines and the summary of product characteristics. We calculated the risk ratio with 95% confidence intervals to study the associations between these characteristics and the type of MAA. Finally, we contextualised our findings by comparing results from approach 1 and 2 with other information related to the comprehensiveness of data.

Results. Of all 752 full MAAs, there were 12 of the 166 SMAs 2309/93 (7%) and 37 of the 466 SMAs 726/2004 (8%) based on uncontrolled trials, whereas this were 11 of the 39 AECs 2309/93 (28%), 11 of the 27 AECs 726/2004 (41%) and 28 of the 54 CMAs (52%). This gave a total of 99 MA approvals that were based on uncontrolled trials of which 43 MA approvals (44%) were for malignant neoplasms. The fifteen different arguments that were used for accepting MA approval based on uncontrolled pivotal trials were the disease-specific guideline, no (satisfactory) treatment, severity of disease, rarity of disease, unethical, effect size, valid surrogate, (clinical) experience, scientific advice, preliminary RCT results, historical control, historical comparison, natural course of the disease, well-conducted and mechanism of action. Arguments to accept MA approval based on non-comprehensive evidence with uncontrolled trials included rarity of disease in 10/11 AECs (91%), no satisfactory treatment in 10/28 CMAs (36%), effect size in 10/28 CMAs (36%) and severity of disease in 6/28 CMAs (21%). Associations between the type of MAA and some treatment- and disease-related characteristics partly confirmed the use of these arguments. For providing comprehensive evidence with uncontrolled trials, arguments were not used at all for 12/37 SMAs 726/2004 (32%) or were based on the disease-specific guideline for 13/37 SMAs 726/2004 (35%). In addition, also other uncertainties such as small sample size and

short follow-up could play a role in which type of MAA was granted. Finally, by comparing MA approvals based on uncontrolled trials under Regulation No. 2309/93 and 726/2004, it became clear that the arguments to accept uncontrolled trials for MAA became more extensive over time.

Conclusions. Overall, we can conclude that uncontrolled trials were more often used for AECs and CMAs than for SMAs. Whereas for AECs and CMAs, the acceptability of uncontrolled trials was often clearly argued, the argumentation why uncontrolled study design could lead to approval of a SMA, and thus provide comprehensive data, was often not sufficiently clear and could be improved to increase the understanding of all stakeholders on type of MAA and factors of comprehensiveness. These findings may give insight in the decision-making over time and may open the door for future research on how after MA approval, MAAs based on uncontrolled trials are evaluated by Health Technology Assessment organisations.

1. Introduction

To protect public health, the European Union (EU) decided in 1993 to use a centralised, EU wide procedure for authorisation of both human and veterinary innovative medicines. This led to the establishment of the European Agency for the Evaluation Medicinal Products (EMEA), later named as the European Medicines Agency (EMA). This agency is responsible for scientific evaluation of the safety, efficacy and quality of medicines by executing a marketing authorisation (MA) procedure.[1,2,3] The requirements for such a MA procedure together with the establishment of the EMA were laid down in Council Regulation (EEC) No. 2309/93 which was binding in its entirety and came into force in all member states on the first of January 1995 (*figure 1*).[1,4]

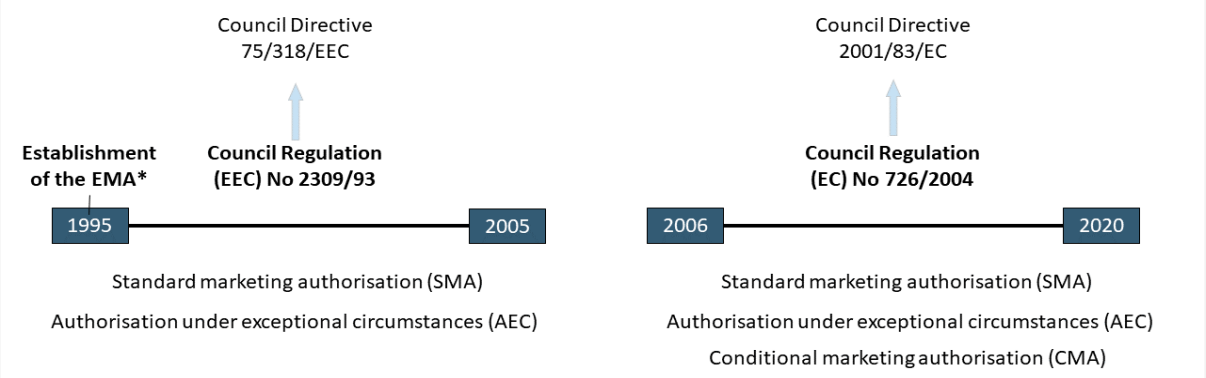


*Figure 1. The regulations and directives over time. Both council regulations refer to the directives in which requirements about the MA procedures are written down. Regulation No. 2309/93 was adopted in 1993 and came into force in 1995. *The European Medicines Agency (EMA) was first called the European Agency for the Evaluation Medicinal Products (EMEA).*

In Regulation No. 2309/93, it was stated that different types of Marketing Authorisation Applications (MAAs) could be granted by the EMA based on the comprehensiveness of data (*figure 1 and 2a*).[1] When for a full MAA data was considered to be comprehensive, a standard marketing authorisation (SMA) could be granted. When data was not (yet) comprehensive at the time of MAA, an authorisation under exceptional circumstances (AEC) could be granted.[1] It was specified that an AEC could only be granted when comprehensive data could not be collected at time of MAA due to the rarity of disease, the current state of scientific knowledge or medical ethics.[5] When one of these requirements applied and an AEC was granted, an annual reassessment and post authorisation studies, the so called specific obligations (SOBs), were obligated. These SOBs most frequently led to comprehensiveness of data after authorisation, resulting in a conversion into a SMA (*figure 2a*).[6]

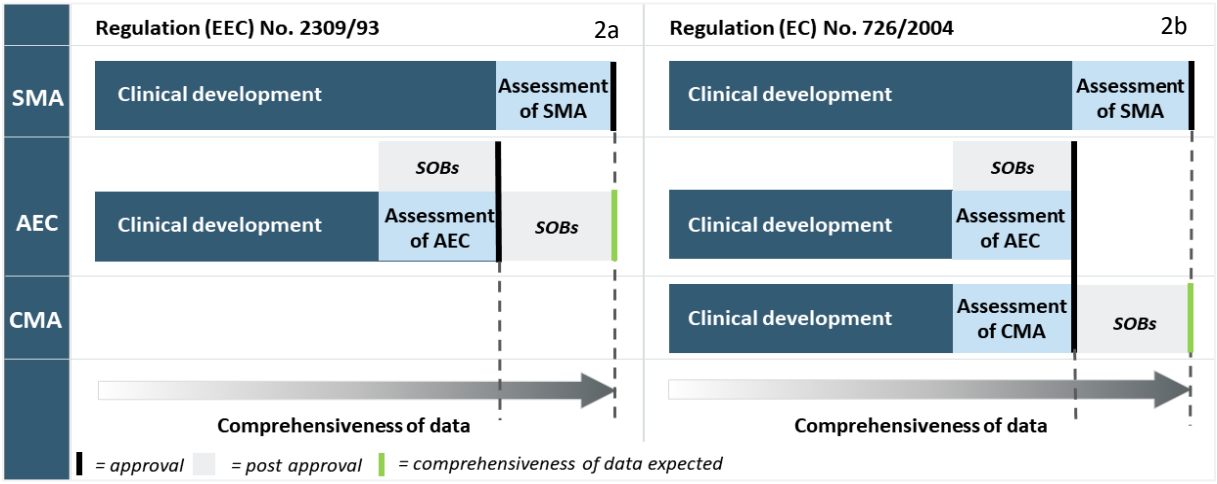


Figure 2. The type of Marketing Authorisation Application (MAA) and the degree of comprehensiveness. The two MAAs under Regulation No. 2309/93 are visualised in figure 2a. For an AEC, comprehensive data could still be collected in the future with specific obligations (SOBs). In figure 2b, the three types of MAAs under Regulation No. 726/2004 are visualised. Only for a CMA, comprehensive data could be collected in the future with SOBs. Based on Hoekman and Boon (2019).[7]

In November 2005, a new regulation (Regulation (EC) No. 726/2004) came into force for the authorisation and supervision of medicinal products for human and veterinary use (*figure 1*).[8] In 2006, conditional marketing authorisation (CMA) was introduced under Regulation (EC) No. 507/2006 as a third type of MAA next to AEC and SMA, falling within the scope of Regulation No. 726/2004. A CMA was introduced for orphan medicines, medicines intended for emergency situations or medicines for life-threatening/ seriously debilitating diseases for which no comprehensive data could be collected at time of MA approval but for which immediate availability was preferred.[9] Such a CMA could only be granted when the medicine fulfilled an unmet medical need meaning that the medicine could have a major therapeutic advantage over established treatment options or was intended for a disease for which no other (satisfactory) treatment was present at MA approval.[9] When the MAA fulfilled all the criteria, a CMA based on non-comprehensive data was granted (*figure 2b*).[9,10] Following approval, comprehensive data was expected to be collected by the applicant with SOBs so a CMA could be converted into a SMA. Whereas conversion into a SMA was common for AECs under Regulation No. 2309/93 as well, the guideline for AECs under Regulation No. 726/2004 stated that it should be unlikely that comprehensive evidence would be collected in the future and that the fulfilments of SOBs would normally not lead to the conversion into a SMA.[11]

Thus, whether clinical development data are comprehensive at MA approval and whether this data can become comprehensive in the future depends on both the type of MAA and the regulation that applies (*figure 2*). This results in five different types of MAAs: SMAs and AECs under Regulation No. 2309/93 and SMAs, AECs and CMAs under Regulation No. 726/2004. These five different types of MAA are an indicator of the comprehensiveness of clinical development data, including the clinical trial designs, at time of MAA.[1,8,9,11]

During the clinical development of a medicine, randomised controlled trial (RCT) designs are most frequently used to evaluate the efficacy.[12] In RCTs, the medicine of interest is compared with a placebo or active control by randomising patients to one of the both arms. [13] An active control can also refer to physician's choice and thus doesn't need to be one specific medicine. When properly designed and conducted, an RCT aims to give an unbiased estimate of the treatment effect and is seen as the golden standard.[13,14] That an RCT is seen as the golden standard already becomes clear in the Council Directive 75/318/EEC, a legal act of the European Union related to the clinical standards and protocols in respect of the testing of medicines.[5] From 1991 onwards the Annex of Directive 75/318/EEC stated that: "In general, clinical trials shall be done as controlled clinical trials and if possible, randomized; any other design shall be justified."[5] This part of the Directive is referred to by Regulation No. 2309/93, which ensured that the use of controlled clinical trials applied in its entirety across the EU.

Nevertheless, there are a few situations in which during clinical development RCTs are not or less often used to estimate the clinical efficacy of medicines and where uncontrolled clinical trials are used instead. In uncontrolled clinical trials, there is no internal control arm against which the outcomes can be compared.[12] A first situation in which RCTs are not used is when it is unethical to randomly allocate people to a control group. For instance, when it is already known that a therapy decreases serious morbidity or improves survival.[12,13] Next to ethical reasons, the changing nature of medicines also challenges the use of an RCT in gathering evidence.[15] Nowadays, blockbuster medicines from the 20th century are replaced by more and more niche products. This change towards niche products leads to a decrease in the target population size, making it sometimes unfeasible to gather evidence by using RCTs.[15] Finally, the use of a RCT can be challenging in obtaining sufficient data in medicines for rare diseases. Rare diseases have a prevalence of five cases or less per 10000, making it difficult to enroll enough patients to estimate treatment effects with RCTs with sufficient precision.[16] So, although RCTs

are the golden standard, in some situations, clinical efficacy data can only be collected using other designs such as uncontrolled clinical trials.

As uncontrolled clinical trials are other designs than controlled clinical trials, their use should be justified for SMAs according to the old Directive and the currently valid Directive 2001/83/EC (Annex I, part I).[5,17] Also for AECs and CMAs, it seems that the uncontrolled clinical study design should be justified.[9,11,17] In the CMA guideline is for instance mentioned that: "The data requirements laid down in Annex I of Directive 2001/83/EC are also applicable for products granted CMA. However, in the case of CMAs the evidence at the time of initial authorisation may be less comprehensive than normally required.''[9] For AECs, Directive 2001/83/EC states that for specific MAAs including AECs, requirements of the MAA dossier from Annex I need to be adapted. However, for AECs specifically, only the requirements for AEC and the inclusion of SOBs to the MAA dossier are mentioned as change to the normal requirements.[17] Also, in the AEC guideline nothing is mentioned about the acceptation of other study designs than controlled clinical trials.[11]

In addition to the guidelines for the different types of MAAs, some disease-specific guidelines do mention that an uncontrolled trial design is acceptable. In the guideline for the use of human normal immunoglobulins is from 2018 onwards stated that: "Efficacy should be proven in an open label, single-arm clinical trial of one year duration in primary immunodeficiency syndromes." [18] Also for coagulation factors, the visualised clinical trial design in Annex I of the guideline doesn't show the need of a controlled trial.[19] However, for most medicines the use of an uncontrolled trial design still needs to be justified.

Two studies which already investigated the use of uncontrolled trials for European MA approvals are the studies by Hatswell *et al.*, (2016)[12] and Tenhunen *et al.*, (2020).[20] Hatswell *et al.* reviewed authorisations for new medicines by the EMA and the United States Food and Drug Administration (FDA) to investigate how often MA approvals were made on the basis of uncontrolled trials. In their study, they focused on medicines that were approved between January 1999 and May 2014 without either the pivotal or the supportive study being RCTs. Pivotal studies are clinical trials that serve as the main basis for MA and supportive studies are additional to these.[21] Hatswell *et al.* concluded that 1) approximately three MA approvals per year by the EMA were based solely on uncontrolled data, 2) that MA approval based on uncontrolled studies was most frequent for solid and haematological malignancies covering 49 of the 74 (66%) indications based on uncontrolled pivotal and supportive trials in total and 3) that the level of evidence to support MA based on uncontrolled trials did appear not to be the same between the different pharmaceutical companies.[12] The study by Tenhunen *et al.* (2020) investigated medicines in the field of oncology which were approved by the EMA between 2010-2019 based on uncontrolled efficacy and safety trials. They analysed the European Public Assessment Reports (EPARs) of these medicines to describe the data behind MA approvals based on uncontrolled trials and found that 22 initial MAAs were based on uncontrolled trials of which six were SMAs and sixteen were CMAs. Other results were not separated based on type of MAA but were described for the whole study cohort.[20]

However, none of these studies studied the relation between MA approvals based on uncontrolled trials and the different types of MAAs and thus the question when uncontrolled trials could provide comprehensive or non-comprehensive evidence. Moreover, although both studies looked over a long period of time, they did not focus on possible changes between Regulation No. 2309/93 and Regulation No. 726/2004 in the acceptation of uncontrolled trials for MA approval. To fill these knowledge gaps, we aimed to get insight in the acceptation of MA approval based on uncontrolled trials and the different types of MAAs and whether this has changed over time. Therefore, we used two different approaches. We first studied the arguments used to accept uncontrolled trials for MA approval in

relation to the different types of MAA. Secondly, we looked at associations between the type of MAA and treatment-, disease- and study-related characteristics. We expected to find that for SMAs, uncontrolled trials were used less than for CMAs and AECs, since it would be more acceptable to use an uncontrolled trial for MAAs where comprehensive evidence at MA approval is not (yet) collected. Moreover, we supposed to identify different arguments for SMAs than for AECs and CMAs.

