Major research project final report

Interactions between drug regulatory authorities and academia: motivations, barriers, and suggestions

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ABSTRACT

Background and objectives Academic engagement is the knowledge-related interaction between academic institutions like universities and external organizations. It can be classified into University-Industry (U-I) interactions and University-Government (U-G) interactions. Existing literature places more focus on the former and commercialization activities of universities. Among the few studies that looked at U-G interactions, none was about University-Regulator (U-R) interactions. However, regulators also play a crucial role in academic engagement, especially in the field of drug development. In terms of developing novel therapeutics and providing clinical perspectives, academia has a lot to offer to the regulators-the key decision makers on the approval of therapeutics. Our aim was therefore to bridge the current knowledge gap by investigating various attributes of U-R interactions in the context of drug development and regulation.

Methods To gain further insights into U-R interactions in drug development and regulation, we conducted interviews that were divided into two steps. The majority of the participants were from the Netherlands, with a few from other European countries. Previous literature was used for setting up general directions and core concepts behind the interview design. In our step one piloting interviews, senior experts from regulatory authorities and academia provided an overview of the topic. They described their observations of U-R interactions on the systemic level. In the interviews, they asked questions on ongoing U-R activities in drug development, motivations and barriers perceived by both sides, and suggestions for improvement. Building on their input, we shaped the interview protocol for step two interviews that focused on U-R interaction experiences on the personal level and involved more participants. The online interviews were later transcribed and qualitatively analyzed with inductive coding.

Results In total, 4 respondents were interviewed in the piloting interviews, and 17 in step two interviews. The participants' profiles of step two interviews were more diverse than those in piloting interviews. We involved more institutions and participants with different expertise. Among the feedback we received, we identified the most frequently mentioned motivations, barriers, and suggestions for both regulators and academics in U-R interactions in drug development and regulations. For academics, the motivations to interact with regulators are ensuring regulatory requirements for product development plans, applying research to real-world applications, and having an impact on decision-making. Regulators are motivated to access academic knowledge and educate academia on the regulatory system. Barriers encountered by academics include a lack of time, money, and regulatory skills to interact. Lack of funding and maintaining independence were the barriers experienced by the regulators. Respondents suggested educating academics on regulatory affairs, promoting the value of regulatory science, involving regulators early in the development plans, regulatory authorities increasing the number of engaging regulators to interact with academia, routinely reviewing the efficiency of regulatory procedures for academic drug applicants, and enhancing human

resources exchange between academia and regulatory authorities.

Conclusion When it comes to the context of interactions, some people-based academic engagement activities in U-I and U-G interactions such as giving lectures and advising were found in U-R interactions in drug development and regulations as well. But the interactions that involve getting approval from regulators like registering drugs were exclusive to U-R interactions. Ensuring regulatory requirements and having an impact on decision-making that motivated academics to interact with regulators were not identified in studies on U-I and U-G interactions. Generally speaking, regulators and academics were motivated to interact with each other despite the barriers mentioned in the study. Lacking funding appeared to be a mutual barrier both academics and regulators faced. Suggestions to potentially overcome these barriers and overall improve the U-R interaction situation were given. Increasing the quality and quantity of U-R interactions through promoting the value of regulatory science, educating academics on the regulatory system, and enhancing human resource exchange between both sides were some suggested concrete measures that could be implemented. We expected the provided insights to strengthen the bond between academia and regulatory authorities, assisting policy-making in public health.

SUMMARY

In recent decades, there's been a growing trend in universities to interact with non-academic partners. The term 'academic engagement' describes the interactions and activities between academia and these partners, including industries and governmental organizations. Commercialization activities that involve patenting, licensing, and establishing spin-out companies are common for the interactions between university and industry, or so-called University-Industry (U-I) interactions. Examples of University-Government (U-G) interactions previously identified in the literature include advising, school projects, and public exhibitions.

Among different U-G interactions, University-Regulator (U-R) interactions refer to those relevant to policymaking and granting legal approval. This study focused on the ones between universities and drug regulatory authorities. U-R interactions in drug development appealed to us for a couple of reasons. Compared to other fields of expertise, U-R interactions in drug development are more common and the bond between academia and regulatory authorities is fairly tight. Moreover, further insights on U-R interactions in drug development were expected to optimize the drug development procedure.

We conducted an interview study to understand the context of U-R interactions in drug development and regulations, motivations for academics and regulators to interact with each other, potential barriers in these interactions, and suggestions perceived by both parties to improve the situation. In total, 21 experts from Dutch academia and Dutch and European regulatory authorities participated in the interviews. The online interviews were recorded and transcribed. The transcripts were later analyzed qualitatively to answer our research questions.

This study revealed some U-R interactions in drug development that overlapped with U-I and general U-G interactions. People-based activities such as giving lectures and advising were examples of these mutual interactions. On the other hand, interactions on the approval of products were exclusive to U-R interactions, given the regulators' distinct roles as policy and decision makers. Furthermore, this study concluded that academics and regulators were motivated to interact with each other. We also discovered specific motivations that matched certain contexts of U-R interactions. Optimizing drug development procedures that bring patients timely access to drugs as their mutual goal, academics and regulators identified current barriers to overcome and provided potential suggestions to strengthen U-R relationships in drug development. On top of the barriers respectively experienced by academics and regulators such as lacking time and having to maintain independence, lacking funding was found to be a joint barrier that both sides shared. The suggestions given by the respondents in the study surrounded the concepts of improving either the quality or quantity of U-R interactions in drug development. While educating academics on regulatory affairs could improve U-R interaction's quality, engaging regulators early in development plans could increase its quantity. To sum up, the results of this study offered valuable insights that would assist drug regulators in making future policies that bring substantial benefits to public health.

INTRODUCTION

In recent decades, universities have started taking on different roles. Rather than being independent research institutes that focus on scientific goals, they are increasingly interacting with non-academic parties through academic engagement. Academic engagement indicates the involvement of interactions and knowledge transfer between academia and non-academic organizations (1-3). Academics vary in the extent to which they take up this role. While some academics value academic autonomy and pursue strictly scientific impact, many others are encouraged to interact with different stakeholders and generate societal impact closely linked to broader practical issues on topics ranging from economy to global crisis (4). Academic engagement has also picked up various forms. While true that most interactions are formal contracted activities, informal interactions like advising and networking are also gaining popularity (5). With the relationships between academia and non-academic parties intensified and complexed over time, these activities have also drawn the attention of policymakers and academics. An effort is put into examining the multiple determinants and characteristics of such interactions.

In general, the level where academic activities take place and their degree of formality are ways to classify and understand the context of academic engagement (2, 6, 7). People-based and community-based activities are examples of the different levels of academic activities. People-based activities focus more on the interpersonal interactions based on individuals. Examples of these activities are giving lectures, networking, advising, training employees from non-academic sectors, and student placement (6). Under the same classification, hiring of graduates or interns is termed as the exchange of human resources in a study by De Fuentes and Dutrénit (2012). On the contrary, community-based activities involve groups and take place publicly, including school projects and public exhibitions. They are more presented in University-Government (U-G) interactions (2). The degree of formality in academic engagement activities is mostly introduced in University-Industry (U-I) interactions literature on industrial involvements and academic entrepreneurship. Adding the element of commercialization, a study by Abreu and Grinevich (2013) classifies U-I activities as formal commercial activities, informal commercial activities, and non-commercial activities. The most common examples of formal commercial activities include licensing and establishing spin-out companies, while informal commercial activities refer to consultancy, joint research and development (R&D) projects, and contract research, in which the intellectual property is less protected compared to that in formal commercial activities. On the other hand, non-commercial activities such as advising and public lectures involve little financial rewards and profit generation (1, 6-9).

