Translating Academic Drug Discovery Into Clinical Development: A Survey of the Awareness of Regulatory Support and Requirements Among Stakeholders in Europe

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Important discoveries by academic drug developers hold the promise of bringing innovative treatments that address unmet medical needs to the market. However, the drug development process has proved to be challenging and demanding for academic researchers, and regulatory challenges are an important barrier to implementing academic findings in clinical practice. European regulators offer varying degrees of support services to help drug developers meet regulatory standards and requirements. "Strengthening Training of Academia in Regulatory Sciences and Supporting Regulatory Scientific Advice" (STARS) is a European Commission–funded consortium aiming to strengthen the training of academics in regulatory science and requirements. Here, we report the results of four surveys that investigated the awareness and utilization of support tools offered by European regulators and identified the regulatory challenges and support needs of researchers. The surveys targeted four main European stakeholders in academic medicines research: academic research groups (706 respondents), academic research centers (99), funding organizations (49), and regulators (22). The results show that while European regulators provide various regulatory support tools, less than half of the responding academic researchers were aware of these tools and many experienced challenges in reaching a sufficient level of regulatory knowledge. There was a general lack of understanding of the regulatory environment that was aggravated by poor communication between stakeholders. The results of this study form a foundation for an improved European medicines regulatory network, in which regulatory challenges faced by academia are tackled.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The drug development process has proven to be challenging and demanding for academic drug researchers. Due to a disconnect with regulatory expectations, translation of academic study results into clinical practice and patient care is hampered.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ How are regulatory support practices that are currently offered by European regulators used by academic drug developers and what challenges do developers face in the current regulatory framework?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The study provides a comprehensive overview of the regulatory landscape and challenges that exist in the regulation of European academic drug development according to three important stakeholders: academia, regulatory authorities, and funding organizations. The study shows that there is a lack of understanding of regulatory science and requirements among academic researchers, aggravated by a gap in communication and engagement between the stakeholders.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ A better understanding of the regulatory challenges that academics are facing will help in finding feasible solutions to improve the regulatory framework in Europe and empower academia-based translational research.

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Received May 24, 2022; accepted October 29, 2022. doi:10.1002/cpt.2789

A new era of industry–academia partner programs and funding opportunities that offer sustainable cooperation and financing for academia-led development projects has changed the drug-development ecosystem globally.[1] An increasing number of lead compounds discovered in academic research have entered clinical development phases in recent years.[2] In addition, novel methodologies to support drug development are increasingly codeveloped by academics or public–private partnerships.[3] These moves toward academic drug discovery and development promise to deliver innovative medicines to patients more quickly and more economically. However, translating academic study results into clinical development programs leading to marketing authorization has proved to be demanding for academic researchers across the globe.[4,5] This has been partly attributed to lack of knowledge of regulatory requirements and lack of skills to navigate the complex regulatory system.[6,7]

To assist academic researchers in complying with current regulatory requirements in their medicinal-product development programs, national competent authorities (NCAs), the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the International Conference on Harmonization have created numerous guidelines and services. Further, supported by an European Commission grant, the Strengthening Training of Academia in Regulatory Sciences and Supporting Regulatory Scientific Advice (STARS) project was launched, involving 21 European NCAs and the EMA.[6] The main objectives of STARS were to assist academic drug developers, to enhance regulatory science knowledge in academia, to strengthen academics' ability to navigate the regulatory system, and to increase the public impact of academic medical research. The STARS project launched a series of surveys to identify what type of research activities are undertaken in European Union (EU) academic institutes, what type of regulatory support tools are currently offered by EU regulators to assist these research activities, and what experiences academics have with these regulatory support tools. The surveys targeted four main EU stakeholders in academic medicines research: academic research groups, academic research centers, health research funding organizations, and EU regulators (NCAs and the EMA). In this paper, we describe the results of these surveys and discuss how the data can assist in improving regulatory support and communication between academic researchers and EU regulators to close existing gaps in regulatory knowledge.

MATERIALS AND METHODS

Study design

We developed and conducted four online surveys aimed at four stakeholder groups in the European health research ecosystem: research groups (Survey 1), research centers (Survey 2), NCAs and the EMA (Survey 3), and health research funding organizations (Survey 4) as illustrated in **Table 1**. English-language surveys were designed by the STARS consortium and were delivered using the SurveyMonkey service (SurveyMonkey Inc., Palo Alto, CA). The surveys were pilot-tested and subsequently adapted. The surveys complied with the General Data Protection Regulation. STARS partners approached research centers, funding organizations, NCAs and the EMA to participate in the surveys. The selection criteria for the research centers and funding organizations are described in **Table 1**. Research centers were asked to recruit research groups from their own institutes for Survey 1. No incentives were provided for the respondents. A voice-call helpdesk was available to support respondents in completing the questionnaires. The surveys were open from June to October 2019.

Survey questions

The surveys were adapted to the specific stakeholder groups and ranged from 23 to 37 questions. The surveys considered a broad spectrum of demographic and regulatory topics as well as research and regulatory-support activities undertaken between 2014 and 2018.

In Survey 1 and Survey 2, sent to the academic research groups and research centers, the main topics of the questions were demographics and background information, field of research and project information (e.g., topic of research, stage of research, involvement in drug development, type of clinical studies performed, involvement of research partners), known sources of national and European regulatory support and their usage, provision of regulatory support within the organization (for Survey 2 only), reasons for which regulatory support was sought and areas where difficulties were encountered when asking for scientific advice (SA) from regulatory authorities, challenges in regulatory matters for academic researchers (including questions on clinical trial application (CTA)) and gaps in the current regulatory support system, and regulatory training needs.

In Survey 3, addressed to NCAs and the EMA, the main topics of the questions were name and remit of the agency, type of support and SA offered by the agency, details on the SA (including procedure, fees, type of applicants, topics and frequency of SA requests in 2014–2018), problems that academic researchers are facing when applying for SA and their regulatory knowledge and preparedness, number of CTAs submitted to the agency by academics in 2014–2018 and success rate of these applications, and channels that the agency is using to disseminate information on support activities to academic researchers.