2. Methods

2.1 Cohort Selection

A retrospective cohort study was performed consisting of all medicines for which initial MAA was based on pivotal uncontrolled trials and which were approved by the EMA between 1995 and 2020. These MA approvals were identified from the table of all human medicines ever approved by the EMA.[1] This table was for the last time accessed on the first of March 2021 to make sure all approved MAs of 2020 were included.

Before we specified the pivotal study designs used for the MAAs, we excluded MA refusals, diagnostic tools, vaccines and duplicate MAs. A duplicate MA is an application for a medicine that is identical to an earlier authorised medicine.[2] We identified authorisations as being duplicates when the EPAR and/ or the Summary of Product Characteristics (SmPC) were exactly the same or when different medicines had the same initial indication, the same MA date and the same marketing authorization holder (MAH). Duplicate MAs were excluded to make sure we included every MAA and its MA procedure only once. Similar to Hatswell *et al*., we excluded diagnostic tools and vaccines since for diagnostic tools no therapeutic effect needs to be measured and for vaccines often immunogenicity studies instead of efficacy studies are most essential, resulting in different kind of MAAs than the MAAs of interest.[12,22]

In addition, as we aimed for MA approvals based on full MAAs, we used the legal basis to exclude generics 10(1), hybrids 10(3), biosimilars 10(4), well-established use 10(a), fixed dose combinations (FDCs) 10(b) and MAAs based on informed consent 10(c). The used article numbers are from Directive 2001/83/EC.[17] These MAAs were excluded since they already had particular similarities to other MAAs and thus were not full MAAs. Fixed dose combinations (FDCs*) which had a full MAA but in which two already authorised products were present were also excluded. Already authorised products are MAAs for which the individual active substances in the medicine already have been assessed on an Europe wide level and are approved by the European Commission via the centralised procedure.[3] For MAAs between 2008 and 2020, the legal basis was well described in the EPAR and in the annual reports of the EMA. For the other MAAs, we used an internal EMA database including characteristics of all medicines approved by the EMA to indicate the legal basis.

For all MA approvals based on full MAAs, we specified the type of MAA to be able to look at the use of uncontrolled studies versus controlled studies for providing (non-)comprehensive evidence. There were three types of MAAs used by the EMA for marketing authorisation: SMA, AEC and CMA.[23] Of these types of MAAs, five groups could be made by taking into account Regulation No. 2309/93 and 726/2004: SMA 2309/93, AEC 2309/93, SMA 726/2004, AEC 726/2004 and CMA. Since the CMA was only established from 2006 onwards and because some descriptions of AECs 2309/93 suggested that these could be converted into SMAs whereas this was more an exception for AECs 726/2004, it was important to separate the type of MAA by the two different regulations.

2.2 Cohort specification

Selection whether MA approvals were based on uncontrolled pivotal trial(s) was done manually by reading and screening the individual EPARs. Missing EPARs were requested from the EMA. The possible study designs of the pivotal trials were: uncontrolled trials, controlled trials, cross-over studies, observational studies and literature studies. Uncontrolled trials were defined as trials in which no internal placebo or internal active control was used. The cross-over studies, observational studies and

[1] *https://www.ema.europa.eu/en/medicines/download-medicine-data*

[2] *Amendment of Regulation No 726/2004: Commission Notice Handling of duplicate marketing authorisation applications of pharmaceutical products under Article 82(1) of Regulation (EC) No 726/2004 2021/C76/01*

literature studies were later on named as 'other study designs'. When within one initial MA approval, there was more than one indication (a medical condition that a medicine is used for) we looked at the pivotal trial design for each indication at time of approval. We only looked at initial indications and not at indication extensions after MA approval since we are interested in the relation between the type of MAA and the use of uncontrolled trials at time of MA approval only. After selection of all European MA approvals for which at least one initial indication was based on uncontrolled pivotal trial(s), we determined this group as our study cohort and assigned them to the similar five groups as we used for all full MAAs.

2.3 Data extraction

For our whole study cohort, we first collected basic characteristics of the MA approvals such as time of marketing authorisation, number of indications per MA approval that were based on uncontrolled study design and therapeutic area to specify our study cohort. A detailed overview of which data was extracted from which dataset, can be found in *Annex I, table S1*. To access our aim, we used a first approach for which arguments for the acceptability of the use of uncontrolled trials to support MA approval were extracted. These arguments were collected from the efficacy, safety and benefit-risk discussion sections in the EPARs on product level and not on indication level, since for one MA approval often general arguments for the acceptability of uncontrolled trials were used. We extracted these arguments for all MA approvals under Regulation No. 2309/93 and Regulation No. 726/2004.

Since not all important characteristics which could make MA approval based on uncontrolled trials acceptable needed to be mentioned in the EPAR as an argument, we used a second approach to access our aim. For our second approach, we looked at associations between type of MAA and treatment-, disease- and study-related characteristics at MA approval. We only looked at associations for MA approvals under Regulation No. 726/2004 since these type of MAAs and rules corresponded the most with the MA procedure used nowadays. Moreover, through the requirements of transparency under Regulation 726/2004, these EPARs are more extensive.[24–26] We extracted most data from the EPARs, the European Commission (EC) community register, an internal EMA database, the table of all human and veterinary medicines and the SmPC. A more detailed overview of which data was extracted from which dataset, can be found in *Annex I, table S2*. Depending on the characteristic that was collected, it was extracted on product level or indication level. Some characteristics were on indication level, because for MA approvals with more initial indications at time of approval, these characteristics related to the treatment, the disease or the study could be indication specific.

To place the data from the first and second approach into context, we identified other factors related to the (non-)comprehensiveness of data which also could influence the type of MAA besides the uncontrolled study design. This included the uncertainties and their causes at time of MA approval. In addition, we collected data specific for the type of MAA, including the AEC and CMA scope, the design of SOBs for CMAs and whether something was said about the (non-)comprehensiveness of data (*Annex I, table S3*). All data were collected on product level, since factors related to the (non-)comprehensiveness of data often applied for the MA approval in general.

For the full study cohort, data extraction was performed by J. Schelhaas. When there were uncertainties or data points which were sensitive for subjectivity, these were discussed with L.T. Bloem until consensus was reached. Also, meetings with C.A. Herberts and P.B. van Hennik took place to make sure that data from the EPARs were interpreted correctly and that the MA approvals were categorised in the right therapeutic area with the right number of initial indications. *Annex II* shows in detail how data that left room for own interpretation was extracted.

2.4 Data categorisation

For our first approach, MA approvals were categorised based on the type of MAA by taking into account the different regulations. In addition, we made categories for the therapeutic area to make a comparison between the use of the therapeutic areas and the type of MAA. For the categorisation of the therapeutic area, we used the International Classification of Diseases and Related Health Problems (ICD-10) codes since this is an internationally used classification of diseases which allows a clear and comprehensive classification of the therapeutic areas where the MA approvals are intended for.[27] There are different levels used in this classification, ranging from broad therapeutic areas in level one to very specific therapeutic areas in level four. We used level two when possible, but in some cases level one was used to prevent that the categories became too detailed. Four of the twelve categories are at level one and are marked with an asterisk: 1. Malignant neoplasms 2. Infectious diseases* 3. Coagulation defects, purpura and other haemorrhagic conditions 4. Certain disorders involving the immune mechanism 5. Metabolic disorders 6. Disorders of other endocrine glands 7. Injury, poisoning and certain other consequences of external causes* 8. Diseases of nervous system* 9. Diseases of liver 10. Factors influencing health status and contact with health services* 11. Other disorders of kidney and ureter and 12. Neoplasms of uncertain or unknown behaviour.[27]

For our second approach, the only characteristic that was categorised was the prevalence of disease. We made four categories including non-rare, rare, very rare and ultra-rare. A rare disease is a disease occurring in 1-5:10.000 people, a very rare disease occurs in 1-9:100.000 people and an ultra-rare disease in 1-9:1.000.000 people. This is in line with the categorisation used by the European association for orphan diseases, EURORDIS, on their website Orphanet[28], a webpage cofunded by the European Commission that want to increase the knowledge on rare diseases.[29] We systematically collected the prevalence of disease by extracting it from the EPAR of the MA approval of interest, EPARs from other MA approvals for the same disease (preferably with a maximum of a 5 year difference between the marketing authorization dates) and from Orphanet. When the disease was not mentioned on Orphanet and the prevalence was not mentioned in the EPAR, the prevalence was marked as 'unknown'. When the disease was on Orphanet but the prevalence was unknown, the prevalence was marked as 'unknown but rare'.

2.5 Outcome definitions

For our first approach, we identified arguments that were used to accept the use of uncontrolled trials as a basis for MA approval and came up with sixteen possible arguments which we divided over three main outcomes: treatment-, disease- and study-related outcomes (*table 1*). Outcomes are main categories where the arguments to accept the use of uncontrolled trials as a basis for MA approval can be assigned to. The first seven arguments were identified based on regulatory knowledge and research experience and are described in *table 1* and have an asterisk. After reading all the clinical efficacy discussions, the clinical safety discussions and the benefit-risk balances of the whole study cohort and after meetings with L.T. Bloem, C.A. Herberts and P.B. van Hennik, eight additional arguments were added. This gave us a total of fifteen arguments which were mentioned in the EPARs explicitly or implicitly (*table 1*). A fourth outcome we added was 'no data' which included MA approvals where no arguments to accept the use of an uncontrolled trial as basis for MA approval were mentioned. These sixteen arguments are explained in more detail in *table 1*.

For our second approach, we assigned the extracted characteristics to the same three main outcomes and linked them to one of the sixteen arguments from approach 1 (*table 1*). Also the factors that were related to the (non-)comprehensiveness of data (and thus the type of MAA) and were used to place the results from the approach 1 and 2 into context were divided over the same three main outcomes and the sixteen arguments. These data are shown in *italics* in *table 1*.

Table 1. Outcome definitions together with an explanation of data from approach 1 and approach 2. For approach 1, the arguments that make an uncontrolled trial acceptable are explained and for approach 2 the characteristics that were related to the arguments and used to calculate the RR were summarised. In Italics, other factors related to the (non-) comprehensiveness of data are described.

Outcome	Explanation of the arguments for approach 1	Characteristics for approach 2 and *factors related to comprehensiveness of data*
Treatment-related outcomes		
No (satisfactory) treatment*	No (satisfactory) treatments at time of MA made the use of an RCT not possible	The lack of a (satisfactory) treatment in general.
		CMAs for which there was no (satisfactory) treatment
Effect size*	High/ outstanding effect sizes made it likely that the medicines caused the effect and made a RCT less important	*CMAs for which there was a major therapeutic advantage over established treatment options.*
Unethical*	An RCT with a placebo or active control was seen as unethical since treatment effects of the medicine were already known	*AECs for which medical ethics was used as a reason*
Valid surrogate	Pathology-related endpoints and relevant biochemical endpoints made a RCT not needed	-
(Clinical) experience	Experience within patients from earlier studies gave additional evidence and made the use of an RCT less important	The active substance status (new or known)
Mechanism of action	A well-known mechanism of action reduced the importance of a RCT	-
Disease-related outcomes		
Rarity of disease*	Rarity of a disease could limit the number of patients which could obstruct the use of a RCT	Orphan designation, prevalence of disease and the efficacy and safety population
		AECs for which rarity of disease was used as a reason
Severity of disease*	The severity of a disease could make evidence based on uncontrolled trials more acceptable when this led to earlier access	The line of treatment. Possible treatment options become exhausted.
Guideline*	Disease-specific guidelines in which uncontrolled trials were mentioned as a valid study design.	-
Natural course of the disease	The well-known natural course of the disease could make to use of a control arm to determine the effect not necessary	-
Study-related outcomes		
Historical comparison	A comparison with other data in the literature made the uncontrolled trial acceptable	-
Historical control*	The use of a historical control made the uncontrolled study designs acceptable	The use of a historical control in general.
Scientific advice	The uncontrolled study design was acceptable based on SA or PA	The presence of scientific advice or protocol assistance
Preliminary RCT results	A supportive RCT study gave promising results which made the uncontrolled pivotal trial acceptable	Supportive study designs
Well-conducted	The uncontrolled study was well-conducted according to the CHMP and thus acceptable	-
No data		
No argument mentioned	No arguments were used for the acceptance of approval based on uncontrolled trials.	*Opinion about (non-)comprehensiveness of data for SMAs, AECs and CMAs*

2.6 Data analysis

We characterized the cohort by describing basic characteristics of the medicines including among others the time of marketing authorisation, the therapeutic area and the number of initial indications. For the first approach, we visualised the arguments used for the acceptability of uncontrolled trials per type of MAA for MA approvals under Regulation No. 2309/93 and Regulation No. 726/2004 by using UpSet plots.[30] For the second approach, we described the associations between treatment-, disease- and study-related characteristics and the different types of MAAs by calculating risk ratios (RR) and 95% confidence intervals (CI).[31] Since the cohort of MA approvals studied is the complete population for European MA approvals based on uncontrolled trials, the risk ratio is the actual risk ratio and significance testing was not deemed necessary. For the comparison of continuous variables between the type of MAAs, the non-parametric Mann-Whitney U test was used.[32] As explained in the data extraction section, only the MA approvals under Regulation No. 726/2004 were used for this calculation. Depending on the sort of characteristic, data were analysed on product level or indication level. When for a MA approval a certain characteristic was unknown, this MA approval was left out of the analysis for the characteristic in question. Finally, we contextualised our findings by identifying other factors related to the (non-)comprehensiveness of data and by comparing this with the results from approach 1 and 2.