Studies have also examined the motivations behind interactions with non-academic partners. Among the diverse motivations for academics to interact, extrinsic motivations such as monetary rewards appear to be the major attribute researchers looked at in previous

studies (3, 8-12). Increase in income, access to grants, and securing funding are the motivations examined the most. Though the financial benefit is not the only motivation of academic engagement, it is a major one academics keep an eye on when interacting (2, 8, 11). Aside from extrinsic motivations such as financial and reputational rewards, studies have also focused on the roles of intrinsic motivations. These are the ones that satisfy the inquisitive nature of scientists, including applying their research, gaining intellectual knowledge, and fulfilling their interests in contributing to society (3, 8, 9, 12). Some studies also examined individual characteristics like demographic variables, work experiences, researchers' mobility, gender, etc. (1, 11, 13, 14)

However, it is worthy of mentioning that U-I interactions, the primary focus of most existing literature studying academic engagement with non-academic organizations, in fact account for only part of the wide extent of academic engagement (2). Academic engagement also entails U-G interactions with community-based activities that are studied less frequently. Of the few studies that investigated U-G interactions, none investigated interactions between academia and regulators, let alone regulators involved in drug development and authorisation. As a matter of fact, regulators are heavily involved in a drug's life cycle. The most obvious role of theirs is to decide whether a drug enters the market. Before coming to this stage, a drug should have gone through multiple different phases. To begin with, scientists in labs first discover a new drug substance. After its basic properties such as pharmacokinetics and toxicology are examined, the drug then enters clinical development, where it gets administered in humans and tested on safety and efficacy in clinical trials. With the data from clinical trials, drug developers submit it to regulatory authorities for evaluation and apply for marketing authorization. Once the drug is approved by regulators and granted marketing authorization, it can be released to the market. In contrast to the past where marketing authorization applicants and regulators only meet at the evaluation phase, there seems to be a growing trend that they interact much earlier before the clinical development phase. In the early phase, regulators issue guidance and answer questions applicants might have upon request. This is supposed to help drug developers better design their studies to demonstrate drug safety and efficacy (15).

This makes University-Regulator (U-R) interactions regarding drug development an important area of study for there have always been gaps between lab findings of pharmaceutical products and their implementation in clinical settings (16). Lack of effective communication and collaborations between researchers and regulators could delay the application of innovative drugs and place the target patient population at risk of not receiving them in time. Another reason that makes drug development a relevant candidate to examine U-R interactions is the vast number of ongoing interactions. Compared to other fields of expertise, U-R interactions in drug development are more common and the bond between academia and regulatory authorities is fairly tight (16). Despite the fact that U-I, U-G, and U-R

interactions share some similarities, many features and characteristics may differ. Although most studies examined commercialization and academic entrepreneurship, which often involve patenting and launching new products, these activities are not dominant in U-R interactions. While true that regulators invest in keeping up with the advancement in innovative products, they do not participate closely in developing and launching them. The main tasks of regulators are overseeing product development and evaluating their benefits and risks (17). Moreover, the motivations and barriers observed in U-I and U-G interactions might not be extrapolatable to U-R interactions.

Consequently, a specific study analysing interactions between academia and regulatory authorities in the context of drug development could broaden the scope of research on academic engagement to regulators and add new insights into the dynamic interactions of academics with various stakeholders. Starokozhko et al. provided a fundamental basis of ongoing issues and existing barriers between academia and regulators (16). The study pointed out the lack of mutual understanding and reliability of research findings as examples of barriers in drug development. Little attention on quality control and manufacturing guidelines in labs can hinder the application of academic findings to practice. In addition, academics' lack of knowledge of regulatory requirements and ethical issues also indicates the inefficiency of current communication media which regulators use to reach academia. Another barrier regarding communication mentioned in the study is its unidirectional feature. One-way conversation from regulators to academia could lead to limited interaction and the widening of gaps, further delaying the application of pharmaceutical findings to clinical patients. Also, many academics see insufficient incentives in interacting with regulators. Since publications and citations remain to be the most important goals for academics, an optimized reward system would be crucial for stimulating the involvement of academia, suggested by Starokozhko et al. The objective to overcome these barriers thus gave way to the STARS (Strengthening Training of Academia in Regulatory Science) project, which proposes regulatory science training as a means to achieve closer collaboration and efficient dialogue among academics in 22 European countries and European Medicine Agency (EMA) (16). We aimed to expand on the study of Starokozhko et al. and the broader academic engagement literature by providing insight into U-R interactions in the Netherlands in the context of drug development and regulation. In hope of gaining insights into how academia and regulatory authorities viewed their relationships, we conducted this interview study with specific research questions in mind. Firstly, what context of interactions are there between academia and regulators regarding drug development and regulation? Secondly, what could be the motivations for them to interact? Thirdly, what could be the motivations for them not to interact? And how do the points mentioned above compare with those of U-I and general U-G interactions? Lastly, what suggestions could be given to improve U-R interactions in drug development and regulation?

The focus on motivations and barriers which personnel from both sides perceive was expected to add value to the STARS project and give birth to more efficient measures that help strengthen the relationships between academia and regulators in drug development. With the mechanisms more understood, we supposed the observations from the study would assist policymakers, especially in the Netherlands, in making future decisions involving other parties. This was of specific relevance given the coming of EMA from London to Amsterdam due to Brexit. In addition to strengthening their relationships, we expected to detect new contexts of interactions that might exist in U-R interactions but not in other forms. Motivations to interact with academia valued by regulators were also expected to be more or less different from those valued by industrial partners. In academic engagement, different attributes like the non-academic party that's involved and the content of activities affect each other and the interaction as a whole. Therefore, the intricate relationships among these factors are crucial in shaping interactions between academia and non-academic parties. With more profound insights, we hoped to bring about harmonised relationships between drug regulatory agencies and academia.

METHODS

Study Design

This was an interview study in 2021 involving different professionals from Dutch academia and regulatory agencies. Referring to the findings of previous literature, we formulated our interviews protocols and divided them into 2 steps. A study that investigated academic motivations in U-I interactions served as a main template for our design (3). 4 piloting interviews were first conducted to get a general overview of the topic. After that, we expanded the scope and performed 17 more interviews where more specific and closed questions were asked to understand personal experiences. After both steps of interviews were done, the transcripts from the interviews were reviewed and analyzed with qualitative methods. Basic principles of inductive coding were used when analyzing the transcripts in this study. Inductive coding uses mainly the texts from the transcripts to generate nodes and has the benefit to yield a thorough and complete overview of the data.

Study Population

For the piloting interviews, 4 experts with a leading position in the field were selected for their comprehensive overview of U-R interactions in drug development and regulations. They were either senior regulators or academics who had links with both regulatory and academic environments. Ongoing direct participation in specific U-R activities at the time when these interviews were conducted was not the focus in this step. However, the selected interviewees had profound insights and extensive experiences in this regard. Among the 4 interviewees, 2 were from regulatory authorities and the other 2 were academics affiliated to Utrecht University, the Netherlands.

For the second step interviews, we included more individuals from regulatory authorities and Dutch academia. To gain more insights into specific examples and personal experiences, the interviewees were selected for their previous or ongoing participation in U-R interactions in drug development and regulations. Interviewees of this step covered a wider range of seniority, from junior researchers to board members of institutions. In the end, 2 regulators, 13 academics, and 2 experts from other organizations were interviewed in the second step interviews, with some academics (n = 7) having experiences in dual roles in both regulatory authorities and academia.

Data collection

This was a qualitative study with a two-step approach. We decided to conduct small-scale piloting interviews as the first step to get qualitative data on the overview of U-R interactions. Performing piloting interviews enabled us to map the current situation and relationships between academia and regulatory authorities in the context of Dutch and European drug development and regulation. Additionally, the piloting interviews served as the foundation for

the interview protocol for the following step 2 interviews. Previous studies on U-I interactions offered relevant materials that set the basis for the characteristics we could examine when studying U-R interactions (2, 3, 5-8). These studies further helped incorporate our interests into the outline of the interview protocol. Utrecht University's stakeholder report was used as the main framework for phrasing specific questions for the interview protocol (18). Since the focus of the report was broader than that of this study, we made some modifications to fit our study aims in drug development and regulations. The final protocol for piloting interviews consisted of questions on motivations, barriers, modes of interactions, and room for improvement (*Annex I*).