In Survey 4, sent to the funding organizations, the main topics of the questions were demographics and background information, activities at the organization (including number of funded projects in 2014–2018), research priorities and type of research projects funded, requirements for project submission, evaluation and monitoring, possibility of fee reimbursement for regulatory support, type of interaction of the funding organization with the regulatory authorities, characterization of advice sought and funding organization experiences with regulatory authorities, regulatory training and support needs by the funding organization, and possibility of putting more emphasis on regulatory matters in the grant approval procedure.

Analysis

Respondents were included in the analysis if they provided an informed consent to use their data and answered the first demographic question. In the analyses, the total number of respondents per question could differ. Proportions of respondents were calculated for each question based on all respondents giving a particular answer, divided by all subjects answering the question, but excluding those that ticked the box that this question did not apply to them. For example, respondents could indicate that questions on seeking clinical trial information were not applicable to them as they only performed preclinical lab work. The proportion of responses was then multiplied by 100 to generate percentages. The number of respondents per question is indicated in the figure caption. For Survey 3, a clarification telephone call was organized with NCA or EMA respondents who had provided ambiguous answers. Data were analyzed descriptively. The analysis focused on the collective results at a European level without assessing possible country-specific aspects. The answers to open-ended questions regarding the most critical gaps or deficiencies in the current regulatory support system were grouped into 11 response categories using word-density analysis and clustering tools (SEOScout Ltd., Bristol, UK). Microsoft Excel (Microsoft, Redmond, WA), R (R Foundation for Statistical Computing, Vienna, Austria) and PowerPoint (Microsoft) were used to create the figures.

Table 1 STARS surveys target stakeholder categories and respondents, and workflow of surveys preparation, respondent selection process, and implementation

	Target stakeholder category	Respondents
Survey 1	Academic research groups involved in nonclinical/clinic research, medical device development, public health research and/or health technology assessment	One representative from each invited research group (the respondent was typically principal investigator, lead researcher, or senior clinician working in the group)
Survey 2	Academic research centers (universities, hospitals, nonprofit CROs, government research organizations)	One representative from each invited research center (the respondent was typically representative of the center's clinical trial/innovation office)
Survey 3	National competent authorities and EMA	One respondent from each NCA (the respondent was typically representative of the NCA's clinical trial/innovation office) and EMA
Survey 4	Funding organizations (government, public/private foundation, charity organization)	One representative from each invited funding organization
Survey tool selection	The features of six online survey software were tested by the STARS consortium. Based on the results, SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA) was selected for implementation of the surveys.	
Survey building	English-language surveys were designed by the STARS consortium and constructed using SurveyMonkey service. This iterative process consisted of several rounds of discussions during which the surveys' layouts, contents, and questions were prepared. A data analysis plan was developed by the consortium to illustrate what data will be analyzed and how.	
Survey piloting	To make sure that the survey questions were unambiguous, logical, and fitting the purpose of collecting high-quality data, the surveys were piloted by four health research experts. All recommendations for changes by the experts were implemented in the final surveys.	
Respondent selection process	The STARS consortium selected 3–8 diverse research centers and 1–4 funding organizations from each of the 23 participating European countries. The selected centers fulfilled the following criteria: they possessed a nonprofit status, conducted regulatory relevant research, were sponsors according to 2001/20/EC or EU536/2014, had a contact point who agreed to take the Survey 2 and who had knowledge to whom to send the Survey 1. The selected centers were of different size and covered a broad indication and therapeutic field in each country. The selected funding organizations fulfilled the following criteria: they provided financial support for regulatory relevant research and had a contact point who agreed to take the Survey 4. The selected funding organizations had complementary capital sources and funding instruments.	
Survey implementation	All respondents received the survey web link and instructions by email. The STARS coordinator invited the representatives of the selected research centers, funding organizations and STARS NCAs to take the Survey 2, 3 and 4, respectively. The coordinator also asked the representatives of the participating research centers to forward the Survey 1 link to the relevant research groups in their institute. The surveys were performed in June–October 2019. No incentives or rewards were offered to the respondents for taking the survey. A voice call helpdesk was available to support respondents in completing the questionnaires. Four email reminders were sent to the respondents in each survey.	

CROs, Contract Research Organizations; EMA, European Medicines Agency; NCA, national competent authority; STARS, Strengthening Training of Academia in Regulatory Sciences and Supporting Regulatory Scientific Advice.

Data availability statement

The surveys' questions and raw data are available as article supplements in PDF format (**Supplementary documents 1–4**). Moreover, the files are available in Excel format upon request; apply at science@cbg-meb.nl.

RESULTS

Respondents

We invited 796 research groups, 110 research centers, 52 research-funding organizations, 23 NCAs, and the EMA to participate in the survey. In total, 706 (89%), 99 (90%), 21 (91%), and 49 (94%) of the invited research groups, research centers, NCAs, and funding organizations, respectively, gave informed consent and answered the first demographic question (**Figure 1a**). Also, the EMA provided answers to the survey. A list of the NCA respondents is available in **Table S1**. There was large variability across countries in the number of research groups completing Survey 1. Sixty-five percent of the responses were received from five countries: Spain, Hungary, France, Portugal, and Finland. Other stakeholder-group responses were more equally distributed (**Figure 1b**).