3. Results

3.1 Selection of the study cohort

The MAAs that were included and excluded in the study cohort are shown in *figure 3*. The overall number of MA approvals (n=1454) and the number of full MAAs (n=752) clearly increased over time (*Annex III and Figure 4a*). MA approvals based on uncontrolled pivotal trials also increased over time in absolute numbers (*figure 4a*), but didn't increase relative to all full MAAs. The number of MA approvals based on uncontrolled trials relative to all full MAAs for each 5-year time interval beginning at 1991-1995 showed that uncontrolled trials were used in 0 out of 3 (0%), 7 out of 91 (8%), 16 out of 111 (14%), 16 out of 138 (12%), 23 out of 200 (12%), and 37 out of 209 (18%) full MAAs. We also studied the number of MA approvals based on uncontrolled trials per type of MAA relative to all full MAAs for each type of MAA. The number of MA approvals based on uncontrolled trials per type of MAA were 12 of the 166 SMAs 2309/93 (7%), 11 of the 39 AECs 2309/93 (28%), 37 of the 466 SMAs 726/2004 (8%), 11 of the 27 AECs 726/2004 (41%) and 28 of the 54 CMAs (52%). (*Figure 4*). In total, this resulted in 99 MA approvals that were based on uncontrolled pivotal trials.

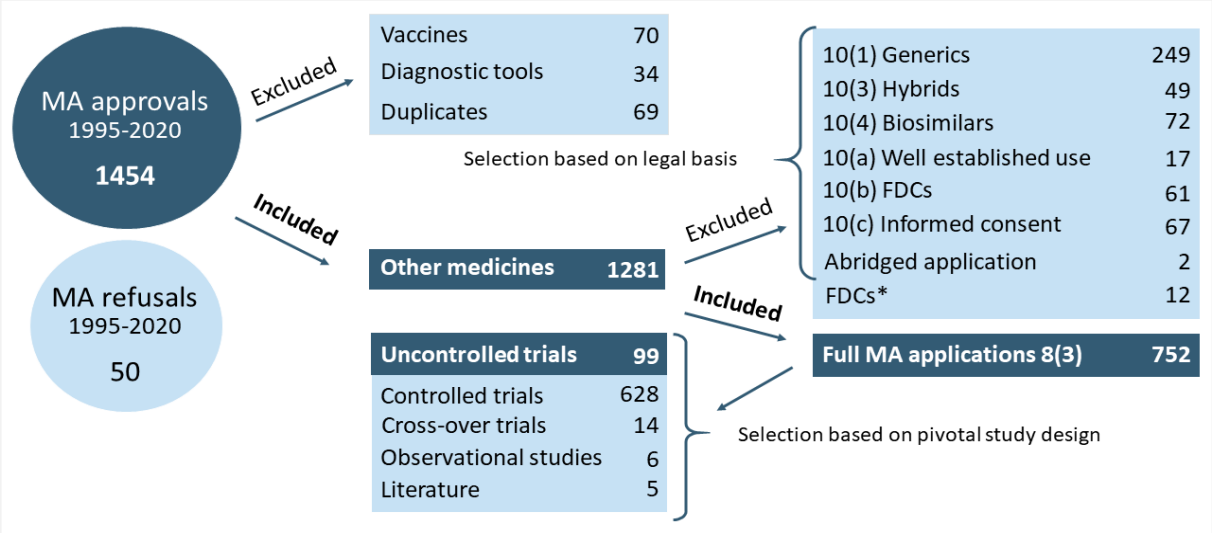


Figure 3. A flow chart showing the selection of MAAs that were approved by the EMA between 1995-2020 based on uncontrolled pivotal trials at first approval.

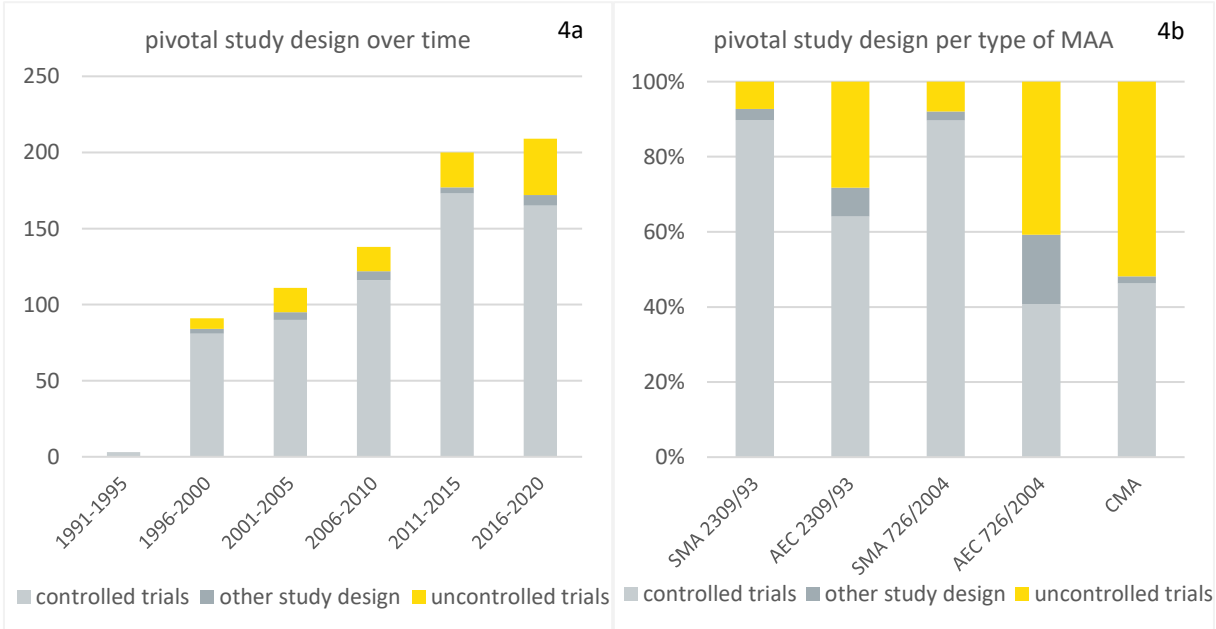


Figure 4. The full MAAs (n=752) over time and per type of MAA. Figure 4a) the pivotal study design for full MAAs over time (5-year time intervals). Figure 4b) the pivotal study design for full MAAs per type of MAA (%).

3.2 Basic characteristics

The basic characteristics of these 99 MA approvals were used to characterize the study cohort in general and for each type of MAA (*table 1)*. One of the basic characteristics was the year of MA. Of the 99 MA approvals in the study cohort, 23 MAs were approved under Regulation No. 2309/93, including twelve SMAs (52%) and eleven AECs (48%) (*table 1*). During Regulation No. 726/2004, 76 MAs were approved based on uncontrolled trials, consisting of 37 SMAs (47%), eleven AECs (14%) and 28 CMAs (37%). In the last two years, no AECs based on uncontrolled trials were approved and most MA approvals based on uncontrolled trials were CMAs: 4 out of 6 in 2019 (67%) and 7 out of 8 in 2020 (88%) (*Annex III, figure S1*).

For the therapeutic area, twelve categories were used based on the ICD-10 codes. The six categories that included the least number of MA approvals were named as 'others'. For all 99 medicines, the malignant neoplasms represented the biggest group consisting of 43 MA approvals (44%). In the MA approvals under Regulation No. 726/2004 each therapeutic area was clearly represented in one type of MAA in both relative and absolute numbers. Of the 37 SMAs 726/2004, eleven were for coagulation defects (30%). Six of the eleven AECs 726/2004 were for metabolic disorders (54%) and of the 28 CMAs, twenty were for malignant neoplasms (71%) (*table 1*). In contrast, under Regulation No. 2309/93 the distribution of the therapeutic areas over the two types of MAAs was more scattered (*table 1*).

For each MA approval, we also studied the number of initial indications based on uncontrolled trials (*table 1*). For the 99 MA approvals, there were a total of 130 indications at first approval. 73 medicines had one indication (74%), 22 had two indications (22%), three medicines had three indications (3%) and one had four indications (1%). The SMAs 726/2004 included most MA approvals with a second indication. Of these 99 MA approvals still 89 were authorised (90%) on the first of March 2021. Ten MA approvals were withdrawn (10%), including three SMAs 2309/93, one AEC 2309/93, one SMA 726/2004, three AECs 726/2004 and two CMAs. Besides the basic characteristics per type of MAA, we also visualised the basic characteristics over time in *figure S1, Annex III*.

*Table 1: Basic characteristics of the study cohort (n=99) overall and per type of MAA. *The full name of this therapeutic area is Coagulation defects, purpura and other haemorrhagic conditions. ATMP = Advanced Therapy Medicinal Products.*

Drug characteristics at approval	SMA 2309/93 (n=12)	AEC 2309/93 (n=11)	SMA 726/2004 (n=37)	AEC 726/2004 (n=11)	CMA (n=28)	Overall (n=99)
Year of MA						
1995-2000	4 (33%)	3 (27%)	NA	NA	NA	7 (7%)
2001-2005	8 (67%)	8 (73%)	NA	NA	NA	16 (16%)
2006-2010	NA	NA	10 (27%)	4 (36%)	2 (7%)	16 (16%)
2011-2015	NA	NA	11 (30%)	5 (45%)	7 (25%)	23 (23%)
2016-2020	NA	NA	16 (43%)	2 (18%)	19 (68%)	37 (38%)
Therapeutic area						
Malignant neoplasms	4 (33%)	5 (45%)	11 (30%)	3 (27%)	**20 (71%)**	43 (44%)
Coagulations defects*	3 (25%)	1 (9%)	**11 (30%)**	1 (9%)	0 (0%)	16 (16%)
Metabolic disorders	1 (8%)	4 (36%)	2 (5%)	**6 (55%)**	1 (4%)	14 (14%)
Infectious disease	2 (17%)	1 (9%)	2 (5%)	0 (0%)	1 (4%)	6 (6%)
Immunodeficiencies	0 (0%)	0 (0%)	**6 (16%)**	0 (0%)	0 (0%)	6 (6%)
Others	2 (17%)	0 (0%)	5 (14%)	1 (9%)	6 (21%)	14 (14%)
Drug type						
Small molecule	7 (58%)	9 (82%)	12 (32%)	5 (45%)	16 (57%)	49 (50%)
Biological	5 (42%)	2 (18%)	21 (57%)	6 (55%)	8 (29%)	42 (42%)
ATMP	NA	NA	4 (11%)	0 (0%)	4 (14%)	8 (8%)
Initial approved indications based on uncontrolled trials						
1	8 (67%)	9 (82%)	22 (59%)	9 (82%)	25 (93%)	73 (74%)
2	3 (25%)	0 (0%)	14 (38%)	2 (18%)	3 (7%)	22 (22%)
3+	1 (8%)	2 (8%)	1 (3%)	0 (0%)	0 (0%)	4 (4%)

3.3 Approach 1 - Arguments for the acceptation of uncontrolled trials per type of MAA

Within the whole study cohort (n=99), the five most common arguments for the acceptation of uncontrolled trials as basis for MA approval were no satisfactory treatment, rarity of disease, effect size, severity of disease and the guideline. For 28 MA approvals, no (satisfactory) treatment was used as an argument (28%). The rarity of disease was used in sixteen MA approvals (16%) and the effect size and severity of disease both in fifteen MA approvals (15%). Lastly, the guideline was used in fourteen MA approvals (14%). In addition, in 25 MA approvals no arguments to accept MA approval based on uncontrolled trials were mentioned (25%) (*Annex IV*).

3.3.1 Arguments per type of MAA during Regulation No. 2309/93

Figure 5 gives an overview of the arguments used for the acceptation of uncontrolled trials as basis for SMAs 2309/93 (*figure 5a*) and AECs 2309/93 (*figure 5b*). For the twelve SMAs under Regulation No. 2309/93, no (satisfactory) treatment was used as an argument in five cases (42%) whereas this was mentioned in three of the eleven AECs 2309/93 (27%). No argument was given in three of the SMAs 2309/93 (25%) and five of the AECs 2309/93 (45%) (*Annex IV*).