People participated in the interviews were contacted and invited via email. The objectives and methodology of this study were explained to the interviewees in the invitation letter. Before the interviews took place, interviewees either signed a consent form or gave consent verbally. The interviews were conducted online through Microsoft Teams in English, and each of them took approximately one hour. The interviews were video-recorded for generating transcripts. The transcribing process was assisted by MS Stream's caption auto-generating function, and the transcript drafts were later reviewed and edited manually to clean verbatim style by the transcriber. Timestamps were used when a new question from the questionnaire was asked by the interviewer. After the transcripts were ready, they were sent to the interviewees should they wish to clarify or modify the statements.

The interview protocol for step 2 interviews was based on the results and feedback from piloting interviews. The results from the piloting interviews appeared relevant to our research questions and provided insights we were expecting for. Therefore, we decided that the questions asked in piloting interviews were relevant and could be carried out with slight modifications in the next step. The main structure and focus of the step 2 interview protocol remained the same, only the questions were more closed and focused on personal experiences. For instance, instead of asking general motivations for academics as a whole to interact with regulators, personal motivations for academics as an individual to interact were asked in step 2 interviews. Using the protocol described in *Annex II*, we approached the interviewees, conducted the interviews, and handled the recordings the same way as done for piloting interviews.

Data analysis

The completed transcripts were imported into NVivo 12 Pro for qualitative analysis. Keeping our research questions and the way interviews were conducted in mind, we decided to apply the basic principles of inductive coding to analyze the texts from both piloting interviews and step 2 interviews. Inductive coding is an analytical approach where predetermined codes were absent. Instead of searching for texts that fit predetermined codes, codes were generated from the dataset being analyzed. Even though there wasn't a set of predetermined codes in

our case, major themes were set before analyzing the transcripts. These themes were the context of U-R interactions in drug development, motivations for academics and regulators to interact, barriers faced by respondents when interacting, and suggestions to improve U-R interactions in drug development. For the codes under different themes, they were directly derived from the responses of the interviews as we didn't use other existing frameworks or codebooks. That way, we could have a thorough and less biased look at the topic. In some cases, the same quote could be coded under different codes.

RESULTS

A total of 21 people were interviewed from May to September, 2021. 11 of which were academics, 4 regulators, 4 with dual roles in academia and regulatory authorities, and 2 from other organizations in the Netherlands. Academics interviewed were mostly researchers in Dutch Universities or University Medical Centers. On the other hand, the regulators were employed either by European Medicine Agency or Dutch national regulatory authority. Among all the interviewees, about half of them were male, and the other half female. In terms of seniority, we included people of all levels, ranging from junior researchers to senior professionals in more advanced stages in their careers. The characteristics of all respondents are depicted in *table 1*.

Table 1. Characteristics of respondents. RA: Regulatory Authority. NRA: National Regulatory Authority or inspectorate services. EMA: European Medicine Agency.

Respondent	Category	Organization	Role	Expertise	Regulatory Affiliation
R1	RA	NRA	Product-program manager		
R2	RA	EMA	Policy maker		
R3	Academia	University	Faculty	Regulatory science	Former board member at NRA
R4	Academia	Medical Center	Faculty	Clinical epidemiology	Former board member at NRA
R5	Academia	Medical Center	Pharmacist	Regulatory science	Former expert at EMA Former assessor at NRA
R6	Academia	University	Faculty	Toxicology	Regulatory project collaboration
R7	Academia	University	Faculty	Pharmacology	
R8	Academia	University	Faculty	Sustainability	
R9	Academia	University	Business developer/ Policy maker	Business development	
R10	Academia/RA	University/EMA /NRA	Faculty/ Assessor	Regulatory science	
R11	Academia/RA	University/EMA /NRA	Faculty/ Assessor	Pharmacovigilance	
R12	Academia/RA	Medical Center/ NRA	Faculty	Pharmaco-epidemiology	
R13	Academia	Medical Center	Non-faculty	Regulatory science	

R14	Other	Funding agency	Business developer/ Policy maker		
R15	RA	EMA	Project-program manager	External collaboration	
R16	Other		Consultant		Former expert at EMA Former assessor at NRA
R17	Academia	Medical Center	Physician/ Faculty	Oncology	
R18	Academia	University	Faculty	Pharmaco-epidemiology	Regulatory project collaboration
R19	RA	NRA	Assessor	Methodology	
R20	Academia/RA	University/NRA	Faculty/ Assessor	Statistics	
R21	Academia	Medical Center	Product-program manager		

Context of interaction

Respondents described the interactions between academia and regulatory authorities as complex. It's important to note that most interactions also involved other stakeholders. Without other players, the picture that paints the holistic view of public health care and its regulations would not have been complete. However, certain interactions involving mostly the regulators and academics were identified in the interviews. Degree of formality and involvement of money aside, the context of these U-R interactions in drug development could be roughly categorized into product-specific and non-product specific interactions. The forms through which academics and regulators interact differed depending on this context.

For product specific interactions between academics and regulators, the aim was relatively clear-to get an approval of the product or a new indication. In this case, the discussions focused mainly on regulatory requirements, validity of the data, design of product development plans, etc. According to the interviews, an increasing number of academics was trying to file drug's registrations on their own, rather than collaborating with industries. They turned to regulatory authorities to look for possibilities for achieving this goal. Common interactions included scientific advice and, in some cases, informal discussions on drug development plans.

Furthermore, regulatory authorities and academia were also involved in non-product specific interactions. The contexts of these interactions were much broader in comparison to those oriented towards products, and were usually driven by knowledge exchange. Common

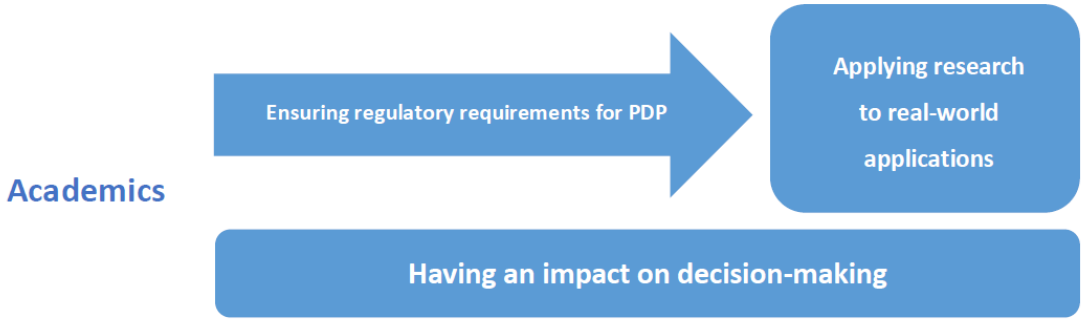
interactions of this kind were consultations, conferences, workshops, etc. Regulators made use of these interactions to keep up to date with the latest research findings, while academics gave advice on improving regulatory tools, methods or approaches or provided input from academic perspectives on public health issues. Additionally, these interactions were also one of the means for academics and regulators to discuss relevant research topics and potential collaborations to improve methodology or optimize regulatory systems. Despite the fact that these interactions were all about knowledge exchange, academics involved could take on different roles. For instance, some academics were part-time hired by regulatory authorities as seconded experts, while some presented their work as guest speakers. Seconded experts interviewed in the study were often academics who were consulted by regulators for their field of profession to inform the decision-making process. Even though the seconded experts weren't directly involved in making decisions, they contributed indirectly to the process by providing relevant knowledge. Some academics also came to regulators to get approval on the type of work they do. For example, getting a qualification procedure or an experimental method validated.

