Queries Raised During Oncology Business Pipeline Meetings at the European Medicines Agency: A 5-Year Retrospective Analysis

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The European Medicines Agency (EMA) offers guidance and support to pharmaceutical companies through bilateral discussions called business pipeline meetings (BPMs). An analysis of BPMs in oncology over a 5-year period was conducted to identify common topics and recurring queries. The documents of all BPMs available at the EMA regarding the field of oncology from January 1, 2018, to Decemer 31, 2022, were reviewed. For every query, a main category was assigned, and in case of multiple relevant topics, a secondary category was appointed too. For all queries, the follow-up offered by the EMA was documented, and whether the requested information was available. Subsequently, all queries were scanned for overlapping topics between meetings. From 2018 to 2022, 31 BPMs were held between the EMA and pharmaceutical companies to discuss oncology-related questions, for a total of 397 queries raised. They were classified into 24 topics, of which 15 were common topics ($n \geq 10$ queries) with regulatory pathways/guidelines and trial design having the most queries. Post-BPM actions were taken or recommended by the EMA for 41.3% of queries, such as referrals to scientific advice or published guidelines. Forty-three queries were raised at more than one BPM. Targeted therapy, companion diagnostics, institutional collaboration, trial design, and regulatory pathways/guidelines were the most discussed topics in oncology BPMs, with molecular developments being the common denominator. Creating Q&A documents, publishing new guidelines, providing a framework for discussions, and questionnaire-based follow-up research can improve the quality of BPMs, and the accessibility of the information requested during the BPMs.

Study highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ This is the first published analysis of the business pipeline meeting platform offered at the European Medicine Agency.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The study addresses the value of the business pipeline meeting platform as a tool to support the development and evaluation of new and innovative medicinal products.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The study shows how the business pipeline meeting platform represents a valuable tool for the developers of medicinal products and provide insight on key challenges in the development of oncology medicines.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The business pipeline meeting is a further layer of interaction the developer can have with the regulators to initiate early-stage dialogue on their pharmaceutical development, in preparation for subsequent product-specific and multi-stakeholder discussions.

The European Medicines Agency (EMA) is a medicine regulatory authority which aims to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union.[1,2] A regulatory environment that supports innovation is necessary to achieve these goals. Pharmaceutical companies can obtain guidance and support for the development of medicinal products through different modalities.[1,3–11] For instance, one of the core responsibilities of the EMA is to offer scientific advice to pharmaceutical companies on individual medicinal products before their respective marketing authorization applications are submitted.[1,7,11] Furthermore, the EMA holds bilateral discussions with applicants of marketing authorization in so-called "business pipeline meetings" (BPMs) as part of its business analysis and forecasting strategy.[9,12]

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Both scientific advice meetings and BPMs are confidential discussions between the EMA and pharmaceutical companies but they differ in scope. Where scientific advice meetings focus on individual products, BPMs provide a platform for an overarching dialogue regarding medicine pipelines. The BPMs enable the EMA to stay up to date with advancements in science and drug development, and improve regulatory science.[9,12] These BPMs are initiated by large pharmaceutical companies seeking guidance from regulators on the optimal approach to develop and submit their product portfolio. The discussions in BPMs cover broad queries that, for example, apply to multiple comparable products, or improve regulatory pathways, including matters such as legal issues, pediatric investigation plans, regulatory aspects, and other queries which are outside the scope of scientific advice meetings.[13] The primary focus of BPMs is the discussion of key features, obstacles, and innovations associated with medicine pipelines. The information obtained during BPMs is swiftly shared throughout the regulatory network, enabling the EMA to make informed decisions about its activities and work plan. BPMs also facilitate early-stage conversations that serve as precursors to subsequent product-specific and multistakeholder discussions. Regulators can critically evaluate the regulatory framework while gaining exposure to the challenges associated with drug development and changes in the pharmaceutical industry. Moreover, BPMs have contributed to defining the EMA's regulatory science strategy to 2025.[14]

The rapid advancements in the field of oncology in research techniques and treatment opportunities pose new challenges for pharmaceutical companies, particularly in clinical trial development and regulatory pathway protocols.[15–20] Therefore, oncology is an interesting field to determine the added value of the BPMs in the development of medicine pipelines. In this paper, we describe an analysis of BPMs in oncology over a 5-year period to identify common topics, recurring queries among different BPMs, and the availability of requested information to pharmaceutical companies.