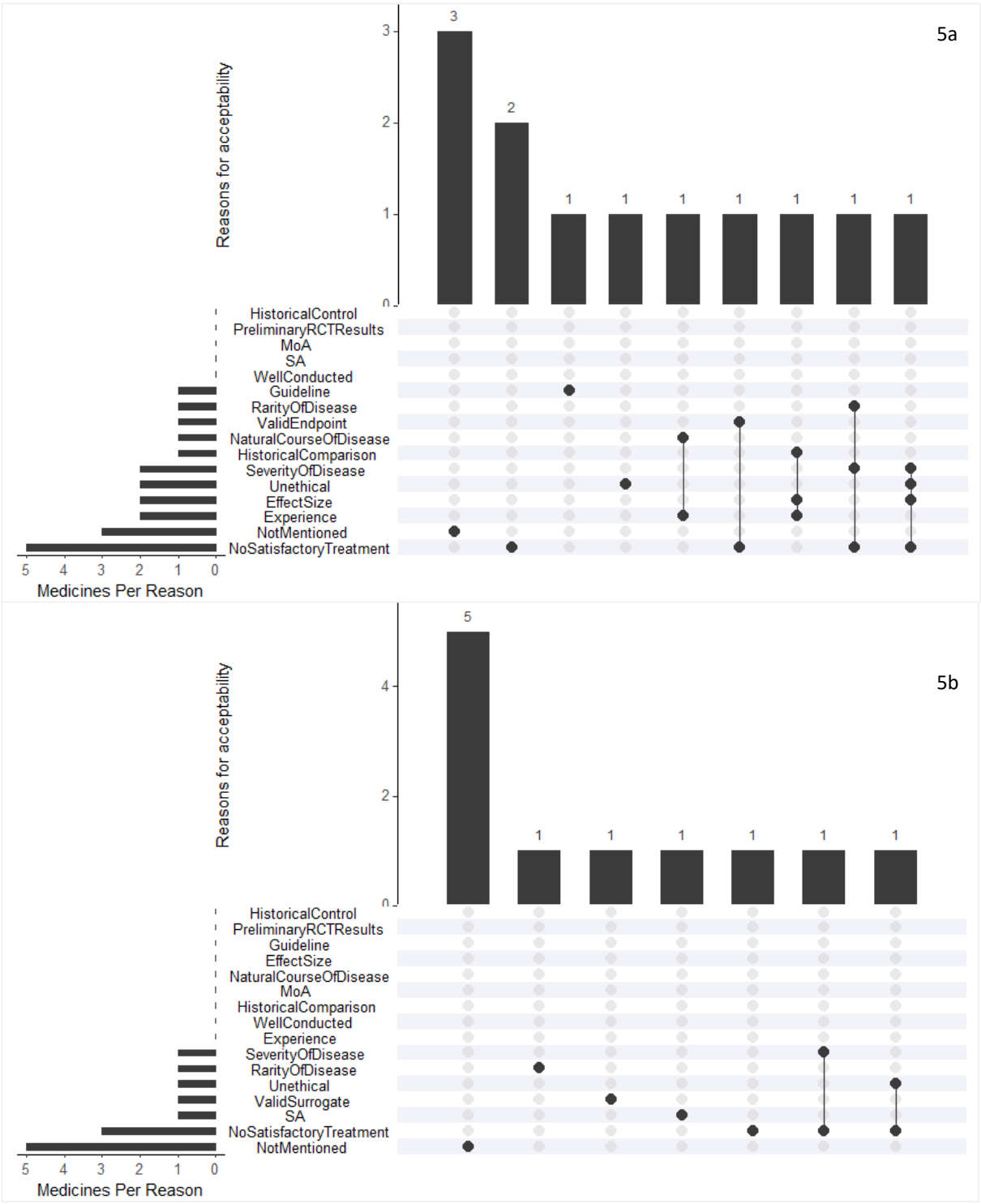
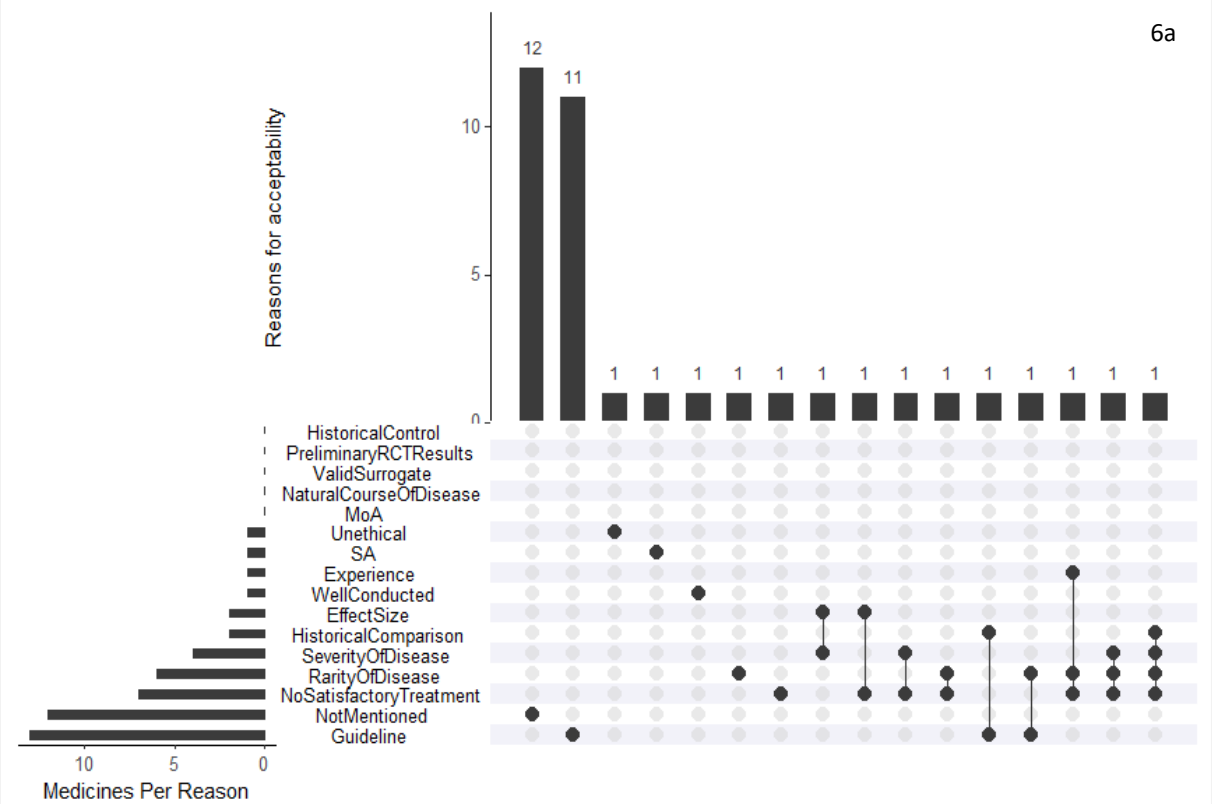
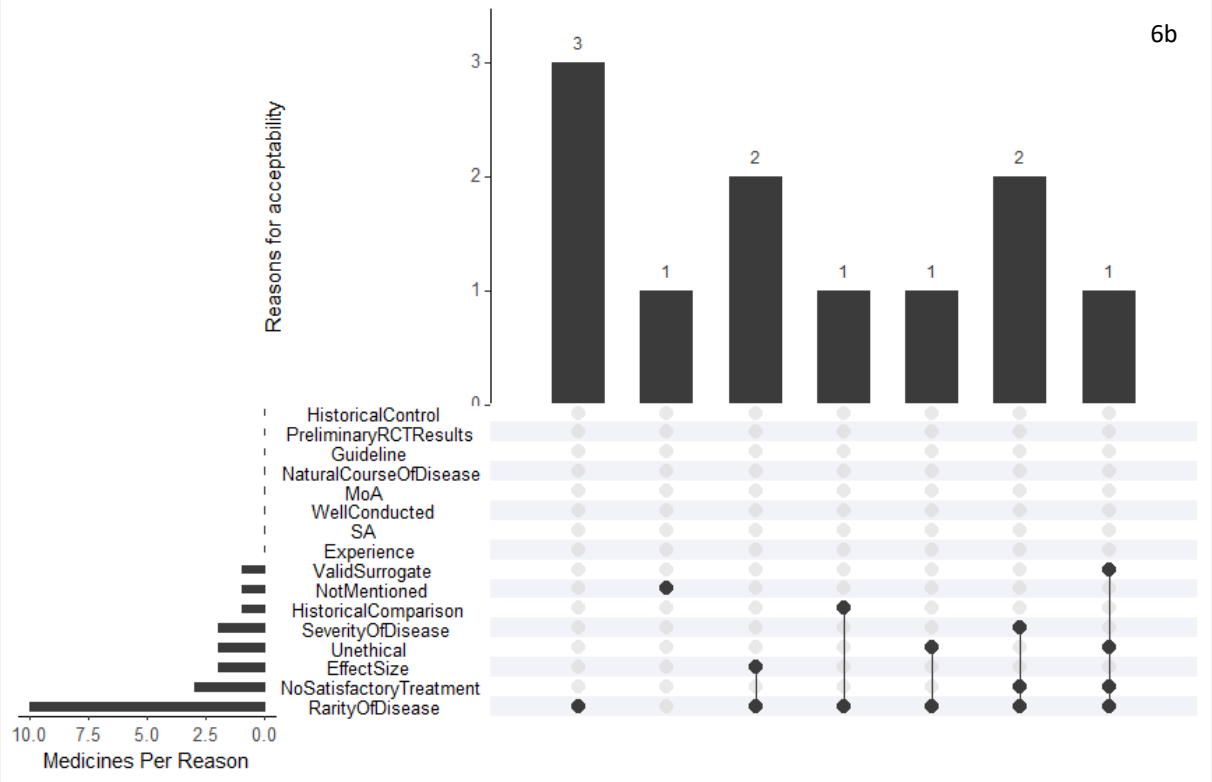


Figure 5. Arguments for the acceptation of uncontrolled pivotal study designs for MA approval under Regulation No. 2309/93. On the left side next to the mentioned categories, horizontal bars show how often each argument is mentioned in total. The vertical bars above the different dots show how often certain combinations occur. These vertical bars are from left to right first ordered by degree and then by frequency. Figure 5a shows the arguments for SMA 2309/93 and figure 5b for AEC 2309/93. MoA = mechanism of Action, SA = scientific advice.

3.3.2 Arguments per type of MAA during Regulation No. 726/2004

Figure 6 gives an overview of the arguments used for the acceptation of uncontrolled trials as basis for SMAs 726/2004 (*figure 6a*), AECs 726/2004 (*figure 6b*) and CMAs (*figure 6c*).





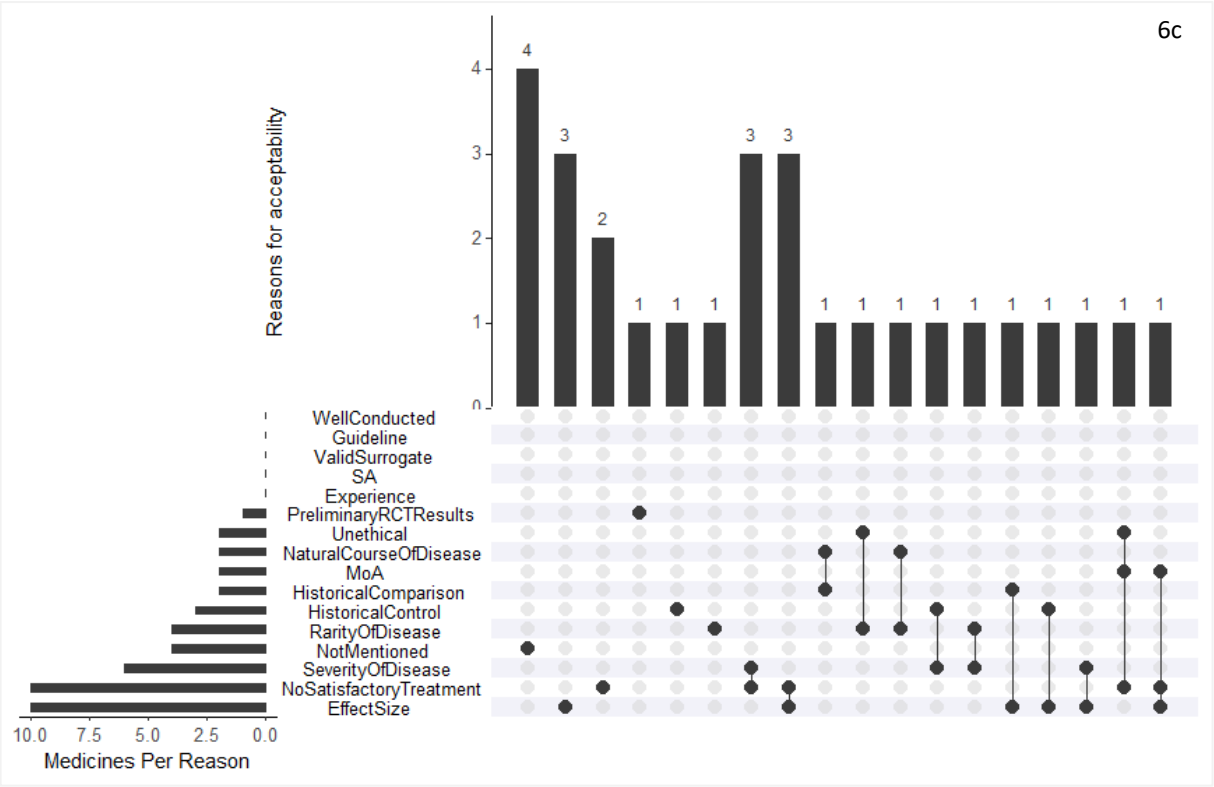


Figure 6. Arguments for the acceptation of MA approval based on uncontrolled pivotal study designs for each type of MAA under Regulation No. 726/2004. On the left side next to the mentioned categories, horizontal bars show how often each argument is mentioned in total. The vertical bars above the different dots show how often certain combinations occur. These vertical bars are from left to right first ordered by degree and then by frequency. Figure 6a, 6b and 6c show the arguments for SMAs 726/2004, AECs 726/2004 and CMAs respectively.

The four most frequently used arguments for accepting an uncontrolled trial as the basis for MA approval in relative and absolute numbers were the guideline for SMAs 726/2004, the rarity of disease for AECs 726/2004 and the effect size and no (satisfactory) treatment for CMAs. Of the 37 SMAs 726/2004, thirteen (35%) MA approvals referred to the guideline as an argument, whereas this argument was not used at all in AECs 726/2004 and CMAs (*Annex IV*). An example is the MAA for NovoEight where the disease-specific guideline was used as an argument: "In general, the studies were conducted in accordance with the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products." The rarity of disease was used as an argument in all of the eleven AECs 726/2004 except one (91%) and only in six of the SMAs (16%) and four of the 28 CMAs (14%). Effect size and no (satisfactory) treatment were both mentioned in ten of the CMAs (36%) (*Annex IV*). A fifth argument which was commonly used for the acceptation of MA approval based on uncontrolled trials was the severity of the disease. This argument was always used in combination with other arguments and was used in four SMAs 726/2004 (11%), two AECs 726/2004 (18%) and six CMAs (21%) (*Figure 6c* and *Annex IV).* An example where it was clearly used with other arguments was in the EPAR of Rydapt: 'Considering that these are rare life-threatening conditions with large unmet medical need, the lack of a randomized controlled trial was considered acceptable.'

Two arguments that were mentioned in all types of MAAs under Regulation No. 726/2004 but were uncommon were the arguments historical comparison and unethical to perform an RCT (*figure 6)*. In addition, eight arguments were only used in one type of MAA under Regulation No. 726/2004. Below, some of these arguments are contextualised by citations from the EPARs.

Clinical experience from prior studies as an argument for the acceptation of MA approval based on uncontrolled trials was only used for one of the 37 SMAs 726/2004 (3%). For two SMAs 726/2004 (5%),

the arguments mentioned were limited to a general comment about the given scientific advice. In the EPAR of Iclusig this was described as follows: "The limitations of single arm open labelled studies are known. In this case the criteria, when a single arm study might be acceptable, have been previously discussed in the CHMP scientific advice given to the applicant." In two other SMAs 726/2004 there was only mentioned that the study was well-conducted which made the use of an uncontrolled trial for MA approval acceptable (5%) (*Annex IV)*. In the EPAR of Odomzo there was mentioned that: "The CHMP expressed concern over the design of the BOLT study, where there was no control arm. The use of placebo or best investigator's choice as control arm would have been preferred. Nevertheless, the CHMP accepted that robust efficacy and safety data could still be derived from this study to support the applied indication as there were no critical issues raised with the conduct of study as such."

A valid surrogate was only used as an argument for one of the eleven AECs 726/2004 (9%). This was for Metreleptin which is used as adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients. The argument in the EPAR of Metreleptin was as follows: "In addition, the studies' efficacy endpoints are objective measurements, including HbA1c, triglycerides and plasma glucose levels, and thus treatment effects can be appropriately evaluated with a single-arm (baseline-controlled, within patient) design."

The MoA and the historical control were two arguments which were both only used in two of the 28 CMAs (7%) (*Annex IV*). The preliminary RCT results of a supportive study were only used as an argument in one CMA (4%). In the EPAR of Votubia, preliminary RCT results were used as an argument for the acceptation of MA approval based on an uncontrolled trial as follows: "The CHMP acknowledged the limitations of the phase II study (C2485) and the inherent challenges of determining the relationship between volume or size reduction of SEGA and treatment with Everolimus due to the lack of a control arm. Preliminary, high level results of the ongoing placebo controlled phase III trial (M2301) were submitted. The preliminary data supported the data from the phase II trial." Finally, the natural course of the disease was mentioned as an argument in one of the CMAs (4%) (*Annex IV*). This became very clear from the EPAR of Erivedge: "Despite the non-randomised design of the pivotal trial, the antitumor activity in terms of tumour shrinkage (ORR) observed in the pivotal trial can reasonably be attributed to vismodegib in view of the natural history of the disease, without the need for a parallel control."