Motivations to interact for academics

Based on the interviews, the top three motivations for academics to interact with regulatory authorities were (I) ensuring regulatory requirements for product development plan, (II) applying research to real-world applications, and (III) having an impact on decision-making.

Notably, ensuring regulatory requirements for product development plan and applying research to real-world applications could be seen as separate elements, but also linked with each another to some degree (*Figure 1*). With applying research to real-world applications as the ultimate motivation, ensuring regulatory requirements for product development plan is a pathway or a sub-motivation to fulfil this. That is, increasing the chance of having products approved through ensuring regulatory requirements for product development plan also fulfilled academics' motivation to apply research to real-world applications.

Figure 1. Relationships among motivations to interact for academics. PDP: Product Development Plan



To begin with, academics were motivated to interact with regulators for ensuring their

product development plans. For many academic respondents who were working on product development, it was important to engage regulators at an early stage so they had a better overview of the plans' trajectory. Coming together with regulators allowed academics to know what was expected from regulatory perspectives. Feasibility of data, administrative files, and regulatory requirements were all important topics to discuss for successful product approval. To fill the gaps and make sure the plans were going on the right track was therefore a common incentive for many academics.

R9: "If you talk about market authorization of a new therapeutic, then it's very important that you have the insights from the regulatory authorities: How they will assess your dossier in the end? What data set is required in order for them to give a positive opinion? So it's very important that they are involved in an early stage of the development process. I think that is a strong motivator to interact with regulatory authorities."

R21: "I wanted to learn about what they're (regulators) looking for in data, so that I could support academia more, to be more focused."

R21: "One of the most important interaction I think was with the CBG-MEB, where we discussed the possibility to register the drug ourselves to ensure accessibility."

There were discussions on when to involve regulators in the development process. Normally, it's not mandatory to interact with them until the final evaluation stage. However, applicants were encouraged to come to regulators at an earlier time. An added value of involving regulators earlier in the development process was to prevent waste of effort. According to some academic respondents, detecting deficiencies or limitations of a plan sooner helped prevent the time and energy spent from going in vain. It was easier to fix obstacles when they first appeared than later, when they have grown into too big of a problem to be resolved.

R8: "Being aware of all the barriers together, instead of getting the barriers only at the end. Because then the loss would be way larger."

R9: "You want to prevent that you might be working on something for so long and in the end, the regulators say: 'Oh, this is not what we want.'"

Secondly, applying research findings to real-world applications and solving practical societal issues was crucial for academics regardless of the field of expertise. Respondents expressed their interests in doing research that is useful and answers more than fundamental questions. While publications still served as an important aspect, the feasibility of research in the real-world also played a huge role. For instance, doing research that in the end could improve regulations, or those with a potential to be implemented in industries. Academic respondents believed U-R interaction was the bridge that connected their research with reality, and having regulators in the process when deciding topics of research to dive into ensured its applicability. As a result, they were motivated to work on projects where they could collaborate with regulators. However, the subjects and context of the research project

collaborations were not specified by the respondents.

R6: "I'm also very motivated by working together with regulators in order to do research that's very useful, that could lead to improvements in regulation. So by working together with regulators right from the start of my research projects, we kind of co-create the research. We then make sure that we're doing the research that's really important for the regulators as well. So not only research that answers to fundamental questions, but also research that's really applicable."

Another motivation of academics was having an impact on decision-making. Since regulatory authorities were those that set the policies, it was obvious for academics who wished to make a difference in society to interact with them. Many academics expressed their willingness to voice opinions and provide input in the decision-making process along with regulators. In contrast to applying research to real-world applications, the motivation to have an impact on decision making doesn't necessarily involve bringing a specific finding to real-world. It could be achieved through contributing to the policy and decision-making process with academics' professional knowledge or sharing their perspectives. The consultations and discussions regulatory agencies held provided platforms for academics to do so. It was motivating for them to offer knowledge and perspectives that allow regulators to have a more holistic view when making policies. To some, the need to expand research beyond the scope of satisfying personal curiosity was profound. Giving supportive knowledge that regulators could take into account made academics feel part of the decision-making process that shapes the society.

R18: "I think from the work that we do now, you really have the opportunity to have an impact, broader than your own division. Because you also make decisions that have implications for the academic society. At least for the post marketing studies, you participate in a discussion somehow, so you have a say in that."

Academics interviewed in the study also mentioned for instance drug availability and improving the methodology in drug development as potential areas to improve. The current drug approval process, according to some, might not be suitable for all the medicines out there. Compared to most older drugs that were developed through chemical synthesis, the approaches used in drug development nowadays is different and more complex. This sometimes made clinical trial protocols established long ago inapplicable to novel therapies. Furthermore, drug repurposing-new medical indications for existing drugs-also called for a designated procedure more tailored to this category. With the speed of new chemicals and indications being discovered, many pointed out the importance of optimizing the current drug development procedure in keeping up with the rapid discovery in research. A common way for academics to express their thoughts and give feedback on the current drug approval process was via discussions. In this case, academics could be included in the decision-making process on refining policies of drug approval.

R21: "We explore any possible way to ensure access. We went for a pharmacy preparation, first of all. We also had interactions with all government institutes to see what the problem was, and how we could fix it.

R14: "Nobody really noticed too much about life after registration. The whole system beyond registration is a life of its own, and that has evolved into a whole new planet. Because nowadays it's not just new drugs entering, also old drugs reformulated and repurposed for new…(indications)."

Motivations to interact for regulators

For the regulators participated in the study, the motivations to interact with academics were (I) to access academics' knowledge and (II) to educate and introduce the regulatory system to academia.

To access academics' knowledge was the most frequently mentioned motivation for the regulators to interact with academia. Since regulatory authorities didn't have all the experts in house, they had to look for them externally in academia. This gave way to seminars and workshops where academics were sometimes invited as speakers to share their findings. Some regulators also consulted academics and asked for advice from time to time over phones or personal contact. For longer-term interactions, specific roles such as seconded experts in regulatory authorities were assigned to academics. Being at the forefront of research and knowledge generating centers, regulators believed academia had a lot to offer.

R2: "On our side with regards to being the regulator, access to expertise is a major motivator. Because academia is the knowledge centers-not just in Europe, but globally-it's very important, especially for a modern regulator, to have ready access to their expertise."

Knowledge that regulators wanted to access covered a huge range. For the various stages of the drug development process including research and development, quality control, clinical trial design, etc. All of the above interested regulators. Some regulators interviewed believed that academia played a significant role in discovering beneficial therapies for patients, especially those with rare diseases or unmet medical needs.

R10: "I think it's really important that drugs are being developed for the diseases where there's the most needs. And I think that academia is doing lots of research, and really finding new leads and new ideas for treating patients. So I think in that sense, it's really important that we facilitate that academic research is delivering the information we need."

Similarly, some regulators considered accessing knowledge an important way to better support decision-making as well. The intricate nature of the drug development process, inevitably, also brought obstacles of all kinds. It seemed to some regulators that the key to solving these challenges lied within academia.

R2: "One is sometimes to address research needs, and these are applied research needs. There can be a lot of challenges in pharmaceutical development, and obviously then, academia

broadly can help us resolve those challenges."

From a regulator's point of view in one of the piloting interviews, the input from academics helped regulators to reflect on and review regulations. It also served as a foundation for potential refinements of current policies.

R2: "If you've got academic organizations that are involved in running clinical trials in Europe, they can then lobby us regulator to say: 'Hey guys, you know, your guidance in this area is making life impossible.' So it's like influencing standards basically."