METHODS

A review of all internally available documents pertaining to oncology BPMs was conducted at the EMA, including company presentations and meeting minutes from January 1, 2018, to December 31, 2022. Meetings without BPM minutes were excluded. Data collected from each meeting included the requesting company name, the meeting date, the number of queries raised, and the exact wording of each individual query. Queries were categorized by topics based on expert judgment, with each assigned a main category, and in case of multiple relevant topics per query, a secondary category appointed too. Common topics were defined as those with at least 10 queries across main categories and secondary categories combined. The post-BPM actions were documented as taken or recommended by the EMA for each query, as well as the availability of the requested information at the EMA. Recurrent queries were identified and paraphrased, with their main category and frequency of occurrence documented. Statistical analysis was conducted using R version 4.2.1 (The R Foundation, Vienna, Austria) and the tidyverse package.

RESULTS

Over 5 years, 31 BPMs transpired with queries related to oncology (6 BPMs in 2018, 2 in 2019, 8 in 2020, 8 in 2021, and 7 in 2022). One meeting in 2022 was excluded for further analysis because the post-BPM minutes were missing. The 30 remaining BPMs were requested by 20 separate large pharmaceutical companies with a yearly revenue between $0.1 and $100 billion. Fourteen out of the 20 companies convened with the EMA for a BPM once, whereas 4 companies convened with the EMA twice, and 2 companies 4 times.

Query topics

A total of 397 queries related to oncology were raised over the 5-year period, with each BPM receiving a median of 13 queries (range: 3–32 queries). The queries were classified into 24 topics (see **Table 1**). All queries were assigned a main category, and for 282 queries (71%) a secondary category was required to fully encompass the query topic. The assigned main categories and secondary categories were subsequently combined to provide a comprehensive overview of the BPM queries as illustrated in **Figure 1a**. Among these topics, 15 had more queries than the common topic cutoff, with regulatory pathways/guidelines having the most queries ($n = 144$), followed by trial design ($n = 79$), institutional collaboration ($n = 56$), companion diagnostics (CDx; $n = 50$), and targeted therapy ($n = 47$). The percentages of topics for the main categories and the secondary categories separately are portrayed in **Figure 1b,c**, respectively.

Table 1 Query topics in oncology business pipeline meetings

Query topics
Biomarkers
Combination therapy
Companion diagnostics
Control therapy
Current affairs[a]
Digitization
Drug administration
End points
Grievances
Inspections
Institutional collaboration[b]
Legal affairs
Non-clinical data
Orphan drugs
Pediatric development
Post-authorization data
Practical matters
Product details
Real-world evidence
Regulatory pathways/guidance
Safety
Targeted therapy
Trial design
Unmet medical need/priority medicines (PRIME)

COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; EU, European Union.
[a]For example, COVID-19 and Brexit. [b]Either between bodies in the EUand the EMA or between bodies outside of the EU and the EMA.