Most respondents in research groups were leading scientists (59% of the total) working in a university or hospital (83%), with more than 10 years of work experience (76%) (**Table S2**). Similarly, most respondents in research centers were directors or unit heads (37% of the total respondents) working in a university or hospital (78%) that employs over 100 scientists (61%) (**Table S2**). The majority of respondents in funding organizations worked in a government organization (65% of the total) that grants public funds

(a)

	Research groups (Survey 1)	Research centers (Survey 2)	NCAs and EMA (Survey 3)	Funding organizations (Survey 4)
Invited	796	110	24	52
Did not give informed consent or did not answer the first demographic question	90 (11%)	11 (10%)	2 (8%)	3 (6%)
Responders	706 (89%)	99 (90%)	22 (92%)	49 (94%)

(b)

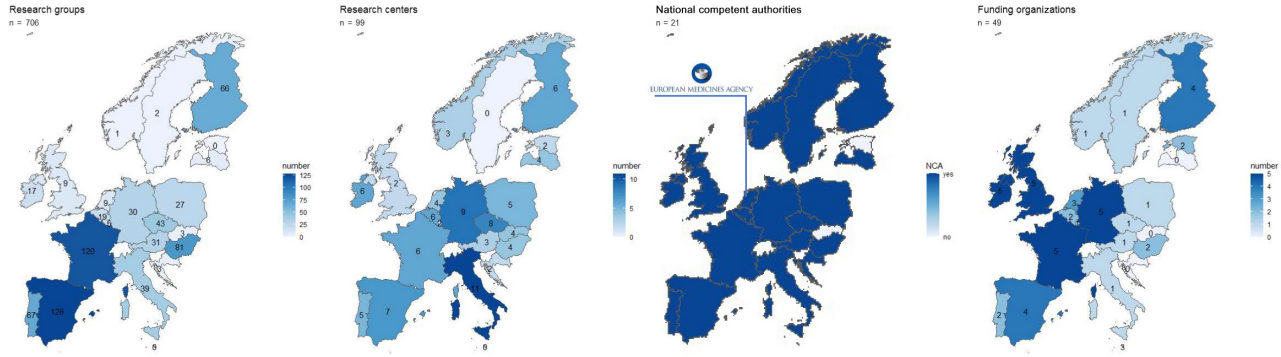

Figure 1 STARS (**a**) surveys' respondent numbers and (**b**) response rates by country. Darker color represents a higher participation rate. EMA, European Medicines Agency; NCAs, national competent authorities; STARS, Strengthening Training of Academia in Regulatory Sciences and Supporting Regulatory Scientific Advice.

(76%), mostly for academic groups in universities and hospitals (**Table S2**).

Academia: Survey 1 and Survey 2 results

Research activities in academia. Eighty-three percent of the research groups focused their research activities during 2014–2018 on interventional clinical studies, 63% on noninterventional studies, and 38% on basic biomedical research. The top three research topics were biological therapies (33%), biomarker research and development (R&D) or validation (30%), and diagnostics R&D (25%) (**Figure 2a**). Similarly, the research centers indicated that during 2014–2018 the most significant research areas in their organization were interventional clinical studies (87% of the centers considered this topic very significant or significant), noninterventional studies (80%), and basic biomedical research (58%, **Figure 2b**). The three most important research topics were diagnostics R&D (67% of the centers considered this topic very significant or significant), biological therapies (67%), and biomarker R&D or validation (66%) (**Figure 2b**). All respondent research centers indicated that they had been involved in product-development projects during 2014–2018: 39% were at clinical phase III of development, 27% were at clinical phases I or II, 21% were at preclinical phase, and 13% were at phase IV.

Awareness and use rates for regulatory support services. In total, 47% and 34% of the research groups were aware of their country's NCAs' and the EMA's regulatory support services, respectively. Research centers were more aware of their NCAs' and the EMA's regulatory support services, 71% and 58%, respectively. Most known services were web-based support tools, such as document templates, Q&A pages, and guidelines: 62% and 47% of the research groups and 91% and 86% of the research centers were aware of these, respectively (**Figure 3a**). The possibility of requesting SA from an NCA, which provides individualized regulatory support to academic researchers, was known by 53% of the research groups and 83% of the research centers. Other support tools were not as well known by the respondents. For example, only 28% of research groups were aware of the EMA's priority medicines scheme (PRIME) that supports the development of medicines targeting an unmet medical need and 27% were aware of the innovation meetings offered by the EMA (Innovation Task Force meetings, ITF) in which informal discussions about the scientific, technical, and regulatory issues for innovative developments take place. Among research centers, 46% and 42% knew of these two tools, respectively (**Figure 3a**).

Among the research groups that were aware of the NCAs' and EMA's web-based support tools, 63% and 48% had used them at least once during 2014–2018, respectively (**Figure 3b**). With respect to NCAs' and EMA's SA, 52% and 20% of the research groups that were aware of this service had used it at least once during 2014–2018, respectively (**Figure 3b**). A similar pattern of use of regulatory support tools emerged from those research centers who were aware of these services (**Figure 3b**). Interestingly, apart from the website tools, respondents seemed to make more use of other regulatory support tools (e.g., SA) offered by NCAs than by the EMA. Moreover, the Survey 1 data indicate that a small portion of the research groups had used NCAs' SA very actively;