There were also many MA approvals were no argument for the acceptability of uncontrolled trials was used. Of the 37 SMAs 726/2004, twelve didn't include an argument (32%). For the CMAs and the AECs 726/2004 this was only the case for four CMAs (14%) and one AEC (9%) (*Annex IV)*. By analysing basic and study-related characteristics belonging to these twelve SMAs, three SMAs included an historical control and for three other SMAs the active substance was known (KAS). Of the other six SMAs, two were for coagulation defects and four for malignant neoplasms.

As described by the basic characteristics, the therapeutic area of MA approvals under Regulation 726/2004 clearly differed per type of MAA. Therefore, we visualised the arguments used in *Annex V figure s2 f*or the most common therapeutic areas per type of MAA. Under SMAs 726/2004, we saw that for treatment of coagulation defects, the guideline was mentioned most frequently as an argument (*figure s2a*), namely in nine of the eleven coagulation defects (82%). The other four SMAs 726/2004 where the guideline was mentioned as an argument were for immunodeficiencies. For the six AECs 726/2004 for metabolic disorders, all AECs used the argument rarity of disease (100%). For the twenty CMAs for malignant neoplasms, no (satisfactory) treatment and effect size were both used as an argument in eight MA approvals (40%). Also by looking at the therapeutic area overall and omitting the type of MAA, we found that for coagulation defects, metabolic disorders and malignant neoplasms, the same arguments were still used most frequently.

3.3.3. Differences in arguments between Regulation No. 2309/93 and No. 726/2004

No (satisfactory) treatment was the most frequently used argument for the acceptation of uncontrolled trials as a basis for SMAs 2309/93, whereas this was the disease-specific guideline for SMAs under Regulation No. 726/2004. While for the whole study cohort consisting of 99 medicines no (satisfactory) treatment was mentioned 28 times in total (28%), it was only used six times as an individual argument (6%) (*Annex IV*). When looking at combinations of arguments in general, we saw that only for seven of the 23 MA approvals under Regulation No. 2309/93 more than one argument was used (30%) (*Figure 5*). This were 33 of the 76 MA approvals under Regulation No. 726/2004 (43%) (*Figure 6*).

Besides no (satisfactory) treatment, there was frequently no argument used under Regulation No. 2309/93. In eight of the MA approvals under Regulation No. 2309/93 no argument was given (35%). Of the MA approvals under Regulation No. 726/2004, thirteen MA approvals didn't include an argument for the acceptability of uncontrolled trials for MA approval (17%). So in absolute numbers there was an increase in the number of MA approvals in which no arguments were given, whereas there was a twofold decrease in relative numbers.

3.4 Approach 2 - Associations between characteristics & type of MAA (Regulation No. 726/2004)

Table 2 gives insight in the associations between the type of MAA and treatment-, disease- and study related characteristics for MA approvals under Regulation No. 726/2004. *Table 3* shows the association between the type of MAA and the efficacy and safety population. Depending on the characteristic, data are shown on product level (n= 99) or indication level (n=130). The characteristics and their distribution over time are visualised in bar plots in *Annex VI, figure S3* (characteristics on indication level) and *figure S4* (characteristics on product level).

*Table 2. The risk ratio (RR) and 95% confidence intervals (CI) for characteristics on product level and indication level. This risk ratio shows the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. The unexposed group are the SMAs and are used as a control group. The exposed group are the AECs 726/2004 and CMAs. Calculation is based on Altman, 1991.[31] When the RR is > 1, the characteristic is more likely to be present in the AECs or CMAs. The numbers in bold are significant. *The total number of products/ indications is lower because information about the characteristic in question is unknown. ** With orphan designation we mean whether the MAs got an orphan designation at approval. This orphan designation is introduced by the EMA since 16-12-1999.*

Characteristics	n	%	Risk ratio	95% CI
Treatment-related outcomes				
No (satisfactory) treatment	**Indication level**			
Standard 726/2004	19/53	36%	Ref.	
Exceptional 726/2004	12/13	92%	**2.57**	(1.74-3.81)
Conditional	28/31	90%	**2.52**	(1.73-3.68)
New active substance (NAS)	**Product level**			
Standard 726/2004	27/37	73%	Ref.	
Exceptional 726/2004	10/11	91%	1.25	(0.95-1.63)
Conditional	27/28	96%	**1.32**	(1.07-1.63)
Disease-related outcomes				
Medicines for >2 line of treatment	**Indication level**			
Standard 726/2004	5/53	9,4%	Ref.	
Exceptional 726/2004	4/13	31%	**3.26**	(1.10-10.47)
Conditional	8/31	26%	2.74	(0.98-7.63)
Very rare diseases (≤ 9-100.000)	**Indication level**			
Standard 726/2004	34/47*	72%	Ref.	
Exceptional 726/2004	7/12*	58%	0.81	(0.48-1.34)
Conditional	10/18*	56%	0.77	(0.49-1.20)
Orphan designation**	**Product level**			
Standard 726/2004	16/37	43%	Ref.	
Exceptional 726/2004	9/11	82%	**1.89**	(1.19-3.00)
Conditional	18/28	64%	1.49	(0.94-2.36)
Study-related outcomes				
Use of historical control	**Indication level**			
Standard 726/2004	8/53	15%	Ref.	
Exceptional 726/2004	3/13	23%	1.53	(0.47-4.98)
Conditional	9/31	29%	1.92	(0.83-4.47)
Use of controlled supportive study design	**Indication level**			
Standard 726/2004	2/53	4%	Ref.	
Exceptional 726/2004	1/13	8%	2.04	(0.20-20.80)
Conditional	5/31	16%	4.27	(0.88-20.73)
Scientific advice or protocol assistance	**Product level**			
Standard 726/2004	23/30*	77%	Ref.	
Exceptional 726/2004	7/8*	88%	1.14	(0.82-1.58)
Conditional	24/27*	89%	1.16	(0.91-1.47)

Table 3. The median, quartile 1 (Q1), quartile 3 (Q3), the interquartile ranges (IQR) and p-values for the efficacy and safety populations per type of MAA. The p-values are calculated by using the Mann-Whitney U test.

Number of patients per type of MAA	Median	Q1	Q3	IQR	p-value (≤ 0.05)
Efficacy population					
SMA 726/2004	46	20	97	77	Ref.
AEC 726/2004	29	13	66	53	0.12
CMA	94	52	117	65	**0.02**
Safety population					
SMA 726/2004	137	89	238	149	Ref.
AEC 726/2004	113	54	459	405	0.50
CMA	295	70	504	434	**0.01**

The most common outcomes from the first approach were the guideline, no (satisfactory) treatment, severity of disease, effect size and rarity of disease. For all these arguments except the guideline and the effect size, we studied related characteristics with our second approach.

For no (satisfactory) treatment we looked at the available treatments for the approved initial indications in general, and found for AECs 726/2004 versus SMAs 726/2004 an RR of 2.57 (95% CI of 1.74-3.81). For CMAs versus SMAs 726/2004 we found an almost similar RR of 2.52 (95% CI of 1.73-3.68) (*table 2*). Thus it is more likely that there is no (satisfactory) treatment for MA approvals that got a AEC or CMA. Besides no (satisfactory) treatment, we studied the line of treatment which is related to the severity of disease (*table 2).* We found that AECs 726/2004 and CMAs were more frequently used for medicines that were for a third or higher line of treatment, resulting in positive RRs of 3.26 (95% CI of 1.10-10.47) and 2.74 (95% CI of 0.98-7.63) respectively.

Characteristics related to the rarity of disease included the orphan designation, the prevalence of disease and the efficacy and safety population. For the orphan designation we found a positive RR of 1.89 (95% CI of 1.19-3.00) and 1.49 (95% CI of 0.94-2.36) for AEC 726/2004 and CMAs versus SMAs 726/2004 respectively (*table 2*). For the prevalence of the disease, we didn't find a positive RR. Looking at rare vs. very rare diseases, the RR for AECs 726/2004 was 0.81 (0.49-1.34) and for CMAs 0.77 (0.49-1.21) (*table 2*). Of both AECs 726/2004 and SMAs 726/2004, more than 85% of the MA approvals were at least for a rare disease (1-5:10.000) and 40% even for diseases with a prevalence of ≤ 9:100.000 (*Annex III, figure s2*). Also for the efficacy and safety population, we compared both the AECs 726/2004 and CMAs with the SMAs 726/2004 by calculating the median, interquartile range (IQR) and p-values (*table 3)* and found that the efficacy population and safety population were significant smaller in SMAs 726/2004 compared with CMAs (*p=0,02* and *p=0,01*). For AECs 726/2004 compared with SMAs 726/2004, we didn't find significance differences for the efficacy population (*p=0,12*) and the safety population (*p=0,50*) (*table 3).*

Less common outcomes from the first approach were scientific advice, historical control, preliminary RCT results and clinical experience. By looking at whether scientific advice or protocol assistance was given in AECs 726/2004 and CMAs compared with SMAs 726/2004, a small but positive RR of 1.14 (0.82-1.58) and 1.16 (0.91-1.47) were found respectively. The use of a historical control for AECs 726/2004 and CMAs gave a small positive RR of 1.53 (95% CI of 0.47-4.98) and 1.92 (95% CI of 0.83-4.47) as well. The RR for AECs 726/2004 and CMAs for the use of a controlled study design were 2.04 (0.20-20.80) and 4.27 (0.88-20.73) respectively. A final characteristic related to clinical experience was the active substance status. By studying the amount of MA approvals with new active substances, AECs 726/2004 gave an RR of 1.25 (95% CI of 0.95-1.62) and CMAs an RR of 1.32 (95% CI of 1.07-1.63) by comparison with SMAs 726/2004.

3.5 Discussion on comprehensiveness and SOBs at time of MAA

In some EPARs it was clearly stated that comprehensive evidence couldn't be collected because of the lack of controlled data. An example form the EPAR of Crysvita: "Since no control group without active treatment was included, a comparison of such (paediatric) open-label study results with external historical controls on conventional therapy thus did not allow a fully comprehensive assessment of efficacy." However, besides the uncontrolled study design, also other factors could cause uncertainties at time of approval, influencing the comprehensiveness of data and thus the type of MAA. An example from the EPAR of Erivedge: "with respect to the limited efficacy and safety data, further clinical studies are warranted to provide comprehensive data on the benefit-risk balance." In 87 of the 99 MA approvals there were uncertainties for the PK/ PD, efficacy or safety mentioned (88%). In addition to the uncontrolled study design, the most common causes of uncertainties for efficacy and safety were a small sample size and/ or limited follow-up. A small sample size was mentioned in 16 MA approvals (16%), a limited follow-up in 17 MA approvals (17%) and both together in 29 MA approvals (29%) (*Annex VII, table S5)*. How frequently each uncertainty was mentioned per type of MAA is shown in the Annex as well. Other factors that could cause uncertainties but were less common in our study cohort were an historical control, the in- and exclusion criteria for patients in the trials and the representation of the patient population. When sample size and short follow-up were not mentioned as causes of uncertainties, still in 25 MA approvals one or more other causes of uncertainties were mentioned (25%). In addition, there were twelve MA approvals where no uncertainties were present at time of approval meaning that also the uncontrolled study design did not cause uncertainties in these MA approvals. These twelve MA approvals included four SMAs 2309/93 and nine SMAs 726/2004.

When besides the uncontrolled study design more aspects led to uncertainties, the CHMP could also decide to restrict the indication to a certain line of treatment or a specific patient group or age group. In this way, it was possible to make a selection in the evidence that would be used for the MA approval. For 23 of the 53 SMA 726/2004 indications, the indication was restricted (43%). For AEC 726/2004 indications, nine of the thirteen were restricted (69%). Of the 31 CMA indications, sixteen were restricted (52%). The uncertainties at MA approval together with a possible restriction of the indication made it possible for the CHMP to access the benefit risk balance for the final indication and to grant a certain type of MAA.

Subsequently, this type of MAA tells us something about the comprehensiveness of data. As approval based on non-comprehensive evidence goes along with certain requirements, we looked at these requirements and how these were met by the AEC and CMA approvals of our study cohort. For five of the eleven AECs 2309/93s, no reasons were given why they met the requirements for granting an AEC, whereas for all eleven AECs 726/2004 it became clear that no comprehensive data could be collected due to the rarity of disease (100%). A clear example was given in the EPAR of Atriance: "It is acknowledged that the indication for which the medicine is intended, is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive data on the clinical efficacy and safety of the medicine." In two AECs 726/2004, both rarity of disease and medical ethics were mentioned as a reason (18%). In addition, there were no AECs 726/2004 and only one AEC 2309/03 in the study cohort where because of the current state of scientific knowledge no comprehensive data could be collected.

For all 28 CMAs, MA approval based on non-comprehensive evidence was accepted because all MA approvals except one were for life threatening diseases (96%) and because an unmet medical need was fulfilled. For fifteen of the CMAs (54%), the unmet medical need was fulfilled because there was no (satisfactory) treatment and in thirteen CMAs (46%) the unmet medical need was addressed by a major therapeutic advantage. Another requirement before CMAs could be granted was that it should

be likely that the applicant could provide comprehensive evidence in the future with the use of SOBs. By looking at the planned SOBs at time of approval, for 15 of the CMAs (54%) at least one RCT was needed to provide comprehensive evidence. This was for example mentioned in the EPAR of Arzerra: "The applicant will provide comprehensive clinical data from ongoing Phase III randomized, controlled clinical studies in earlier disease setting." However, in thirteen of the CMAs (46%) there was mentioned that uncontrolled trials were enough to collect comprehensive evidence. In the EPAR of Zynteglo was for example stated that the applicant would be able to provide comprehensive data relevant to the initial indication post initial approval from the following studies: HGB-207, HGB-212 and LTF-303. These studies were all uncontrolled, making uncontrolled studies valid to use. For nine of the thirteen CMAs for which uncontrolled SOBs were planned, an unmet medical need was fulfilled since there was no other (satisfactory) treatment and nine of the thirteen CMAs (which partly overlapped with the CMAs where there was no (satisfactory) treatment) were for malignant neoplasms.