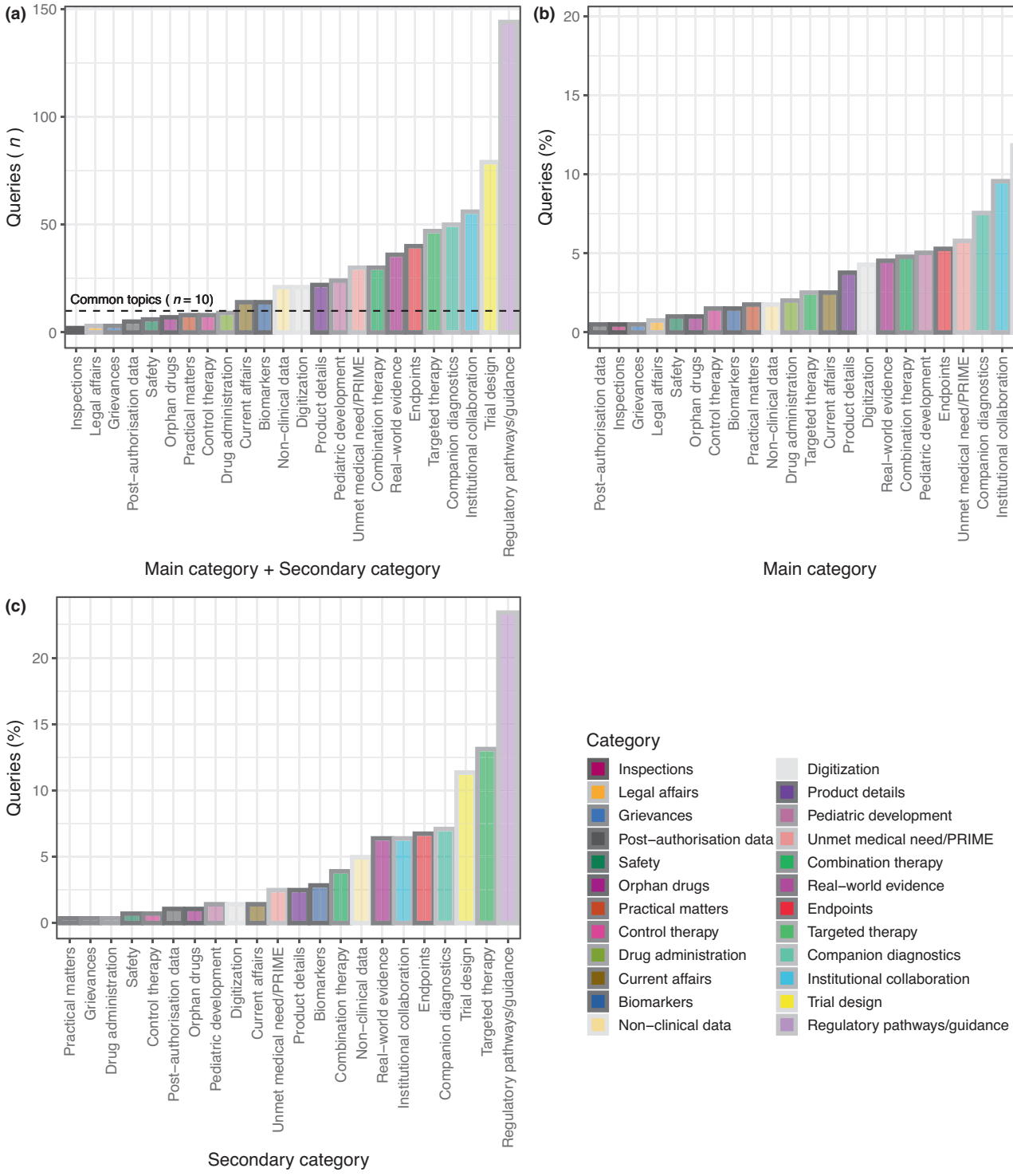

Figure 1 Categorized business pipeline meeting queries in oncology between January 1, 2018, and December 31, 2022. (**a**) Main categories and secondary categories combined. Dashed line is cutoff of 10 queries for common topics. (**b**) Main categories only. (**c**) Secondary categories only.

Information availability and post-BPM actions

The information requested by the companies was available for 320 queries, whereas it was unavailable for the remaining 77 queries (ongoing discussion at the EMA: $n = 28$, out of scope/time: $n = 49$). As depicted in **Figure 2**, post-BPM actions were taken or recommended by the EMA for 41.3% of queries in the form of a referral to scientific advice ($n = 63$), a referral to published guidance either at the EMA website or available online elsewhere ($n = 32$), an adaptation of guidance or the writing of novel guidance ($n = 23$), a referral to pre-submission meetings, *post hoc*