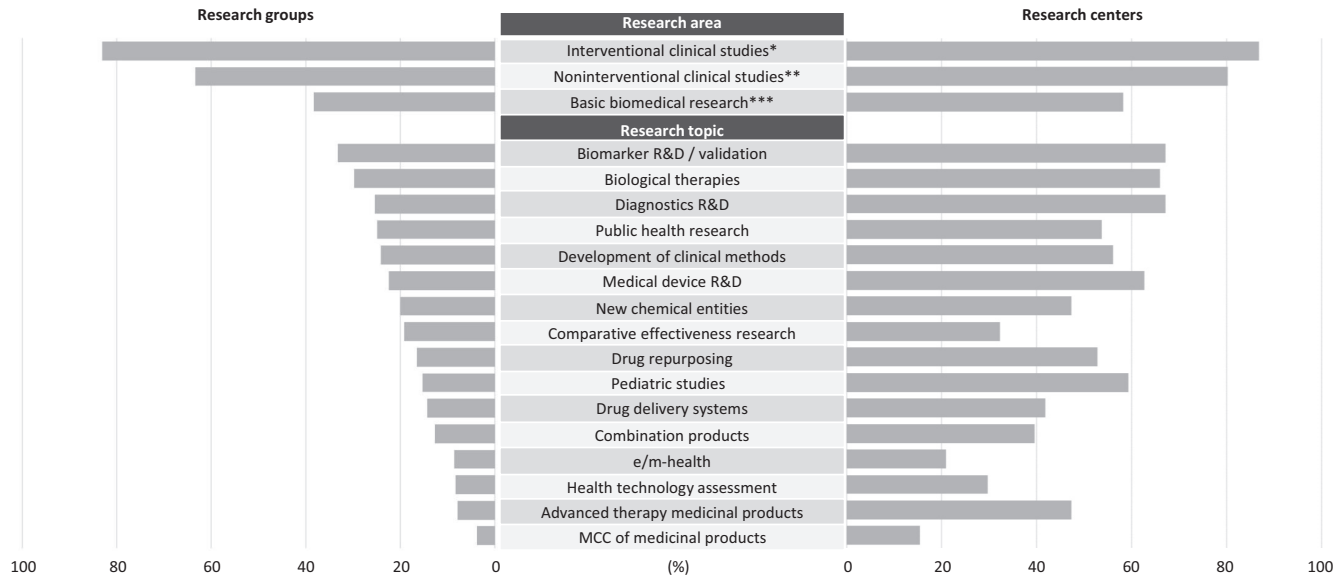

Figure 2 Research activities in the respondent research groups and research centers. The left side shows percentages of the research groups that were working on a designated research area or topic. On the right side is shown percentages of the research centers that considered a designated research area or topic to be very significant or significant. *Single-arm, two-arm, and multiarm studies and basket or umbrella trials. **Observational, registry, and case-control studies. ***Preclinical studies, for example on pathways, biological mechanisms, or pathophysiology. A total of 684 research groups and 91 research centers answered this question. e/m health, electronic or mobile health solutions (e.g., digital health application/service R&D); MCC, manufacturing, characterization, and control; R&D, research and development.

19 research groups (3%) had each used this service over 10 times during 2014–2018.

Regulatory challenges in academia. Half of the research groups indicated that reaching a sufficient level of knowledge of regulatory science and requirements in their team is a "very big" or "big" challenge (50% of the respondents shared this view). The other top challenges for the research groups concerned designing phase I and first-in-human studies (49%), the availability of regulatory support (46%), and preparation of CTAs (41%, **Figure 4**). The research groups that had previously prepared and submitted a CTA to the authorities (n = 189, 27% of all Survey 1 respondents) reported fewer challenges in regulatory matters compared with the entire group of Survey 1 respondents (data not shown). During the CTA process, manufacturing certificates and pharmacological aspects were the most challenging topics for this Survey 1 subgroup (**Figure S1**).

These challenges were reflected in the topics on which academic developers sought support from regulatory authorities or local innovation offices at their research center. The research groups had contacted the national authorities most often concerning the design of clinical studies (58% of the Survey 1 respondents); general information, such as document templates (51%); and clinical safety reporting (33%) (**Figure 5**). Similarly, general regulatory matters (84% of the Survey 2 respondents) and clinical study design (73%), were the top two topics for which the research groups had requested regulatory support from their host organization, followed by matters about clinical study statistics (73%), patient recruitment/selection (65%), and clinical safety reporting (63%) (**Figure 5**).

Gaps in the regulatory system according to academia. We asked the research groups and research centers what was, in their opinion, the most critical gap or deficiency in the current regulatory system. The research groups and research centers gave 272 and 101 open answers, respectively. Communication and inadequate levels of regulatory knowledge were the top two deficits named by both the research groups (20% of the Survey 1 respondents) and the research centers (21% of the Survey 2 respondents; **Figure 6**). Respondents felt that communication between the authorities and researchers was not frequent enough nor clear: respondents indicated that the two parties did not understand each other well. Moreover, the respondents indicated that an insufficient level of regulatory knowledge and unawareness of the available support tools among academic research groups was another critical gap (**Figure 6**).

The complexity of regulatory processes and the high number of guidelines and requirements were raised as significant challenges by 15% of the research groups and 7% of the research centers. Furthermore, some of the research groups (13%) and research centers (5%) felt that the regulatory processes were often slow and led to delays. In addition, 5% of the research groups and 17% of the research centers indicated that the range of available support tools did not always meet the needs of academic researchers. Research centers also indicated that there was a lack of support for questions related to clinical trials and insufficient user support for authorities' electronic services. Moreover, 12% of research centers and 4% of research groups indicated that the level of regulatory harmonization needs to be further improved; most comments concerned inadequate harmonization between the EU member states in the context of multinational trials (**Figure 6**).