Another motivation that was mentioned less frequently for regulators to interact was to educate and introduce the regulatory system to academia, and further change their perceptions of regulators and the regulatory system. As part of the STARS aims, they believed it would be beneficial to foster awareness among academics of the regulations and practical aspects if their applications had to go through regulators. For example, filing drug registrations or methodology approval. They wanted to change how academics view regulatory affairs. Not just a regulatory body with bureaucratic impressions, but a team player that's also trying to improve public health together with other stakeholders. It seems like regulators recognized that there existed a lack of regulatory knowledge in academia, and elaborating the system helped academics more easily translate their findings. To improve this, regulators attended lectures on regulatory science as guest speakers, and EMA also assigned academic engagement officers to strengthen their connections with academia through discussions and issuing guidance for academic applicants.

R10: "We also provide some teaching on how we approved medicines. There we look at drug development programs, and how we make those assessments. To understand a little bit better how you satisfy the needs of the regulators if you want to advance drug development further than just having a nice publication in the end."

Motivations not to interact or barriers for academics

Frankly speaking, there were no motivations not to interact with regulators for academics found in the study. The relevance of coming together and collaborating was implicit. However, certain barriers were mentioned. According to the interviews, the three main ones were (I) lack of time, (II) lack of money or funding and (III) lack of regulatory skills to interact.

Lacking time was deemed the most frequently mentioned barrier for academics when interacting with regulators. This appeared to be universal to all contexts of U-R interactions in drug development. Since interacting with regulators was not part of their daily tasks, academics had to somehow sacrifice their free time to interact. In most cases, the life of academics and health care professionals was so hectic that it was hard for them to find extra time to be interacting. Therefore, some interviewees mentioned that U-R interactions were deprioritized over other research work or medical practice.

R11: "Well, they're (academics) not sitting there and waiting for us to ask a question, so they

might not have the time. That could be a barrier."

R20: "A lot of academics have to focus on research. They might say they don't have time to interact.

Under the same respect, interacting with regulators itself appeared to be time-consuming for the respondents. To really have an outcome, multiple times of discussions and back and forth meetings were needed before reaching a conclusion or making decisions. Since changes didn't happen overnight, most decisions took a fair amount of time and were built on long-term interactions. However, positive outcomes could never be guaranteed regardless of the time and effort put into. Some academics didn't find the time invested worth it if the end results failed to meet their expectations. This could be depressing especially for academics looking for alternative approaches to file registrations for their drugs. The discussions could take even longer as they were not following the regular and well-established path.

R13: "It takes very long time, and you don't know if you get an answer that you can work with."

Additionally, most academic respondents considered the time frame assigned by regulatory authorities tight. When regulators made a request for academic knowledge, the time left for academics to deliver the information was often too little. It became challenging for most academics to fulfil the requirements on such short notice. However, the context where these U-R interactions took place was not specified by the academics who reported tight time frames.

R18: "We have a strict timeline of when we should do certain things. And they (regulators) for example, always give very short time frames for reactions. Things like that are sometimes not achievable."

On top of time pressure, lack of money and funding was also reported to make academics less willing to interact with regulators. Most of the projects academics worked on together with regulators had limited, if not none, funding or other monetary rewards. Academics therefore had to seek other incentives to compensate for the lack of monetary benefit. Moreover, not only were the interactions underfunded, but sometimes cost money from the academic side. Regulatory authorities such as EMA and CBG-MEB provided all kinds of services that cost a fee. For instance, scientific advice or assessment was offered for drug applicants upon request and was recommended to have one or two before the end evaluation. Even though the discounts regulatory authorities had for Small-and-Medium Enterprises (SMEs) and academics helped, the fee still created financial burdens for some academics.

R2: "On the academic side, they might say: 'Well, I'd like to work with the regulator, but because there's no money, or because I can't publish… yeah, I have to do something else.'"

R9: "One is the cost involved. Because it's expensive to ask for a scientific opinion, or to have a dossier assessed."

R13: "For academia, it's a HUGE amount of money that you have to pay."

Mentioned almost as frequently as lacking funding, not having the knowledge or skills to

interact with regulators was also a barrier. To start with, many academics were unaware of how the regulatory system works, and had a hard time finding the entrance to their world. There seemed to be cases where academics had many questions in mind related to drug development that could potentially be solved by regulatory authorities, but they didn't know such a service existed. The most common pathway to start an interaction was via acquaintances. On the other hand, lacking connections in regulatory authorities made initiating interactions harder. Some academics had the intentions to interact, but were held back for not knowing the right people to speak with or the right organizations to go to. This barrier also appeared to be universal to the general contexts of U-R interactions in drug development, but especially in interactions where academics tried to file drug registrations.

R13: "For almost all academics in the Netherlands, they either don't know that the CBG exists, what they do, and what they can get from it."

R8: "It becomes easier when you have personal contacts already within CBG or EMA. So you need to build up these networks, and that takes a while."

More challenges followed after the interactions started. Most academics participated in this study struggled with the terms and the jargons regulators used. Because of this, regulators appeared to be somehow non-approachable. Furthermore, for academics whose profession was not regulatory science, it was overwhelming when all kinds of regulations and protocols were being introduced to them. However common and normal these might seem for regulators, the knowledge was quite beyond the scope of academics. This could potentially prevent academics with novel therapeutic findings from applying for drug registration.

R14: "The regulators spark all these sort of laws, and that's something the academics have never heard of."

R19: "I think an obstacle is that they (academics) are unfamiliar with the procedure with the expectations on what level of quality is expected, what documentation they should hand in."

Lacking regulatory skills to interact seemed to result in the inefficiency of U-R product specific interactions. Since this widened the knowledge gap between academic applicants and regulators, it took more time to get both parties on the same page compared to that with industrial drug applicants, who were experienced in this type of interaction with regulators like asking for scientific advice. The requirement for academics to fill the regulatory knowledge gap to efficiently reach regulators could potentially extend the already lengthy drug approval process even more time-consuming.

Motivations not to interact or barriers for regulators

Similar to that from academia, most regulators were motivated to interact. However, there were as well quite a few barriers that made interacting hard. The frequently identified barriers from the regulatory side included (I) lack of funding and (II) maintaining independence.

Limited funding stood in the way of U-R interactions in drug development, according to

the interviews. It appears that the budget governmental organizations assigned for regulatory authorities to interact with academia was insufficient. Without much funding, regulators were less driven to launch a project specifically on supporting and reaching out to academics. Likewise, regulatory authorities didn't have enough money to allocate staff for these tasks.

R8: "I don't know how much the budget for regulators is to spend on training and connecting with universities. I can imagine that that is not enough. But they always hoped that the government would give more on that aspect of longer term learning and connecting with research."

R2: "Resources are always limited in any system. But typically civil service and governments tend to be particularly restricted with headcount. So often there's a temptation to focus on short term objectives and deliverables just simply to keep the basic business going. The idea of investing in these longer-term objectives, which we know are good for the overall health of the institution, they can get deprioritized."

Furthermore, maintaining independence was also a barrier regulators faced. As an organization that's supposed to safeguard public health and the well-being of the public, some regulators felt that they should avoid potential conflict of interests as much as possible. Especially when the context was about specific products, regulators who had previous experiences in the vicinity-regardless of direct interaction or not-had to be cautious of maintaining a neutral position. It was also pointed out that there were cases when a research project from academia was conducted in collaboration with industries. In this sense, the involvement of multiple stakeholders made the situation even more complex.

R19: "Well, you can always give like a general advice on how things work, or how you can contact the CBG, or what's expected. But as soon as there's a product involved, you really, really need to be aware of your potential conflicts of interest."

R4: "There are research universities that work together with the industry. And the regulatory authority has to be independent, but then they get money from industries to do the assessment. So it's very, very complicated."

In addition to avoiding conflicts of interest, there seemed to be pressure from the public opinion as well, where interacting with other partners was discouraged.