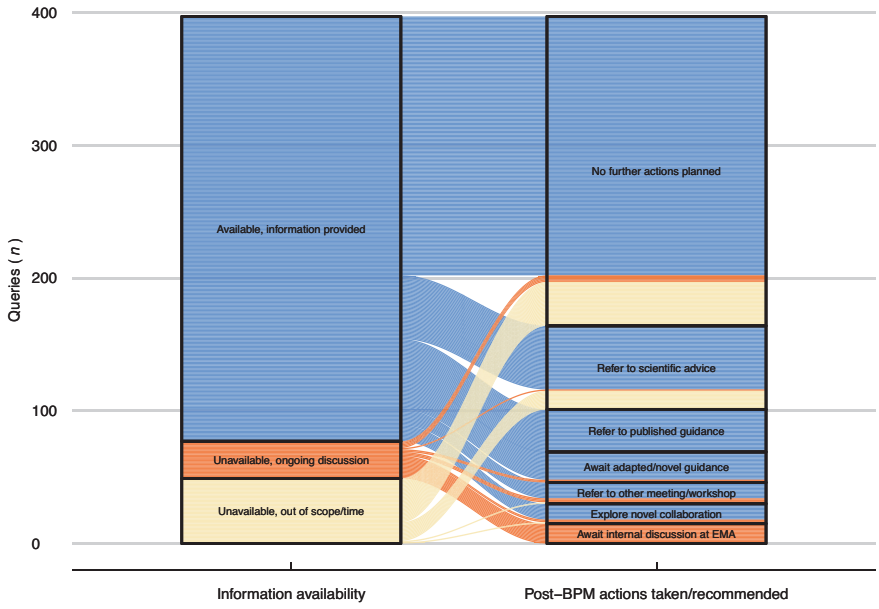

Figure 2 Alluvial diagram of the 397 queries raised during the oncology business pipeline meetings (BPMs) between January 1, 2018, and December 31, 2022. The diagram displays the availability of the information requested by the company, and the actions taken by the European Medicines Agency (EMA) in response to the query.

meetings, or workshops ($n = 16$), a novel collaboration with the company or other relevant stakeholders ($n = 15$), or a referral to follow-up communication following additional consultation at the EMA ($n = 15$). No post-BPM actions were planned for the remaining 58.7% of queries, although it is worth noting that for 195 of these 233 queries the requested information was available at the EMA directly during the meeting.

Recurrent queries

In total, 43 queries, paraphrased in **Table 2**, were raised at more than one BPM. The median number of BPMs in which a query recurred was 3, whereas one query recurred across 12 BPMs. Interestingly, 3 of the 43 recurrent queries were raised during multiple BPMs but were raised by one pharmaceutical company. The main categories of recurrent queries included safety, biomarkers, unmet medical needs/PRIME, targeted therapy (each with one occurrence), current affairs, drug administration, real-world evidence (RWE; each with 2 occurrences), pediatric development, end points (each with 3 occurrences), combination therapy, institutional collaboration (each with 4 occurrences), regulatory pathways/guidance, CDx (each with 5 occurrences), and trial design (with 9 occurrences).

DISCUSSION

Oncology BPMs facilitate bilateral discussions between major pharmaceutical companies and the EMA regarding medicine pipeline challenges in scientific development and regulatory affairs. Over a 5-year period from 2018 to 2022, 15 topics were common ($n \geq 10$) in oncology BPMs, with the 5 most frequently mentioned topics being targeted therapy, CDx, institutional collaboration, trial design, and regulatory pathways/guidelines. Although these common topics accounted for 92% of the queries, only 43 queries for the subject matter had exact correspondence between at least 2 BPMs, and only 40 of these recurrent queries were raised by multiple companies. This indicates that although the topics discussed in BPMs may be limited, the specific information sought varies widely. The EMA was able to provide the requested information for ~80% of queries. However, for 195 of 320 queries, the information was available, but no post-BPM actions were provided or recommended by the EMA. For many of these queries, the answer provided during the BPM will have been sufficient for the company, but to analyze this direct feedback from the companies will be required.

To obtain the overarching theme for the top 10 frequently discussed topics in oncology medicines pipelines, we concluded that the common denominator was molecular developments. Molecular markers have paved the way for targeted therapy, leading to the necessity for the development of CDx to identify which patients would benefit from treatment, for which queries led to the adoption of the In Vitro Diagnostics Medical Device Regulation in 2017.[21] The reclassification of tumors based on molecular markers also raised queries about patient groups with unmet medical needs and the need to explore novel trial designs, including the use of RWE, to compensate for smaller cohort sizes.[16,22] Additionally, molecular markers, such as circulating tumor DNA, can be promising novel end points and potential surrogates for overall survival.[23,24] Moreover, varying points of view between medicines regulatory authorities of preferred regulatory pathways for molecularly classified tumor groups require more institutional collaboration especially when related to pediatric development.[25,26] Finally, tumors with multiple molecular targets create opportunities for combination therapy with targeted therapy, immunotherapy, or chemotherapy.[27]