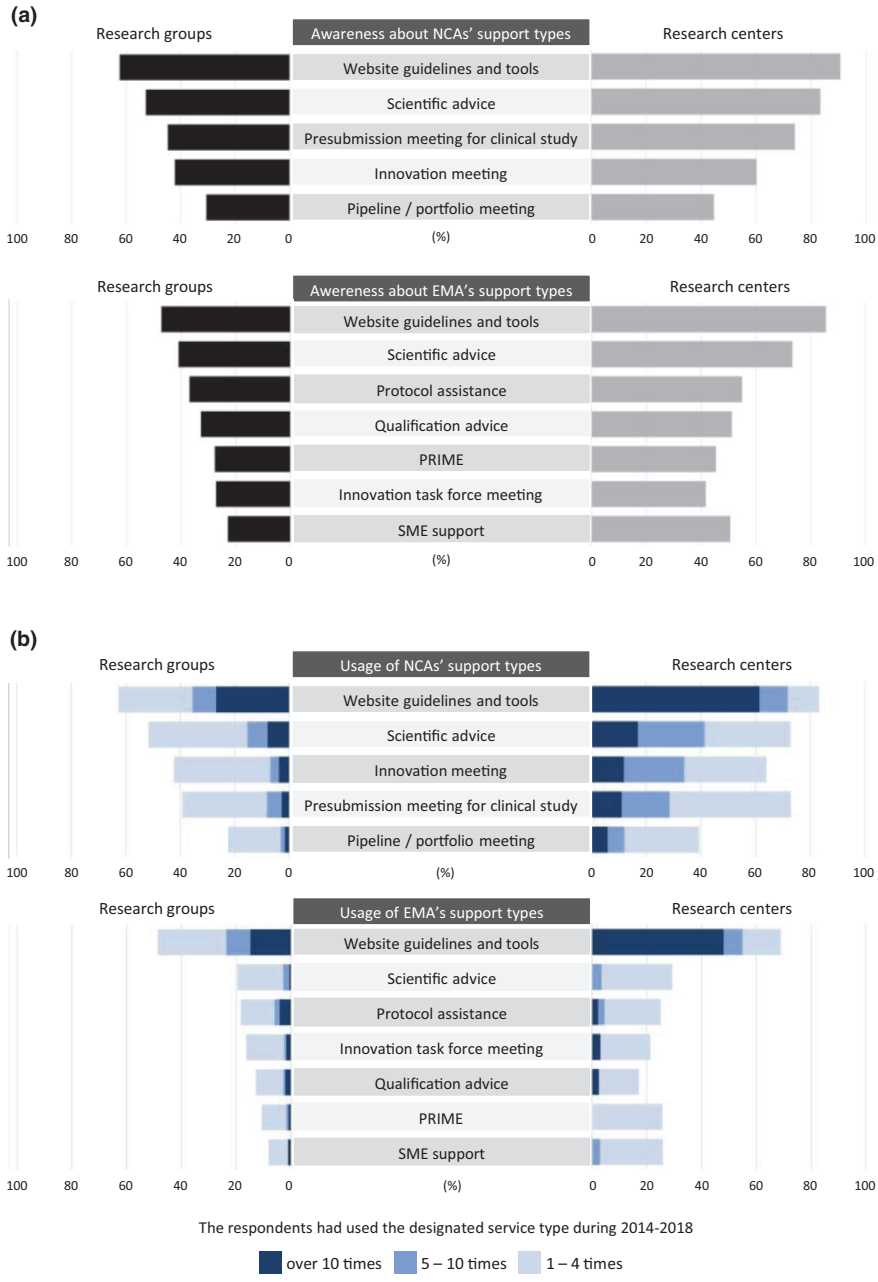

Figure 3 The awareness and use rates of NCAs' and EMA's support services by the research groups and research centers. (**a**) Percentage of the research groups and research centers that were aware of the designated regulatory support type. (**b**) Percentage research groups and research centers that had used the NCAs' and EMA's support services. A total of 498 research groups and 89 research centers answered this question. EMA, European Medicines Agency; NCAs, national competent authorities; PRIME, the EMA's primary medicines scheme; SME, small and medium-sized enterprises.

Training needs for academia. The need for training in regulatory topics was considered very high: 75–88% of the research groups and 83–96% of the research centers indicated that additional training was needed in the designated regulatory topics (**Figure S2A**). The research groups highlighted statistical planning (88%), clinical development planning (88%), and biomarker R&D (87%) as primary training needs (**Figure S2A**). The research centers indicated that medical devices R&D (96%), digital health application/service R&D (e/m-health, 95%), and clinical trial protocols (95%) were the topics for which regulatory training is primarily needed (**Figure S2A**). In terms of the target professional categories, the research groups and research centers both indicated that researchers/clinicians and postgraduate students were the two main categories in need of more regulatory training (**Figure S2B**).

National competent authorities: Survey 3 results. Twenty-one European NCAs and the EMA provided information about their SA support procedures for academic researchers. All but one NCA offered formal SA procedures, and regulatory or procedural

Figure 4 Regulatory challenges experienced by the respondent research groups. The graph shows percentages of the research groups who considered that a designated topic had been a "very big" or "big" challenge for the research team. A total of 455 research groups answered this question.

advice as well as presubmission meetings were offered by 19 NCAs (90%). Qualification procedures (for biomarkers and novel methodologies) and health technology assessment (HTA) advice were both offered by four NCAs (19%).

Nineteen of the NCAs (90%) provided practical information about SA procedures on their websites, 14 NCAs (67%) approached academic researchers at conferences, 9 NCAs (43%) communicated via e-mail about academic research questions, and 5 NCAs (23%) communicated via social media. Also, the EMA used its website, conferences, and email to disseminate information on the agency's regulatory support tools.

At the time of the survey, 5 NCAs (24%) provided complete fee waivers for SA to academic parties and 12 NCAs (57%) offered partial fee waivers. Moreover, five NCAs (24%) offered incentives