Notwithstanding that granting a CMA or AEC already means that non-comprehensive evidence was collected, we finally looked at whether an opinion about the (non-)comprehensiveness of data was explicitly given in all types of MAA and under both regulations. Under Regulation No. 2309/93, in five of the eleven AECs (45%) nothing about comprehensiveness was mentioned. Under Regulation No. 726/2004, three of the eleven AECs 726/2004 (27%) and three of the 28 CMAs (11%) didn't give an argument why approval based on non-comprehensive evidence was accepted for MA approval (*Annex VII, table S5)*. For SMAs under Regulation No. 2309/93 and No. 726/2004, ten of the twelve SMAs (83%) and 29 of the 37 SMAs (78%) didn't give an opinion about comprehensiveness respectively. So whether an opinion was given about the comprehensiveness of data increased somewhat over time and differed per type of MAA. Also whether consensus was reached was more clearly described under Regulation No. 726/2004 than Regulation No. 2309/93 (*Annex VII, table S5*). Finally, we found that in general there was a clear increase in the extensiveness of the EPARs over time going from a total of approximately twenty pages in 1999 (Beromun, Paxene) to 150 pages in 2020 (Libmeldy).

4. Discussion

4.1 Summary of the findings

We aimed to get insight in the relation between the use of uncontrolled trial designs and the type of European Marketing Authorisation Applications (MAAs) taking into account the different regulations over time. This is of importance since for all types of MAAs, the use of other designs than controlled trials should be justified.[5,17] One of the four most important findings which was in line with our expectations was that uncontrolled trials for MA approval were more frequently accepted for AECs and CMAs than for SMAs and that malignant neoplasms represented the biggest treatment group. Secondly, for providing non-comprehensive evidence, uncontrolled trials for AEC approvals were mostly accepted because the disease was rare. For CMAs approvals, the uncontrolled trials were mostly accepted when there was no satisfactory treatment, the effect size was outstanding or the disease was severe. This was usually in line with the results of approach 2 but also showed some discrepancies when placing the data into context. Thirdly, for providing comprehensive evidence, SMA 726/2004 approvals based on uncontrolled trials were mostly accepted when this was stated in the disease specific guideline. In addition, in almost one-third of the SMAs 726/2004, no arguments for the approval based on uncontrolled trials were given. Fourth of all, we found that the arguments for the use of uncontrolled trials became more extensive by comparing MA approvals under Regulation No. 2309/93 and 726/2004.

4.2 Comparison with other studies and relevance

Our first finding that uncontrolled trials were in relative numbers more frequently used for AECs and CMAs than for SMAs and that malignant neoplasms represented the biggest group is confirmed by several studies. In the accelerated approval pathway from the FDA where only non-comprehensive evidence is provided, also two-third of the MA approvals were based on study designs other than RCTs.[14] Another study looking at the use of uncontrolled trials for malignant neoplasms found similar results related to the type of MAA. They found that of the 22 MA approvals based on uncontrolled trials, six were SMAs (27%) and sixteen were CMAs (73%).[20] Another study which looked at the use of uncontrolled studies over different therapeutic areas, concluded that the uncontrolled trials were particularly used in solid and haematological malignancies.[12] Also the MA approvals in general and the CMAs with uncontrolled SOBs in our study cohort were most often for malignant neoplasms. This all together suggests that the use of uncontrolled trials to provide (non-)comprehensive evidence was most frequently accepted in malignant neoplasms. This could be further explained by the guideline for malignant neoplasms where is mentioned that there are situations where other designs than RCTs may need to be considered.[33]

Our second finding was that rarity of disease, no satisfactory treatment, effect size and severity of disease were in relative and absolute numbers the main arguments why uncontrolled trials could be acceptable to grant a CMA and AEC and thus provide non-comprehensive data. In addition, the calculated RR for at least one of the characteristics related the these arguments showed a clear positive association with AECs 726/2004 and/or CMAs. Only for rarity of disease, the associations between the type of MAA and the prevalence of disease and the efficacy and safety population showed some discrepancies with the arguments used. First, we found that there were many indications in the SMA 726/2004 group for very rare diseases, whereas this was not frequently mentioned as an argument for the acceptability of MA approval based on uncontrolled trials. This could be explained by the fact that all coagulation defects are very rare diseases.[28] Since for these MA approvals, the guideline was already used as an argument to accept MA approval based on uncontrolled trials, it wasn't necessary to use the rarity as an argument as well. Secondly, CMA approvals showed a lower percentage of rare diseases than SMAs and AECs which could be explained by the indications as well. Of the CMAs, six initial

indications were for patients with certain mutations in non-small-cell lung carcinoma (NSCLC). NSCLC is not a rare disease and whether the percentages of these mutations (ranging from a ROS-1 positive mutation with an occurrence of 1-2% and an Epidermal Growth Factor Receptor mutation of 10%) make it to a rare disease is unknown.[28] Thirdly, the efficacy and safety patient population were much smaller in SMAs 726/2004 compared with AECs 726/2004 and CMAs which was something we wouldn't expect from the arguments used. This could again be explained by the big group of Ma approvals for coagulation defects in the SMAs 726/2004. These MA approvals namely often include the surgery indication, which according to the disease-specific guideline only needs to include 5 patients.[19]

Whereas we saw for AECs 726/2004 and CMAs most of the time an overlap between results from approach 1 and 2, factors related to the comprehensiveness of data were only partly in line with the arguments used for the acceptation of uncontrolled trials in providing non-comprehensive evidence at MA approval. For all eleven AECs 726/2004, no comprehensive evidence could be collected due to the rarity of disease (100%) whereas this was used as an argument in 91% of the MA approvals. Of the CMAs in the study cohort, 96% were for life threatening diseases, whereas severity of disease was only used as an argument in one-fifth of the CMAs. In addition, the unmet medical need was fulfilled because there was no (satisfactory) treatment (54%) or because there was a major therapeutic advantage over established treatment options (46%). No (satisfactory) treatment and effect size were both used as an argument in 36% of the MA approvals.

At time of writing, for both the FDA and the EMA, no research on the arguments for the acceptability of uncontrolled trials for providing non-comprehensive evidence was done. However, this is of importance since our results showed that for both AECs and CMAs, reasons for providing non-comprehensive evidence doesn't necessarily need to be in line with the arguments used for the acceptation of uncontrolled trials. Moreover, for AECs and CMAs nowhere is stated that the use of uncontrolled trials as a basis for MA approval doesn't need to be justified.[8,9,11,17]

Third of all, we can conclude that for most SMAs 726/2004, the disease specific guideline was used as an argument for the acceptability of uncontrolled trials for MA approval which included MA approvals for immunodeficiencies or coagulation defects. In addition, almost one-third of the SMAs 726/2004 didn't include an argument. Further analysis of the characteristics of the SMAs where no arguments were used led to some possible explanations of the acceptance of uncontrolled trials. For the two MA approvals that were for coagulation defects, the disease specific guideline could be used as an argument. Also for the four MA approvals for malignant neoplasms, the guideline could explain the acceptability of the uncontrolled trials for MA approval. However, there is also mentioned in the guideline that resorting to non-randomized trials should be duly justified (e.g. predictable course of the disease in combination with a large treatment effect on endpoints such as ORR and duration of response reasonably likely to translate in true clinical benefit, and acceptable toxicity).[33] In three other MA approvals where an historical control was done, this could be an argument and in the last three MA approvals the active substance was known (KAS), which made that experience could be a valid argument to accept the approval based on an uncontrolled trial.

These characteristics shows us that for regulators and people with experience about clinical trials and drug characteristics, arguments can be made up through own interpretation and reading between the lines. However, since for most SMAs not much words were explicitly spend on explaining why an uncontrolled trial was accepted for MA approval, it would be hard to find the arguments for patients and health care professionals who only read the EPAR belonging to their medicine of interest. Also, since in the Directive 2001 is stated that: 'In general, clinical trials shall be done as controlled clinical trials and if possible, randomized; any other design shall be justified.', more justification in the EPARs for the use of uncontrolled trials should be needed.[17] This was further confirmed by the study by

Hatswell *et al.* where they mentioned that given the frequency in which uncontrolled trials occur, the role of uncontrolled trials in MA approval required more formal guidance on what represents an acceptable data package.[12]

Our fourth finding that the arguments for the use of uncontrolled trials became more extensive by comparing MA approvals under Regulation No. 2309/93 and 726/2004 is of relevance since this shows a learning process over time. By comparing MA approvals under Regulation No. 2309/93 and 726/2004, the EPARs became more extensive, the MA approvals included more frequently an argument for the acceptation of MA approval based on uncontrolled trials and MA approvals included combinations of different arguments more often. It can be true that under Regulation No. 2309/93, it was not yet common to extensively describe clinical data and the arguments for the use of different study designs. It was indeed the case that after 2010 the EMA focused more on the publication of clinical data and transparency by the introduction of two policies in 2010 and 2015 focusing on the publication of clinical data and transparency of the EMA.[24,25] Such a same trend over time was found by Papathanasiou *et al.* (2016) concluding that from 2006 till 2016 scientific progress had led to an increase in both the complexity and quantity of the information present in the EPARs.[26] This could also explain why earlier benefit-risk discussions were much smaller than the benefit-risk discussion from nowadays and why they included less information about reasons for granting an AEC and whether there was consensus between the CHMP members. That people became more aware of the challenges and the opportunities by using uncontrolled trials was further confirmed by the presence of more and more studies focussing on how to improve the use of uncontrolled trials. Davi *et al.* (2020) and Ghadessi *et al.* (2020) studied for instance the use of uncontrolled trials and opportunities on how to address evidence gaps by using for instance real-world data or historical clinical trial data.[34,35]

4.3 Strengths and limitations

Our study is the first that studies the complete population of European MA approvals that were based on uncontrolled trials and that compares the use of uncontrolled trials between different types of MAAs and the two regulations. These findings can inspire other studies that evaluate regulatory decision-making to look broader than only within one specific timeframe, therapeutic area or type of MAA. Moreover, we used two approaches to answer the research question and discussed other factors related to the comprehensiveness of data to collect a comprehensive set of results. For in the future, this study can help regulators to use a more structured way of assessing MA approvals based on uncontrolled trials. This could be even taken to a broader level, because a new regulation will be set up soon that will replace Regulation No. 726/2004.[36] Since our study investigated the whole history of EMA regulatory decision making with regard to the acceptation of uncontrolled trials for MA approval, this could be relevant for uncontrolled study design related aspects in the new regulation.

However, our study had also several limitations. First of all, even while two different approaches were used and we saw overlap between the most common used arguments and associations, there was also a bit of discrepancy between some arguments and associations between treatment-, disease- and study-related characteristics and the type of MAA. In many studies historical controlled studies were for example done, while this was only used as an argument in two MA approvals. This could be explained by the fact that historical controls are often associated with many challenges and are only useful when conducted right.[34] So whereas in some cases a treatment-, disease- or study-related characteristic could be used as an argument for the acceptation of MA approval based on uncontrolled trials, it was also possible that a same characteristic was not valid as an argument in other cases. A second limitation was that all data was manually extracted making it vulnerable for mistakes. Even while most doubtful data points where discussed during meetings, there always remains some room for own interpretation when collecting arguments and data of the discussion sections. Thirdly,

notwithstanding the collection of other uncertainties at time of approval, we couldn't investigate to which extent these uncertainties influenced the comprehensiveness of data next to the limitations of the uncontrolled study design.

4.4 Future research

With our study, we focused on the MAs that were approved by the EMA based on uncontrolled trials. In addition, it would also be of relevance to study the MA based on uncontrolled trials that were refused to see when uncontrolled trials were not accepted to provide (non-)comprehensive evidence. Moreover, regulatory-decision making is much broader than the authorisation procedure of the EMA. Before medicines can actually reach the market, the MA approvals also need to be evaluated by HTA-regulators. In some studies it was shown that these Health Technology Assessment (HTA)-decision makers mainly gave negative recommendations to medicines without controlled studies.[37] Another study looked only at CMAs and concluded that in this type of MAA, there was only a small proportion of unrestricted positive recommendations as well. Nevertheless, within these CMAs the lack of controlled data was not decisive for the outcome of HTA evaluations in Europe.[38] So even while we see that all types of MAAs got and still get approved based on uncontrolled trials, it is of importance to also study whether the evidence collected with uncontrolled trials can lead to a positive HTA evaluation. This importance is further highlighted by the Regulatory Science to 2025 Strategy of the EMA, in which they want to bridge the gap from evaluation to access.[39]

4.5 Conclusions

Overall, we can conclude that compared with other study designs, uncontrolled trials were as expected more often used in AECs and CMAs than in SMAs. Secondly, whereas the arguments for the acceptability of uncontrolled trials for AECs or CMAs were mostly confirmed by the second approach, there were some discrepancies with the factors related to the comprehensiveness of data. For providing comprehensive evidence, future SMAs should mention a clear argumentation to make sure all stakeholders including patients can understand why MA approval based on an uncontrolled trial was acceptable. Finally, this 25 years learning process from the EMA in the use of uncontrolled trial designs for different types of MAA shows that improvements in the argumentation are made but still can be enhanced. These results may contribute to the establishment of the new incoming regulation and may help to give regulators a broader perspective beyond the different time frames and types of MAAs. This will finally open the doors for future research on how medicines approved based on uncontrolled trials are further evaluated by HTA organisations, bridging the gap from evaluation to access.

5. Acknowledgements

We gratefully acknowledge R. Borup for giving access to the internal EMA database. In addition, we wish to thank C.A. Herberts and P. B. van Hennik from the Medicines Evaluation Board for their helpful insights during data collection and Dr. A. Mantel-Teeuwisse from the Pharmacoepidemiology and Clinical Pharmacology division at the University of Utrecht for her critical review of the draft versions.

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Annex I - Data collection

Table S1. Basic characteristics at time of approval. These characteristics are extracted from different databases. Al data is at time of MA approval.

Basic characteristics at time of MA	Internal EMA database	Table of all human and veterinary medicines	EPARs for each medicine	EC community register	Specific section
Product name		√			Column B
Active substance		√			Column E
Legal basis	√		√		Paragraph 1.1
ATC code		√			Column I
Drug type			√		
Requested initial indication			√		Paragraph 1.1
Approved initial indication			√		Paragraph 1.1
Date of EC decision		√			Column W
Type of initial regulatory MA	√			√	

Table S2. Treatment-, disease- and study-related characteristics for studying associations between these characteristics and the type of MAA.