R2: "Your average civilian would think: The job of the regulator is to regulate medicines. The job of the regulator is not to develop contacts with the academia, universities, etc."

Suggestions for academia

As part of the interview protocol, interviewees were asked if there were suggestions that could improve current U-R interactions. Both academics and regulators mentioned a few points that the other party could implement to potentially facilitate and benefit public health. For academia, (I) educating academics on regulatory affairs, (II) promoting the value of regulatory science, and (III) involving regulators early in development plans were mentioned in the

interviews.

It was considered beneficial to educate academics on regulatory affairs. Since this wasn't a widely taught subject in academia, few researchers or health care professionals had the regarding insights. However, knowledge in this field was considered relevant and helpful in facilitating U-R interactions in drug development. It was mentioned that academics who didn't receive regulatory training struggled with registering drugs. Since drug registrations must go through regulatory authorities, lacking the skills and regulatory knowledge to interact could stand in the way. Based on the interviews, specific subjects worthy of educating were the drug development protocols and the role of regulatory organizations. Having an overview of the protocols gives academics involved in drug registration or clinical trial design directions to follow instead of wasting time and effort navigating through uncertainties. To some academics, knowing where to find the regulators and the right questions to ask was as well a valuable skill. Some academics also suggested the establishment of platforms that help academics reach out and connect with regulatory authorities.

R21: "I think in the long term, the interaction and at least the knowledge in academia should improve on regulations."

R13: "There should be a place where people from academia can go to if they need to approach the CBG, or do anything with drug development. They know what routes there are so they can help them (academics) out, show them the routes to the CBG, and tell them what to expect."

R19: "For example, a person you can contact and say: 'Hey, we want to interact with EMA. Where do we start? What's your advice? When should we go?'"

In addition to gaining knowledge of the regulations, it was noted that academia could improve on promoting the value of regulatory science. Understanding the necessity of these rules in protecting public health and ensuring the safe use of drugs encourages academics to comply with them. Regulatory science, as seen by some interviewees, equally aided in bringing therapies to patients as other research fields did. However, it seems like the importance and popularity of regulatory science was less recognized in academia.

R16: "On the other hand, the researchers perceive regulators as nonscientific. So their topics of interest, which are more pragmatic, are sometimes perceived as inferior science. If you're having a project in pharmacovigilance or regulatory affairs, there will be some scientists who think you are doing inferior science. … I think they should not be that exclusive sometimes? And realize that regulatory science is equally good science."

One of the respondents suggested taking the societal impact of an academic into account to help promote regulatory science. Looking at contributions to society along with publications to evaluate a researcher's accomplishments could encourage more academics to pursue this field.

R10: "For example: How many interactions that academics have with agencies, regulators, or with reimbursement on getting something really developed and out there to patients. I think

that would help, if that is also acknowledged on your academic track records."

Another suggestion for academics was to involve regulators early in product development plans. Some respondents believed it gives applicants a more thorough idea of what to expect, and increases their chances of successful approval. Chances are, the data academics considered valid or enough could sometimes be irrelevant and insufficient for regulators. Understanding the regulatory requirements upfront helps academics think ahead and narrow the focus of their plans.

R21: "I strongly believe that that the academia should interact more and on an earlier level."

R1: "So what they (academics) are developing at least have a higher chance to fulfil these regulatory requirements. It is important that they're coming already at an early stage."

Suggestions for regulatory authorities

According to the interviews, the three main suggestions for regulatory authorities were to (I) increase the number of engaging regulators, (II) routinely review the efficiency of current regulatory procedures for academic drug applicants, and (III) enhance the exchange of human resources between both parties.

Firstly, it was recommended that regulatory authorities increase the number of engaging regulators. Not just being actively engaged in U-R interactions for the sake of interacting, but to adopt the engaging mindset that really helps to overcome barriers and work things out. To most academics, having regulators with an open attitude and that are willing to brainstorm with academics in guiding them through the regulatory process was appreciated.

R14: "Regulators need to be more flexible in how they interact, and how they use any system. They are in charge of the system, but they seem to be sort of fixed on the system."

R3: "Of course, certain rules should always be there. But have an open mind to think about it and to reflect."

It seems like it's rather unlikely that regulators can be born to be engaging. Instead of expecting engaging regulators to show up and interact with academia, some academic respondents pointed out the importance of educating and training regulators, allowing them to pick up the open attitude internally, and to acquire skills that facilitate U-R interactions in drug development.

R3: "That's also an attitude. Also, it needs certain communication skills. Those interactions don't fall from heaven, you have to train them. So it's also a question of training and education."

Moreover, regulatory authorities were suggested by respondents to routinely review the efficiency of current regulatory procedures for academic drug applicants. It would be appreciated if regulators examine the procedures critically from academics' standpoint. One way of achieving this was to ask fundamental questions about the policies. For example, why are these rules in place? Are these rules necessary and applicable to novel therapeutic products? Do these rules actually facilitate or do they place burdens instead? Ensuring

regulatory readiness for emerging innovative therapeutics and developments was considered important. Some interviewees also suggested regulators think about the possibilities of applying alternative approaches that still meet the standards. To sum up, up-to-date regulations that are feasible, have room for negotiation, and provide more flexibility would be appreciated. In some interviewees' opinions, it's important that regulations could be re-evaluated or tailored case by case.

R10: "It's not just: OK. This is the rule. Academic research is not completely following it. Now we need to think of: OK, why do we have that rule? Is this applicable? For this product, could you also get there in a slightly different way?"

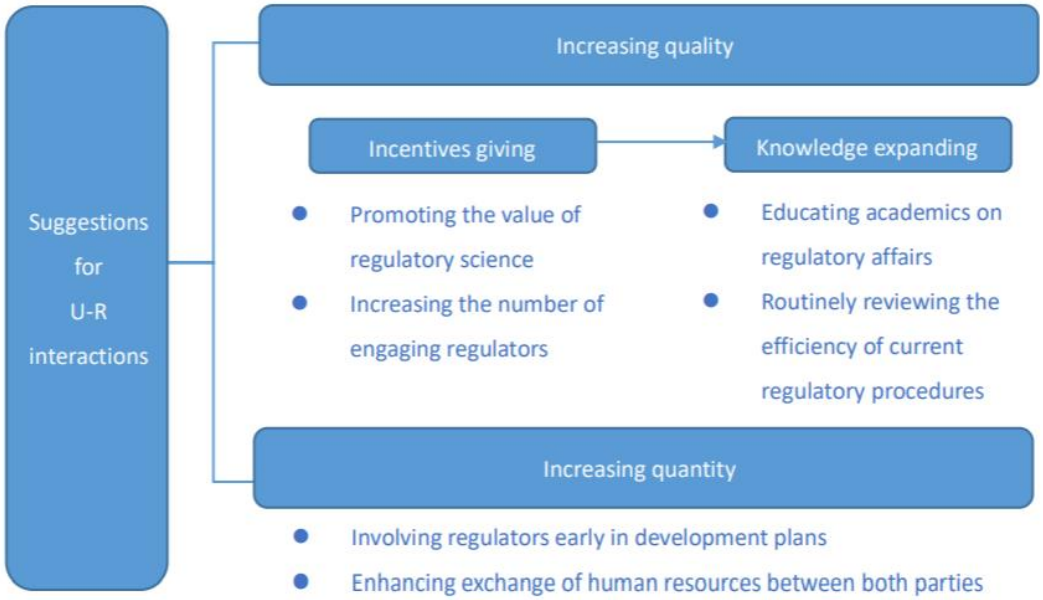
R14: "So they (regulators) need to critically review the system. I'm not an advocate of light registration, but I'm an advocate of trying to link sensible registration to facilitate the goal, which is to have a regulated product available to patients."