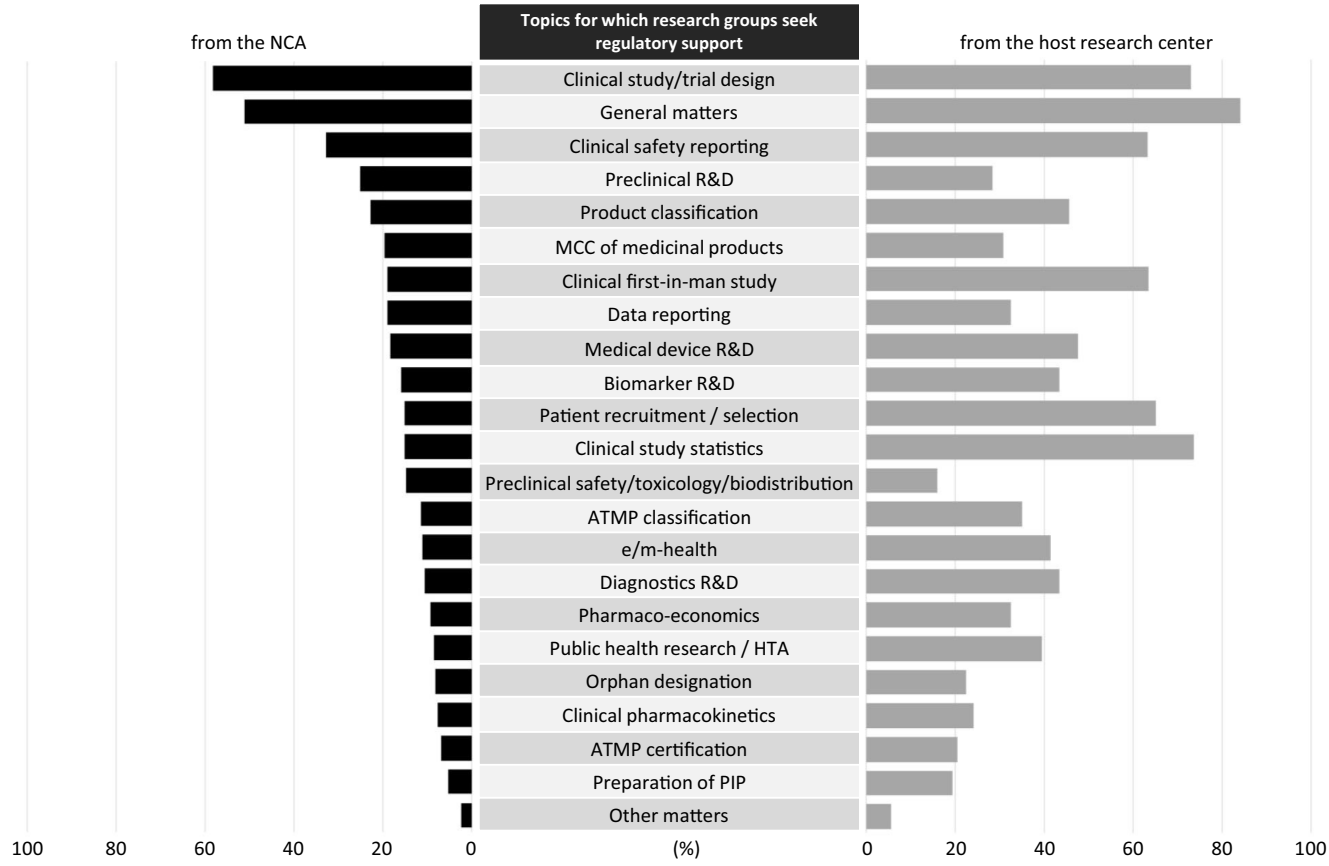

Figure 5 Regulatory support requested in different research topics. The black bars indicate the percentage of research groups that had sought regulatory support on a designated topic from NCAs. The gray bars show the percentage of research centers from which the research groups had sought regulatory support on the designated topics. A total of 498 research groups and 89 research centers answered this question. ATMP, advanced therapy medicinal product; e/m health, electronic or mobile health solutions (e.g., digital health application/service R&D); HTA, health technology assessment; MCC, manufacturing, characterization, and control; NCA, national competent authority; PIP, pediatric investigation plan; R&D, research and development.

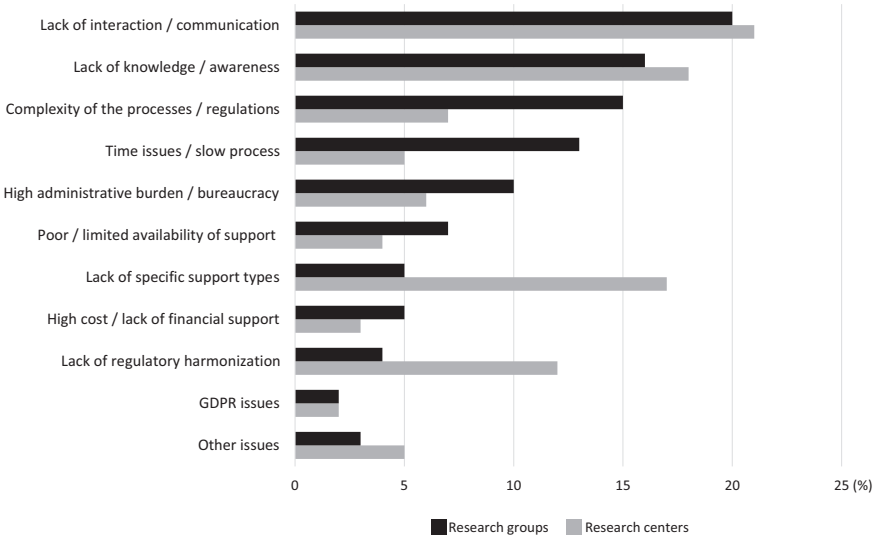

Figure 6 Distribution of open-ended answers to the question, "What is the most critical gap or deficiency in the current regulatory system?" in 11 response categories, shown as percentages of the total responses. The research groups and research centers gave 272 and 101 open answers, respectively. GDPR, general data protection regulation.

on SA fees to academic clients. However, four agencies (19%) collected the same full fee from all clients who received SA. No specific fee reductions for SA were available for academics at the EMA. However, the EMA offered free SA for pediatric developments and orphan medicines for all applicants. According to the NCAs, the three most common SA topics asked by academics were production and research-quality matters (62%), the CTA process (52%), and nonclinical development (52%). Furthermore, the three main areas in which academics faced problems were limited awareness of regulatory support tools, indicated by 17 NCAs (81%), uncertainty whether to seek support from an NCA or the EMA (52%), and differences in terminology between the authorities and academia (52%).

Funding organizations: Survey 4 results

Survey 4 aimed to provide information about how the funding organizations account for regulatory matters in their processes and funding decisions. At the time of submission of grant proposals, the most frequently requested documentation by the funding organizations concerned the costs of planned clinical studies (95%), study protocols (85%), and the patient recruitment or selection plan (76%). A positive decision from an ethics committee (37%) or from an NCA (17%) were requested much less frequently. After a positive funding decision, the grantees were typically requested to submit the final report (90%), annual progress reports (88%), and budget reports (80%). In total, 21 (51%) funding organizations consulted regulatory experts during their decision-making processes. The most frequently consulted experts were academics (81%) and industry professionals (55%) with in-depth expertise of regulatory topics; NCA (40%) and EMA (15%) professionals were less often consulted.