Study and medicines characteristics	EPARs for each medicine	Orphanet	Table of all human and veterinary medicines	SmPC	Specific section
Other available treatments	√				2.1.2 – Epidemiology or 2.1.5. – Management
Active substance			√		Column E
Line of treatment	√				2.1.5. – Management
Prevalence of disease		√			Prevalence section
Orphan medicine (16/12/'99)	√				Paragraph 1.1
Efficacy and safety population	√			√	2.4/2.5 – main studies or 2.6 Safety
Historical control	√				2.4/2.5 – main studies
Supportive study designs	√				2.5 – supportive studies
Scientific advice or protocol assistance yes/no	√				1.1 submission of the dossier

Table S3. Factors related to the comprehensiveness of data. For all included MA approvals, the evidence is extracted from the individual EPARs or Annex II

Characteristics for the contextualisation of comprehensiveness	EPARs for each medicine	Annex II	Specific section
CMA/AEC scope	√		CMA/AEC section
Unmet medical need for CMAs	√		3. Benefit-Risk Balance
Opinion about comprehensiveness at approval	√		3.7 – benefit risk assessment and discussion
Uncertainties – PK/PD, efficacy, safety	√		3.3 / 3.5 / 3.7
Consensus between CHMP members?	√		4. Recommendations
Divergent opinions of CHMP members	√		Appendix
Design of post approval SOBs/ conditions (SAT/RCT)		√	Annex IID and IIE

Annex II – E-methods

Here, we describe the way of characterisation for the efficacy and safety population, (no satisfactory) treatment, restriction of the indication and the line of treatment.

Efficacy and safety population

For the efficacy population we did choose the population from the pivotal trial which was analysed for the final approved indication. Often this was referred to as the full analysis set. This set was used for calculating the primary endpoint and thus most important for assessing the effect size. When the amount of patients who were part of the trial was updated already in the initial EPAR (so at time of approval) this number of patients was taken. When during the study, the medicine was only approved for a subset of the whole population, this number was chosen since the approval is based on the effect size calculated for that specific population. Finally, when the number of patients didn't become clear from the EPAR, the SmPC was read through to find out on which data the efficacy was based.

For the safety population, we took the number of patients where the overview of adverse events was based on and the patients included in datasets which was reviewed to as for example the 'main safety data' or 'overall safety analysis set'. This number of patients is often higher than the efficacy population, since the safety population can include patients from more studies and also from studies outside the original approval in other indications. When the number of patients was not clear from the EPAR, we checked the published SmPC published at time of approval to look which patient population was referred to in the overview of undesirable effects.

No (satisfactory) treatment

When there was an available treatment, but when out of the discussion became clear that this one was not favourable, this was referred to as no satisfactory treatment. When there were treatments, but those were not approved, I marked these as no available treatment. The difference between yes, but not satisfactory can in some cases be discussed about: some are in a grey area. An example of an indication which is categorised as indication for which no satisfactory treatment is available: 'Among patients whose disease has progressed on second-generation TKIs used either in the first- or second-line setting, chemotherapy would be the fall back standard of care. Outcomes with chemotherapy have been modest. There are no agents approved that confer substantial benefit for ALK-positive advanced NSCLC previously treated with 2 or more ALK-TKIs.' Another example for which another treatment is available: 'With IFN the response rate is lower for AP than it is for chronic phase CML although durable responses and suppression of cytogenetic clonal evolution have been reported. The median survival of patients treated with chemotherapy or IFN commonly ranges from 12 to 18 months.'

Restriction of the indication

The restriction of the initial indication can occur in different ways. We looked at: 1) age restricted changes 2) higher line of treatments 3) removal of diseases. What is important to mention is that there is only focused on indications at approval for with an uncontrolled trial is used. Some approvals also include indications for which an RCT is used. This indications are not taken into account for this characteristic. In addition, we analysed the restriction of the indication on indication level and not on product level. So for one product with two different indications at first approval it is possible that there is a restriction of indication 1 but not of indication 2.

The line of treatment

In some indications, more lines of treatments are mentioned for which the medicine can be used. In that case, the lowest line of treatment is mentioned. Adjunctive therapies and combination therapies were seen as first line. When there was mentioned 'who are not candidates for..' or ' 'intolerant',

‘refractory’, ‘inappropriate’ or ‘resistant’ to, the new product was seen as a later line of treatment. After all, this indicates that when the other treatment was possible, this was used as a first line of treatment. So the patient actually skips the one most preferably one and gets the treatment used for second line.

Annex III – Basic characteristics over time

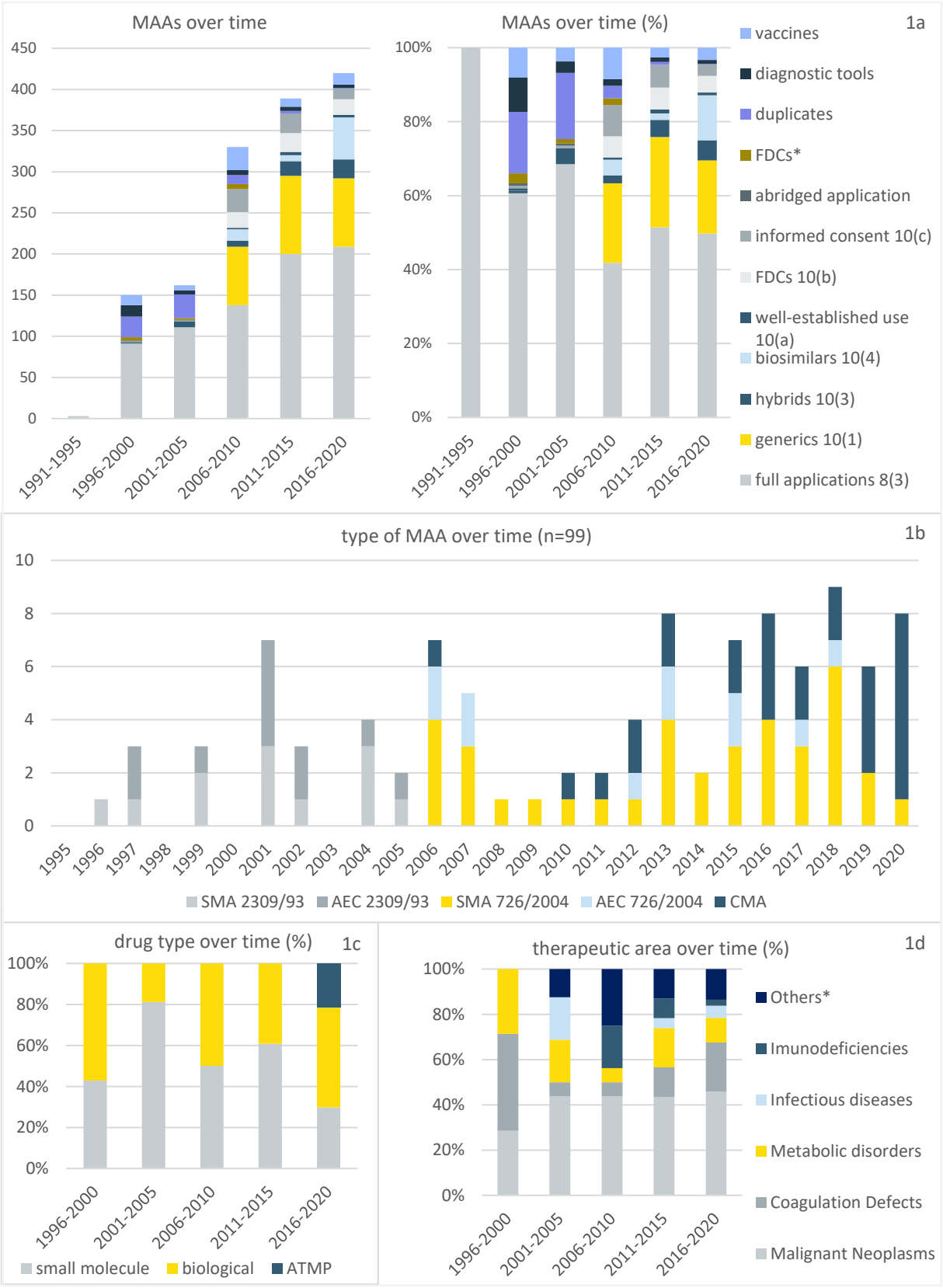


*Figure S1. Basic characteristics over time. Figure S1 a) Marketing Authorisation Applications (MAAs) over time (5-year intervals). From all full MAAs 8(3), the vaccines, duplicates and diagnostic tools are already excluded. Figure S1 b) type of MAA over time for MA approvals based on uncontrolled trials (n=99). Figure S1 c) The drug types over time. Figure S1 d) The therapeutic area over time. *Others include therapeutic areas that were very uncommon in the study cohort.*

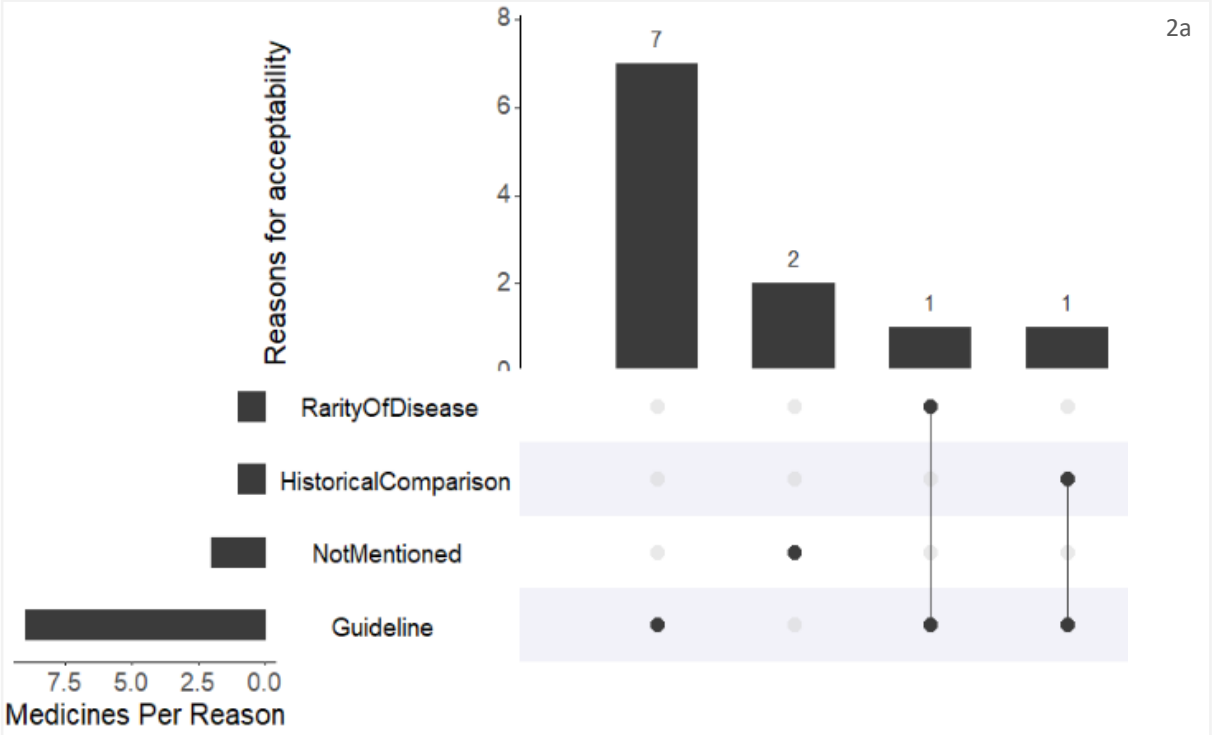
Annex IV – Arguments for acceptation of uncontrolled trials for MA approval

Table S4. The arguments to accept approval based on uncontrolled trials per type of MAA. For each type of MAA, the most mentioned category is bold. For both SMAs 2309/93 and AECs 2309/93, this was 'no satisfactory treatment' (42% and 27% respectively). For SMAs 726/2004, AECs 726/2004 and CMAs this were the guideline (35%), rarity of disease (91%) and no satisfactory treatment (36%) respectively.

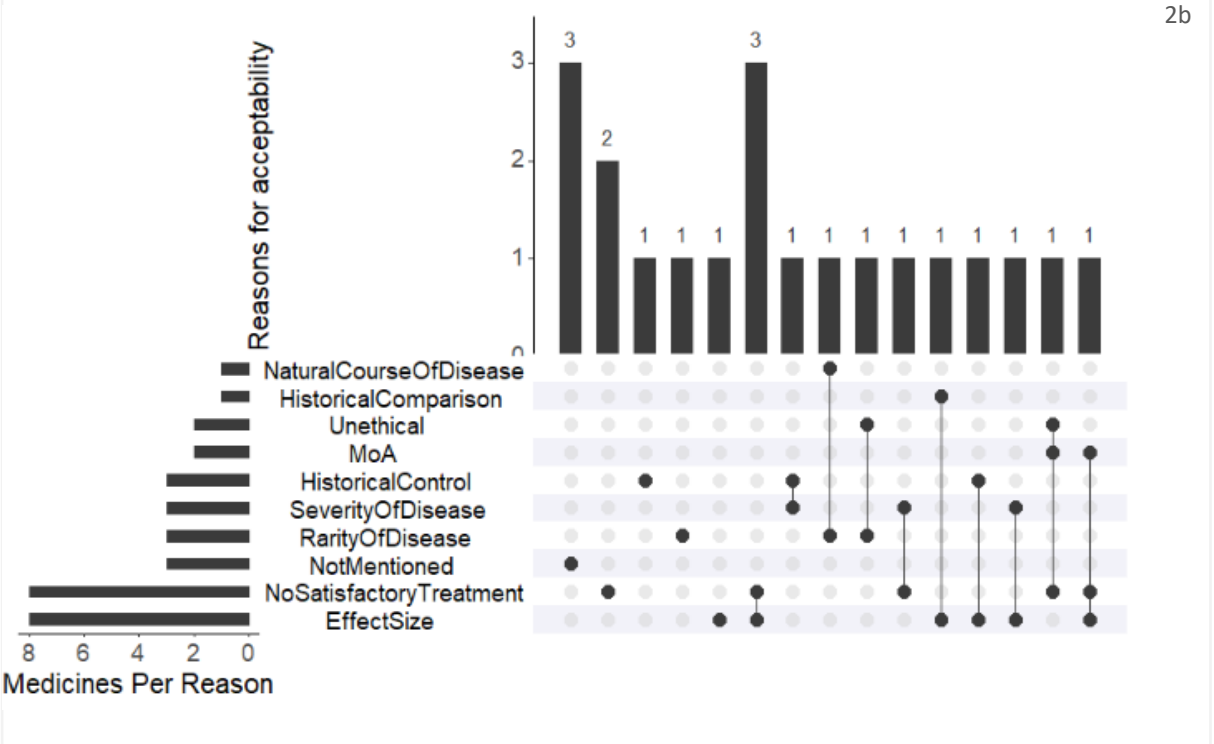
	SMA 2309/93 n=12		AEC 2309/93 N=11		SMA 726/2004 N=37		AEC 726/2004 N=11		CMA N=28		Total N=99	
Treatment-related outcomes												
No satisfactory treatment	**5**	**42%**	**3**	**27%**	7	19%	3	27%	**10**	**36%**	28	28%
Effect size	2	17%	-	-	2	5%	2	18%	10	**36%**	16	16%
Unethical	1	8%	1	9%	1	3%	2	18%	2	7%	7	7%
Valid surrogate	1	8%	1	9%	-	0%	1	9%	-	-	3	3%
Experience	2	17%	-	-	1	3%	-	-	-	-	3	3%
MoA	-	-	-	-	-	0%	-	-	2	7%	2	2%
Disease-related outcomes												
Rarity of disease	1	8%	1	9%	6	16%	**10**	**91%**	4	14%	22	22%
Severity of disease	2	17%	1	9%	4	11%	2	18%	6	21%	15	15%
Guideline	1	8%	-	-	**13**	**35%**	-	-	-	-	14	14%
Natural Course of the disease	1	8%	-	-	-	0%	-	-	2	7%	3	3%
Study-related outcomes												
Historical comparison	1	8%	-	-	2	5%	1	9%	3	11%	7	7%
Historical control	-	-	-	-	-	0%	-	-	2	7%	2	2%
Scientific Advice	-	-	1	9%	1	3%	-	-	-	-	2	2%
Preliminary RCT results	-	-	-	-	-	0%	-	-	1	4%	1	1%
Well-conducted	-	-	-	-	1	3%	-	-	-	-	1	1%
No data												
No argument mentioned	3	25%	5	45%	12	32%	1	9%	4	14%	24	24%