Lastly, some interviewees suggested enhancing the exchange of human resources between academia and regulatory authorities. To have a better understanding of each other, the most efficient way seems to be putting academics in regulatory settings and learning about the system. Having insights on how things work in both systems, these people should be able to comprehend and relate more to why academics and regulators think differently or similarly. With these perspectives, the chance for both parties to meet halfway and collaborate was expected to increase. Seconded experts, PhD students, and academics working in scientific committees are common examples of 'middle-man'. As stated by some respondents, having academics around in the group also makes it easier to keep regulators updated with academic knowledge, in comparison to regulators actively demanding knowledge exchange via holding consultations or workshops.

R16: "I think more regulators should do what they're doing: sponsoring research and funding research, collaborating, participating, doing this half-half part. So bring academia and regulators together. I think this should be continued and increased."

Generally speaking, the suggestions given by the respondents in this study appeared to boil down to two core concepts-increasing either the quality or quantity of U-R interactions in drug development (*Figure 2*). Increasing U-R interactions' quality could be further divided into incentives giving and followed by knowledge expanding. The suggestions of promoting the value of regulatory science and increasing the number of engaging regulators fell into the former, while educating academics on regulatory affairs and routinely reviewing the efficiency of current regulatory procedures belonged to knowledge expanding. The core concept behind involving regulators early in development plans and enhancing the exchange of human resources between both parties, on the other hand, was to increase the quantity of U-R interactions in drug development.

Figure 2. Categorization of the suggestions for U-R interactions in drug development and the core concepts they are based on.


Suggestions for U-R interactions
Increasing quality
Incentives giving
Knowledge expanding
Promoting the value of regulatory science
Increasing the number of engaging regulators
Educating academics on regulatory affairs
Routinely reviewing the efficiency of current regulatory procedures
Increasing quantity
Involving regulators early in development plans
Enhancing exchange of human resources between both parties

DISCUSSION

Summary of the results

Our study provides profound insights on different aspects of U-R interactions in the context of Dutch and European drug development and regulation. The context of interactions described in the study reveals the extensiveness of the fields regulators and academics are working together on. Evaluating products and granting approval are only parts of the whole picture. Our study identified several non-product specific interactions around knowledge exchange which include meetings, discussions, and being guest speakers giving lectures or presentations. Even though the sample population (n=21) in the study might not be sufficient to represent the views of all academics and regulators, we observe a general positive attitude towards U-R interactions from the participants. Academics turn to regulators to ensure regulatory requirements, have real-world applications, and have an impact on decision-making. Regulators reach out to academics for their knowledge and introducing the regulatory system. Like all interactions, certain barriers that might elevate the threshold for interacting do exist. Lack of funding appeared to be a mutual barrier shared by academics and regulators. For specific barriers, lacking the regulatory knowledge and the skills to interact account for the most frequently mentioned barriers that could prevent academics from interacting with regulatory authorities. On the other hand, maintaining independence seemed to be a common concern of the regulators. To improve the current situation, exposing academia to regulatory knowledge and having engaging regulators to reach out to academia seem to be helpful. With identifying the motivations and barriers of U-R interactions in drug development, the study brings more understanding to both sides, and assists in making policies that maximize the benefit of public health.

Implications

Our first finding on the context of U-R interactions suggests that the concept of regulatory science is extremely broad, and the context where U-R interactions take place goes beyond product-specific interactions. Non-product specific interactions such as knowledge exchange, reviewing regulations, and evaluating the regulatory system imply other potential areas for academics and regulators to collaborate on. The different context of interactions we find that are non-product specific aligns with the three regulatory science dimensions described in a previous study, which included (I) keeping up with the best science, (II) developing and validating evaluation tools to assess pharmaceutical products, and (III) evaluating the regulatory system on its impact on enhancing different aspects in public health (17). For the non-product specific interactions found in our study, we could allocate them to the three dimensions with some modifications. The classifications we ended up having are (I) knowledge exchange, (II) validating methods, and (III) evaluating regulatory system.

Many people-based activities in U-I and general U-G interactions mentioned in a

university knowledge exchange study also exist in U-R interactions in drug development and regulations (2). Examples of these activities in U-R interactions include lecture giving, consulting, advising, and student placement. However, interactions that involve getting approval from the regulatory authorities, either on experimental methods or pharmaceutical products, are not recognized in U-I or general U-G interactions. For academics in U-I interactions, extrinsic motivations like financial reward were the main ones academics keep an eye on when interacting (2, 8, 11). By contrast, accessing grants and securing funding don't seem to be as dominant in motivating academics to interact with regulators in drug development U-R interactions.

As the context of interactions varies, there also seems to be a distinction in motivations that underlie different interactions. For product specific interactions like filing a drug's registration, as well as scientific advice and discussions that follow, the main motivations for academic applicants are to have real-world applications and to ensure regulatory requirements for registering the drug. While having real-world applications remains a major motivation for academics, ensuring regulatory requirements is less presented when it comes to non-product specific interactions. Academics in this scenario are instead motivated by having an impact on the decision-making process. This motivation is seen in interactions such as meetings, discussions, advice-giving, and consultations, where academics could provide regulators with input and supportive information when making decisions. Having an impact and applying research to real-world applications correspond to the intrinsic motivations described in previous studies on U-I interactions (8, 9, 11, 12). This suggests that as long as the context of interactions is not about products, the stakeholders involved accounts little for academics' intrinsic motivations to interact. If academics could fulfil their motivations to have an impact or apply their research, interacting with either industry or regulators doesn't seem to make a difference. Although intrinsic motivations were reported more often in our study, it is unclear whether they play a more important role in U-R interactions than in U-I interactions.

For the regulatory side, accessing academic knowledge is the motivation presented in most U-R interactions, especially when regulators are the ones who initiate the interactions. That is, interactions where regulators actively reach out to academics. However, there are different reasons why regulators wish to access academic knowledge. Depending on the context, the underlying reason could be keeping up-to-date with the latest findings, gathering relevant information that better supports decision-making, or reflecting on current regulations and procedures based on academics' opinions. Making use of academics' expertise is another motivation when it comes to research project collaborations and human resources exchange. In comparison to one-time meetings or lectures, these interactions often occur over a longer period of time. *Table 2* summarizes the matching motivations to the different contexts of U-R interactions.

*Table 2. Context of U-R interactions with matching motivations for academics and regulators. The color of the texts under the column 'Context of interactions' represents the different directions of the interactions. Black: bi-directional; Green: from regulators to academics; Blue: from academics to regulators. *: Scientific advice and meetings and discussions are more specific interactions under the broader interaction on drug registration*

	Context of interactions	Motivations for academics	Motivations for regulators
Product specific	Drug registration	Applying research to real-world applications	Being involved is mandatory for product specific interactions
	Scientific advice*	Ensuring regulatory requirements for product development plans	
	Meetings and discussions*	Ensuring regulatory requirements for product development plans	
Non-product specific	**Knowledge exchange**	Having an impact on decision-making Applying research to real-world applications	Accessing academic knowledge to keep up-to-date on the latest findings Accessing academic knowledge to better support decision-making Educating and introducing the regulatory system Accessing and making use of academic expertise for longer term collaborations Accessing and making use of academic expertise for longer term collaborations
	Personal contact		
	Guest speaker at workshops		
	Meetings and discussions		
	Guest speaker at lectures		
	Research project collaboration		
	Human resources exchange		
	Validating methods		

Being consulted or advising on regulation and procedure improvement	Having an impact on decision-making	Accessing academic knowledge to reflect on current regulations and procedures
Getting approval of methodology	Applying research to real-world applications	
Research project collaboration	Applying research to real-world applications	Accessing and making use of academic expertise for longer term collaborations
Human resources exchange		Accessing and making use of academic expertise for longer term collaborations
Evaluating regulatory system		
Meetings and discussions	Having an impact on decision-making	Accessing academic knowledge to reflect on current regulatory system
Research project collaboration	Applying research to real-world applications	Accessing and making use of academic expertise for longer term collaborations

For barriers in U-R interactions, a mutual one that academics and regulators share is lacking money and funding. Previous studies on U-I interactions showed monetary reward being one of the main motivations (2, 8, 11). In this study, we discovered that lacking it could be preventing both academics and regulators from interacting. Academics usually receive very limited funding for regulatory projects. Sometimes they even have to invest money for product specific interactions. It almost appears that regulators are too demanding but unwilling to offer in this regard. Interestingly, however, regulators experience similar issues. Even if they're willing to offer more discounts or funding to academics, it could be challenging to do so if they don't receive enough money from the government. Since they function on the money allocated by governmental organizations, limited budget from the government on facilitating U-R interactions leaves regulators with little flexibility in giving funding. This points out potential room for improvement on a higher level in terms of national policy and resources distribution. Usually, the amount of budget government issues for certain areas corresponds to the amount of attention those areas receive. Areas that have the most need and focus tend to receive more budget. Therefore, promoting the importance of regulatory science and how firm U-R interactions can benefit public health might be a sensible step to take for solving this problem.