In terms of collaboration with the regulatory authorities, funding organizations consulted national authorities much more often than the EMA during the evaluation process of health research proposals; 15 Survey 4 respondents (37%) had consulted an NCA and 2 (5%) had consulted the EMA. NCAs were consulted about general regulatory affairs (37%), regulatory aspects of the submitted application documents (22%), and the feasibility of the proposed study (17%) (**Figure S3A**). The EMA was consulted concerning annual safety reporting (2%) and project auditing (2%).

In addition, funding organizations were asked which actions they would consider to be useful in increasing the weight of regulatory matters in the evaluation of health research proposals in the future. The most useful actions would be the opportunity to consult regulatory authorities (80% of the respondents selected either "somewhat useful" or "very useful" answer option) and local experts (73%) during the evaluation of applications, and increasing availability of regulatory training for grant evaluators (73%) (**Figure S3B**). Finally, 15 out of 41 funding organizations (37%) supported the idea of increased emphasis on regulatory matters in grant-approval procedures. In relation to financial aspects, 61% of funding organizations accepted that regulatory authority service fees are added to project budgets, while 15% did not approve reimbursement of such fees.

DISCUSSION

Our study provides a comprehensive overview of the regulatory landscape and challenges that exist in European academic drug development as perceived by three important stakeholders: academia, regulatory authorities, and funding organizations. A total of 706 research groups, 99 research centers, 49 funding bodies, and 22 regulators (21 NCAs and the EMA) provided responses to our four surveys. The survey results show that there is a lack of understanding of regulatory science and requirements among academic researchers, aggravated by a gap in communication and engagement between the regulatory network and academia. In addition, communication between regulatory authorities and funding organizations regarding regulatory matters could be improved.

Our surveys reached the relevant and representative target groups: a notable number of biomedical and therapy-development

research groups and research centers, most European regulatory agencies (EMA and NCAs), and a relatively large number of European funding organizations. We demonstrated that various support tools are available for academic drug developers, with SA being the most common support offered by regulatory authorities. SA can cover various aspects of the development process and, when followed, positively impacts the marketing-authorization success rate.[8,9] However, only about half of the research groups in our study were aware of the availability of such services and even fewer were actively using them. Somewhat higher awareness and utilization was noted for regulatory website guidelines and tools. This suggests that improving the websites by using search-engine optimization and more clearly outlining various support options might improve the utilization of these and other services by academia. The necessity of enhancing the EMA's website to raise awareness of regulatory support and tools available to academia during a medicinal product's life cycle is also specifically addressed in the EMA's Academia Collaboration Matrix action plan for 2021–2023.[10]

A recent example of an interactive regulatory platform for academia is the US Regulatory Guidance for Academic Research of Drugs and Devices (ReGARDD) platform that was developed by academia to assist the developers in navigating through the regulatory system. The platform is publicly available and provides up-to-date information to support best practice across the regulatory landscape. It helps academic researchers prepare and submit regulatory applications to the FDA, develop and write clinical protocols, and keep pace with changing federal regulations.[11] Importantly, documentation and guidelines provided by the regulatory authorities need to be regularly updated to keep pace with emerging technologies and new methods of assessment.[12]

Generally, EMA services were less known among academics than NCA services. Among other factors, this can be attributed to the fact that NCAs handle the CTAs that are needed to start a clinical study. In addition, NCA services may be preferred by academic researchers due to their lower-threshold access and affordability, such as the opportunity to ask informal or free advice at some NCAs. Importantly, the PRIME and ITF support tools offered by the EMA were shown to be poorly known among academics, yet these are particularly relevant for academic developers, as they usually concern the development of innovative medicines and tools. Furthermore, awareness of SA and other support tools of NCAs and EMA was higher at the management level of academia (most of the Survey 2 respondents), compared with academic research personnel (most of the Survey 1 respondents). This indicates that improving internal information exchange across academic levels could improve the frequency and level of academic developers' communication with the regulators.

One of the major deficiencies in current academic translational medicines research named by both the respondent research groups and health research centers was the difficulty of academic researchers reaching an adequate level of regulatory knowledge. These data are in line with previous studies performed on national levels, which have showed that academic researchers have limited regulatory knowledge and expertise to confidently engage in the regulatory process.[5,13] Therefore, STARS has attempted to provide academic researchers with basic regulatory training through a pilot project.[14] However, despite successful implementation of a single course in three target countries, a more sustainable, Europe-wide, systematic approach to transfer regulatory knowledge to academia and to funding organizations, is needed. The surveys' data indicate the need for regulatory training of a broad target group from graduate students to the top management personnel in academia and grant assessors in the funding organizations. Therefore, implementation of regulatory training in the standard (bio)medical and pharmacy educational programs and offering such training post graduation could be advantageous.

The need for a centralized regulatory-science educational program for early-career scientists and clinical research personnel has been discussed before by various authors, stressing the importance of regulatory authorities' engagement to help shape these programs.[15–17] To this end, the STARS has developed two curricula for academia. First, the *Core Curriculum* specifies essential regulatory knowledge for scientists that should be implemented in current educational programs for (bio)medical and pharmacy programs. Second, the *Comprehensive Curriculum* defines relevant, in-depth regulatory knowledge for specific postgraduate programs to help the community to ensure the preparedness of translational scientists to fulfill increasingly complex regulatory requirements.[18]

Another obstacle facing academic researchers is the problem of timely access to regulatory support. In this respect, specialized local offices that provide on-site regulatory support for research groups involved in product development are in a key position to lower the bar for academic researchers seeking help.[4,19] Our study supports this suggestion and shows that individual academic researchers also actively seek support in their own research centers regarding issues such as trial protocol development, CTA preparation, and general regulatory matters. Therefore, local university offices, underpinned by national regulatory authorities, may serve as a primary contact point for academic developers, providing regulatory, legal, and business expertise. At the same time, such offices may function as a point of contact for regulators to communicate with academia.[6] The EMA has also highlighted the important role of collaborations between academic research centers and regulators to address current gaps in the regulatory framework and to improve the development and evaluation of medicines.[20] Furthermore, to facilitate access to regulatory support for academic researchers, the STARS consortium has published a comprehensive inventory.[21] In this inventory, various regulatory support services provided by NCAs, public actors, and private entities can be filtered by country, expertise area, and support scope.