Annex V- Arguments for the acceptation of uncontrolled trials per therapeutic area

2a



2b



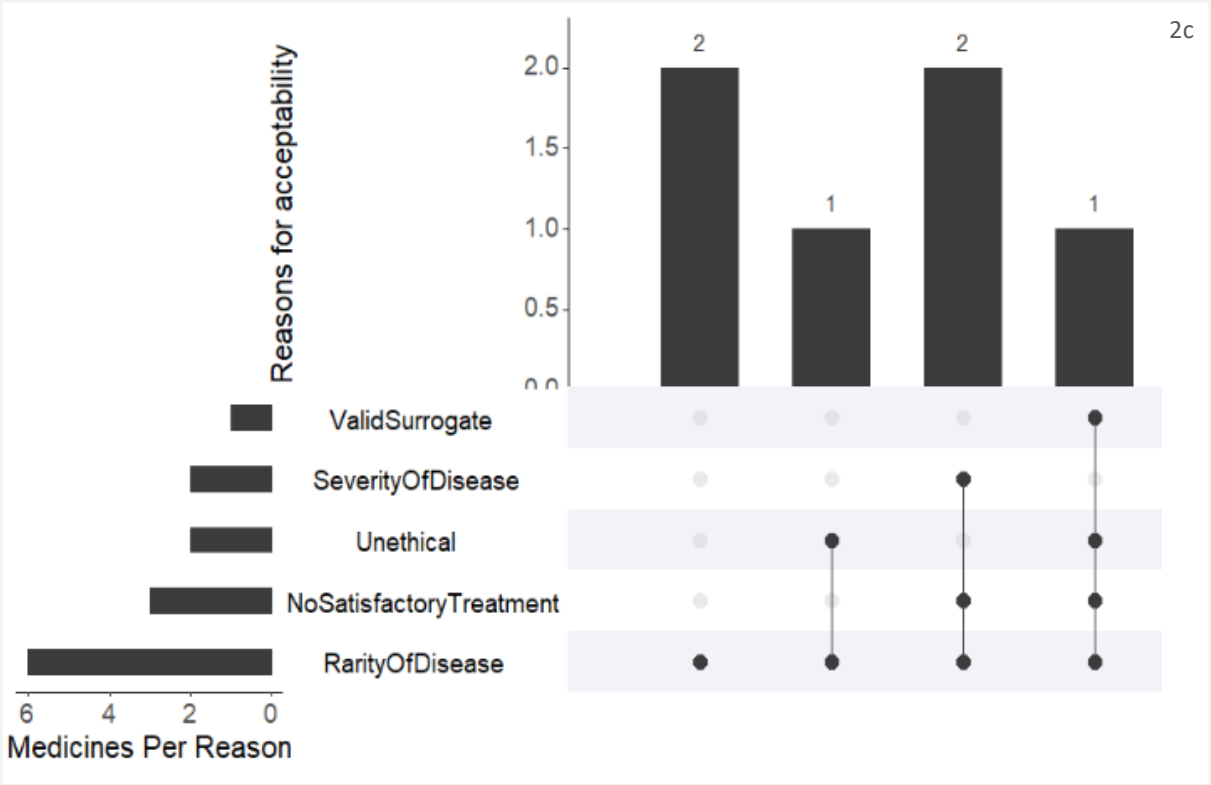


Figure S2. Arguments for the acceptability of uncontrolled trials for the five different therapeutic areas in their most common type of MAA. Figure S2a) MA applications for coagulation defects were most present in SMA 726/2004 approvals. Figure S2b) Arguments used in CMA approvals for malignant neoplasms. Figure S2c) Arguments used in AEC 726/2004 approvals for metabolic disorders.

Annex VI – Associations between characteristics & type of MAA

Figure S3. Characteristics per type of MAA on indication level (n=130). 8a) Available treatments for the indications at time of approval. 8b) Prevalence of disease. 8c) The line of treatment. 8d) The use of a historical control. 8e) The design of the supportive studies.

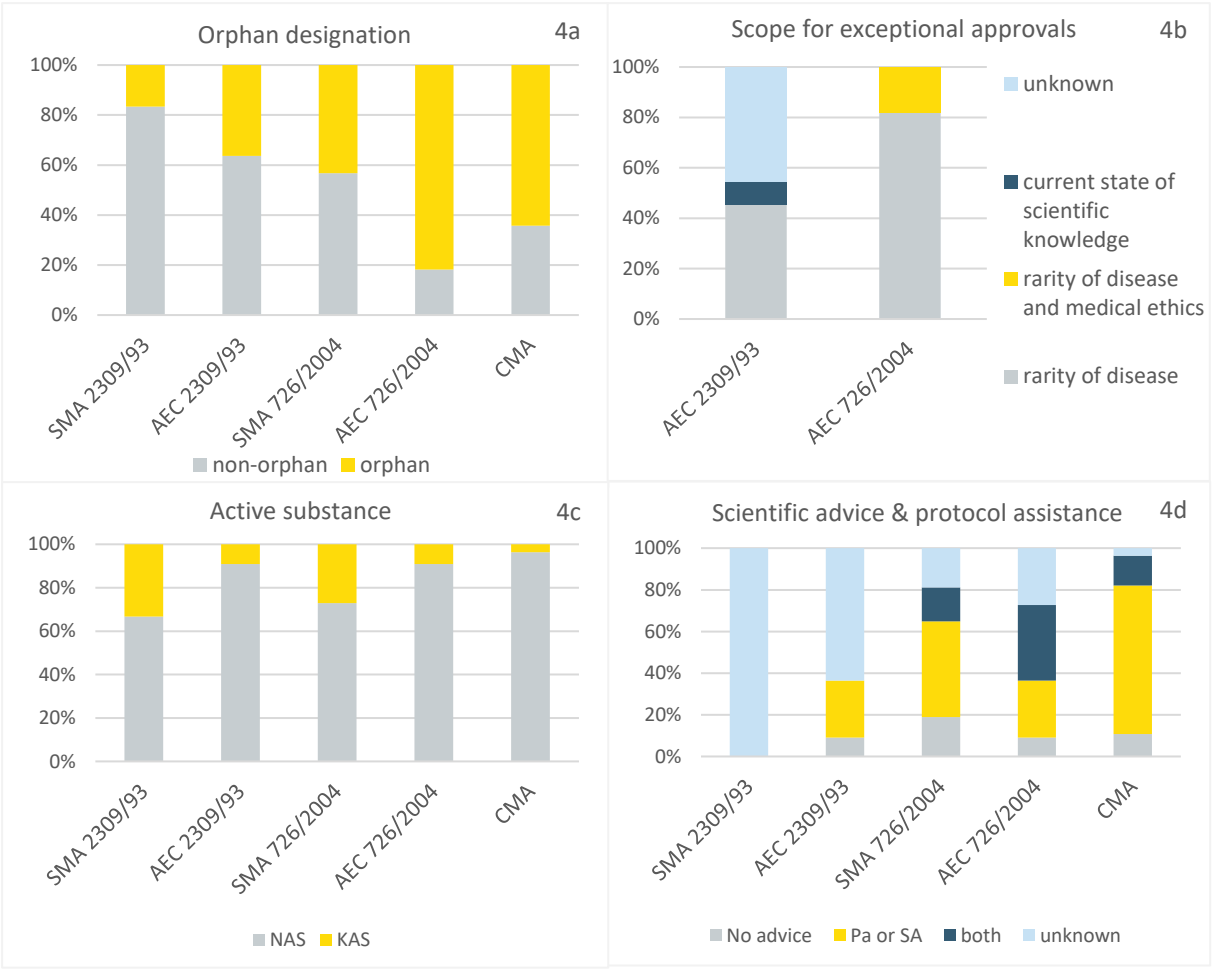


Figure S4. Characteristics per type of MAA in relative numbers on product level (n=99). 4a) Orphan designations given by the EMA at first approval. 4b) Scope for AECs 2309/93 and 726/2004. 4c) Distribution of whether the MAs were for known active substances (KAS) or new active substances (NAS). 4d) Scientific advice (SA) and protocol assistance (PA) given by the EMA.

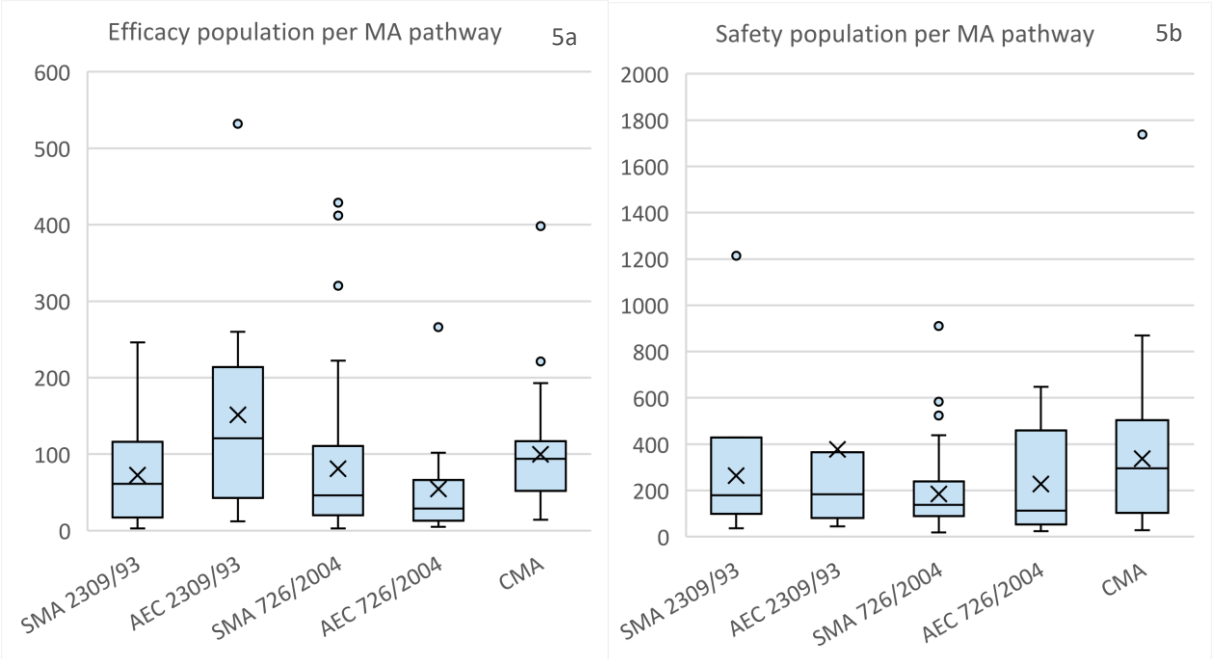


Figure S5. The patient population for efficacy (S5a) and safety (S5b). The boxplots per type of MAA display the median, the Q1 and Q3, the mean (the cross) and some outliers. S5a) The efficacy population where median (Q1,Q3) for SMA 726/2004, AEC 726/2004 and CMA are 46 (20, 97), 29 (13, 66) and 94 (52, 117) patients respectively. S5b) The safety population where median (Q1, Q3) for SMA726/2004, AEC 726/2004 and CMA are 137(89, 238), 113(54, 459) and 295(70, 504) respectively.

Annex VII Data for the discussion about comprehensiveness

Table S5. General and MAA specific characteristics that are related to the comprehensiveness of data. The AEC and CMA specific data are only shown for these type of MAAs since this data are MAA specific.

General and MAA specific characteristics at approval	SMA 2309/93 (n=12)	AEC 2309/93 (n=11)	SMA 726/2004 (n=37)	AEC 726/2004 (n=11)	CMA (n=28)
Causes of uncertainty					
Small sample size	0 (0%)	0 (0%)	4 (11%)	3 (27%)	9 (32%)
Limited follow-up	1 (8%)	3 (27%)	9 (24%)	2 (7%)	2 (7%)
Both	0 (0%)	5 (46%)	9 (24%)	2 (18%)	13 (47%)
Other uncertainties	7 (59%)	2 (18%)	8 (22%)	4 (36%)	4 (14%)
No uncertainties	4 (33%)	1 (9%)	8 (19%)	0 (0%)	0 (0%)
AEC scope					
Rarity of disease	NA	5 (45%)	NA	9 (82%)	NA
Medical ethics	NA	0 (0%)	NA	0 (0%)	NA
Rarity of disease & medical ethics	NA	0 (0%)	NA	2 (18%)	NA
Current state of scientific knowledge	NA	1 (9%)	NA	0 (0%)	NA
Unknown	NA	5 (45%)	NA	0 (0%)	NA
CMA scope					
Serious life debilitating disease (and orphan medicine)	NA	NA	NA	NA	27 (96%)
Orphan medicine	NA	NA	NA	NA	1 (4%)
Reasons for unmet medical need in CMAs					
No (satisfactory) treatment	NA	NA	NA	NA	15 (54%)
Major therapeutic advantage	NA	NA	NA	NA	13 (46%)
Opinion given about comprehensiveness					
Yes	2 (17%)	6 (55%)	8 (22%)	8 (73%)	25 (89%)
No	10 (83%)	5 (45%)	29 (78%)	3 (27%)	3 (11%)
Consensus between CHMP members					
Consensus	9 (75%)	4 (36%)	33 (89%)	8 (73%)	22 (79%)
By majority	0 (0%)	3 (28%)	3 (8%)	3 (27%)	6 (21%)
Unknown	3 (25%)	4 (36%)	1 (3%)	0 (0%)	0 (0%)