When it comes to suggestions, some of them given by the respondents in this study are

in line with the key steps mentioned in the STARS project to improve the regulatory dialogue (16). In the STARS project, for example, academia implementing regulatory science in educational programs and academia planning an early dialogue with regulators were suggested. They match respectively to the suggestions in this study, which are educating academics on regulatory affairs and involving regulators early in development plans. The other suggestions such as promoting the value of regulatory science, increasing the number of engaging regulators, routinely reviewing the efficiency of current regulatory procedures for academic applicants, and enhancing the exchange of human resources between both parties are newly discovered in this study.

From the interviews, it seems like current interactions between academic drug applicants and regulators can be inefficient. In interactions about registering a drug, regulators tend to restate and explain the requirements listed in guidelines. Even though academics seek more guidance, they lack the skills to clearly express their doubts and needs in ways regulators could understand for issuing more specific guidance. This might lead to discussions where no progress is made. To improve the quality and efficiency of this type of U-R interaction, the first step is to give regulators and academics the incentives to interact (*Figure 2*). It is important that they see the benefits their interactions could bring, switching their mindsets from passively participating to actively engaging in U-R interactions. Promoting the value of regulatory science in academia and increasing the number of engaging regulators serve this purpose. After having the incentives, academics and regulators could expand their knowledge of the other side to better understand how each other perceive things. More understanding of both systems should further improve the efficiency of product specific U-R interactions since consensus should be reached more easily. Educating academics on regulatory affairs improves the regulatory knowledge in academia, and regulators taking academic drug applicants into account when reviewing the efficiency of regulatory procedures helps in providing flexibility and making development plans executable for them. In terms of increasing the quantity of U-R interactions, involving regulators early in development plans to have more frequent discussions is suggested. Similarly, regulators are advised to enhance the exchange of human resources between both parties.

Strengths and limitations

As far as we are concerned, this study is the first to look at the interactions between university and regulatory authorities in the context of drug development and regulation. Many contexts of interactions that are absent in U-I and U-G interactions are newly discovered in our study, such as product specific interactions like drug registration and scientific advice. With the various context of U-R interactions, we also found motivations and barriers that are not discussed in previous literature. This is especially due to the policy and decision making role of the regulators. In this case, academics ensuring regulatory requirements for the product

development plan, having an impact on decision-making, and regulators educating and introducing the regulatory system are motivations found in U-R interactions in drug development but not the others. In the same regard, academics lacking the regulatory knowledge to interact with regulators is also an exclusive barrier for U-R interactions in drug development. Moreover, the results were derived from first-hand responses of diverse and experienced experts engaged in U-R interactions. From broad overview to specific personal experiences, their responses allow us to address U-R interactions from all angles.

Like all studies, our study also has some limitations. To begin with, the number of regulatory participants and that of academic participants was uneven. Excluding the participants with dual roles, those who are partially an academic and partially a regulator, there turned out to be 11 academics, but only 4 regulators. This might end up with results that are based on imbalanced academic and regulatory input. Secondly, the total number of participants (n=21) might be too small to represent all academics and regulators in drug development. Our findings could therefore be subject to sampling choices. Furthermore, the transcripts were reviewed and analyzed by one coder. Individual opinions of the coder might affect the interpretations of the transcripts. Lastly, the focus of our study was mainly within the scope of the Netherlands and interactions on drug development. Features and characteristics of the U-R interactions presented in the study might not represent or generalize the U-R interactions taking place in other countries. U-R interactions in contexts other than drug development such as medical devices, food, and cosmetics could also demonstrate different features and characteristics. However, the valuable insights and findings of this study still outweigh its potential limitations.

Future research

The study provides novel insights and establishes a great foundation for future research to expand on. For example, our study could give birth to surveys that investigate the importance of different motivations and barriers. Through surveying a larger population, the responses should generate quantifiable data that reflects broader academic and regulatory perceptions. Furthermore, the surveys could also be expanded and investigate the U-R interactions in other European countries and contexts other than drug development, such as medical devices, food, or cosmetics. Given the complex nature of the drug development process, another potential aspect to investigate is the relationships among various stakeholders involved. For instance, the interactions among industry, academia, and regulatory authorities.

Conclusions

Despite different backgrounds and expertise, both academics and regulatory authorities have the same ultimate goal in mind-bringing timely access to safe and effective drugs to patients. Academics are motivated to bring the latest findings to real-world, and regulators are also

eager to access expertise that benefits patients. For certain barriers pointed out in the study that prevents academics from interacting, this study provides suggestions with practical measures policymakers could implement to improve the situation. For example, educating academics on regulatory affairs through lectures or seminars could overcome barriers for academics like lacking the regulatory skills to interact. Even though there is plenty of room for improvement, the findings of this study provide an insightful starting point for academics and regulators to head together towards the direction of optimizing U-R interactions in drug development.

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ANNEX

Annex I – Interview protocol for piloting interviews

Q1. What do you think the motivations are for academia and regulators to interact?

Q2. What types of interactions are there?

We came up with a potential categorisation of types of interactions (show below table). What do you think of this proposed categorisation? Could you think of interactions that fit in this categorisation? Are there any other interactions that don't fit in this categorisation? Can you think of an alternative categorisation that would better reflect how you view U-R interactions?

	Level of interaction		
	Individual	**Organizational**	**Discipline**
Formal			
Informal			

Q3. Is there a need for improvement of U-R interactions?

Potential following question to ask:

What could be done to facilitate the type of U-R interactions you just pointed out?

Q4. What could be motivations not to interact?

Q5. Are there any drivers or barriers not yet mentioned?

Q6. Are there any other points you would like to raise in regards to U-R interactions? Or perhaps suggestions for this research project?

Annex II – Interview protocol for step two interviews

Part I – Modes of interactions

Q1. Please briefly describe your personal experiences in U-R interactions.

[Keep these questions in mind – are these questions answered?]
With whom have you interacted with?
What were the interactions about?
Reflect on the different categorization method: Is it about a product, a therapeutic category, or systematic procedures? Were there any contracts or money involved?
When you interacted with the regulators, did you interact as an individual? Or did you interact on behalf of your institution/organization as a representative?

Part II – Barriers and facilitators

[Keep the framework from Step 1 interviews in mind, clarify if the interviewees are referring to one of the existing categories when needed]

Q2. What were the factors that motivated you to interact with regulators/academia?

Q3. What could be your motivations not to interact?

Q4. Were there any obstacles you've encountered in these interacting experiences?

Part III – Outcomes of the interactions

Q5. Did the outcomes from the interactions meet your expectations and motivations in the end? How were they met? If not, in what way were they not met?

Q6. Based on your previous experiences, what general suggestions would you give to improve the overall U-R interactions?