Both parties consider challenges in communication between researchers and regulators to be the main shortcoming in the present regulatory framework and processes. The surveys' results show that communication between the authorities and academics was seen as insufficient in quantity and quality. Many respondents felt that the amount of interaction was too low and that the two parties did not understand each other well. One source of these issues is the complexity of the language used by the authorities, which includes multiple regulatory terms and abbreviations. Avoiding regulatory jargon during communication with academic researchers could improve mutual understanding and make communication more efficient.

Furthermore, implementation of a low-threshold contact point with NCAs, such as the informal consultations that some agencies already offer, could help to accelerate the processes and provide earlier signals of potential difficulties in projects. One option could be the creation of an interactive platform for academics to navigate through the regulatory requirements and timelines, similar to the ReGARDD platform.[11] The STARS project has run a pilot in which a one-stop-shop communication platform for Spanish academics was used to stimulate quick and informal communication between regulators and academic researchers. The platform provided not only useful regulatory information, links, and documents, but also an opportunity to ask questions of the regulators free of charge.[22] Extensive deployment of such (joint) communication platforms in Europe may facilitate the creation of a stronger regulatory network and reduce gaps in accessing support and information. Such platforms may also serve as a base for sharing best practice, knowledge, and experience.

The dispersed regulatory framework in Europe adds complexity to translational research.[23] For example, in one recent innovative project, EURE-CART, it was not possible to conduct the clinical trial as originally planned due to regulatory barriers. It was infeasible to obtain clinical-trial approval in all four European member states participating in the project, as genetically modified organism regulations differ in these member states. As a result, the EURE-CART project recently published a white paper on chimeric antigen receptor (CAR) T-cell therapy development discussing regulatory issues and challenges in the harmonization of clinical trial approval processes across Europe.[24] This example highlights the challenges drug developers are facing and emphasizes the need for harmonization across Europe as mentioned in the responses to our surveys. Future solutions may include the use of standardized forms and processes and joint, online service platforms. This example also stresses the importance of funding organizations being aware of the regulatory aspects of submitted proposals so that they can anticipate the possible challenges facing a project.

Furthermore, despite progress in this area, the affordability of regulatory support remains a problem for some academic researchers. Indeed, several NCAs offer service-fee waivers or fee reductions for academic developers. In addition, the EMA offers free SA for orphan and pediatric medicines to stimulate development in these areas. However, no academic-specific approach for regulatory support exists on a European level, and many NCAs provide only informal or early-development advice for free or with fee reductions. The EMA has acknowledged the existing problem and addressed it in two planned actions for 2021–2023: (i) "Reflect on PRIME to improve usability of the incentives for academic medicines developers" and (ii) "Explore widening the scope of Executive Director-decision on academia fee waiver for protocol assistance."[10] For NCAs, the addition of an informal, low-threshold form of SA to agencies' service portfolios and providing waivers or fee discounts for SA to all noncommercial actors may be considered, if not yet implemented. However, the feasibility of this approach and the availability of resources at the NCAs need to be considered.

Funding bodies could also play a crucial role in addressing cost barriers by allowing grant applicants to include regulatory fees and regulatory training costs in project budgets. Favorably, most funding organizations supported the idea of adding regulatory authority service fees to project budgets. Regrettably, however, our Survey 4 results showed that only a minority of the funding organizations considered regulatory matters in their calls. In addition, communication practice between funding organizations and NCAs on regulatory aspects of applications is not yet widely established. Addressing regulatory costs in relevant grant calls and asking the applicants to explain how they implement regulations in their projects may stimulate researchers to consider regulatory matters and to approach regulatory agencies for support. As a result, addressing these issues may also ultimately increase the societal impact of the research, fostering translation of study results. For this to become a reality, changes in the current practices of funding organizations, which partly drive the behavior of researchers, are needed.[7]

A limitation of this study is that responses to Survey 1 were not equally distributed among European countries, with a few countries dominating the responses. Therefore, the results of this survey should be interpreted with the overrepresentation of certain countries in mind, and extrapolation to the whole of Europe should be made cautiously. Additionally, the surveys were distributed primarily among academics involved in drug development, which is a group likely to have more experience with the regulatory framework. This might have led to an over-estimation of the knowledge of the regulatory network in academia.

In conclusion, our study provides a better understanding of the regulatory challenges that academics face and identifies shortcomings in the current regulatory processes. We show that there is a gap between the current regulatory network and academic drug development, with communication between the main stakeholders in this process being inadequate. This appears to be attributable to various factors including the difficulties faced by academic researchers in reaching a sufficient level of regulatory knowledge, the complexity of the current regulatory system, deficient outreach by regulators to academic researchers, and insufficient incentives and resources for academics to consider regulatory requirements. Common efforts should be made to create a robust framework for pursuing academia-based drug development. On the basis of the collected data, the STARS consortium aims to find feasible and meaningful solutions to improve the regulatory framework in Europe and subsequently make recommendations to address the main identified shortcomings.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

We would like to acknowledge the support we received from other STARS members and the steering committee when preparing and performing the survey studies. We also acknowledge all survey participants for their contribution to this study.

FUNDING INFORMATION

The STARS project is funded from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825881.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.J.K. and V.S. wrote the manuscript. All authors designed and performed the research. M.J.K., E.A., M.B., V.S., A.H., W.L., W.B., A.M.G.P., and P.G.M.M. analyzed the data.

DISCLAIMER

This article expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of any of the national competent authorities, the European Medicines Agency, or one of its committees or working parties.

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