Several measures can be taken to enhance the accessibility of information at the EMA such as the creation of online questions and answers documents (Q&As), the publication of new guidelines, and the updates of existing ones. For example, by transforming

Table 2 Paraphrased recurring queries in oncology business pipeline meetings ranked by main category and the number of meetings the query was raised

Main category	Question	Meetings
Trial design	What is the EMA's view on **single arm studies** with historical/RWE data as control?	6
	What is the EMA's view on innovative **trial designs**?	5
	What is the EMA's view on a tumor/tissue agnostic **trial design**?	4
	What is the EMA's role in the adoption and execution of **master protocols**?	3
	What is the EMA's recommended **trial design** when using RWE data?	3
	What is the EMA's view on **patient preference studies**?	3
	What is the EMA's recommended **trial design** for combination therapies?	3
	What is the EMA's view on **remote patient monitoring**?	2
	What is the EMA's view on implementation of **decentralized trials** in member states?	2
CDx	What is the EMA's mode of interaction with NBs regarding **CDx** questions?	5
	What is the EMA's role in reviewing **CDx**?	3
	What is the EMA's view on providing drugs when the **CDx** is still under evaluation?	2
	What is the EMA's mode of interaction regarding **CDx** questions?	2
	What is the EMA's view on the role of the MAH in **CDx** evaluation?	2*
Regulatory pathways and guidance	What is the EMA's aim for **providing guidance** on the use of RWE data?	5
	What is the EMA's aim for **providing guidance** on MRD as a clinical end point?	3
	What is the EMA's aim for **providing guidance** on personalized therapies?	2
	What is the EMA's view on **regulatory requirements** for RWE data?	2*
	What is the EMA's view on **requesting** CMA for a rare indication **after full drug approval**?	2
Institutional collaboration	What is the EMA's view on **multistakeholder** scientific advice?	12
	What is the EMA's mode of interaction with **other Agencies**?	7
	What is the EMA's view on a **multistakeholder** with the EMA and HTA bodies?	2
	What is the EMA's view on a **facilitating role of the MAH** for the drug review?	2*
Combination therapy	What is the EMA's view on monotherapy data for **combination therapy**?	6
	What is the EMA's view on triple **combination therapy** development?	3
	What is the EMA's view on a co-packaging approach for **combination therapy**?	3
	What is the EMA's view on **combination therapy** when components are ineffective?	2
Endpoints	What is the EMA's view on **surrogate end points**?	6
	What is the EMA's view on using ctDNA as a **clinical end point**?	4
	What is the EMA's view on the **magnitude of efficacy** needed for single arm studies?	3
Pediatric development	What is the EMA's view on the development of a single global **pediatric program**?	2
	What is the EMA's recommended strategy for multiple **PIPs** with the same goal?	2
	What is the EMA's mode of interaction for major **PIP modifications**?	2
RWE	What is the EMA's mode of interaction on **RWE** studies?	3
	What is the EMA's view on indications for **RWE** data?	2
Drug administration	What is the EMA's view on the development of **subcutaneous formulations**?	2
	What is the EMA's view on **dose optimization** for monoclonal antibodies?	2
Current affairs	What is the EMA's plan **post-COVID-19** for adaptations related to the pandemic?	2
	What is the EMA's expectation for issues due to the EMA's move after **Brexit**?	2
Targeted therapy	What is the EMA's view on leveraging knowledge between **CAR-T/ADC constructs**?	4
PRIME	What is the EMA's advice for a successful **PRIME** application?	4
Biomarkers	What is the EMA's view on using **ctDNA** for early identification of high-risk patients?	3
Safety	What is the EMA's view on **impurity testing** in ADCs?	2

Indicated in bold are the terms used for the designation of the main category.
The asterisk indicates that the query was raised in multiple meetings, but by the same company.
ADC, antibody-drug conjugate; CAR-T, chimeric antigen receptor T-cell therapy; CDx, companion diagnostics; CMA, conditional marketing authorization; COVID-19, coronavirus disease 2019; ctDNA, circulating tumor DNA; EMA, European Medicines Agency; EU, European Union; HTA, health technology assessment; MAH, marketing authorization holder; MRD, minimal residual disease; NBs, notified bodies; PIP, pediatric investigation plan; PRIME, priority medicines; RWE, real-world evidence.

recurrent queries into Q&A documents published on the EMA website, the information is made available to all pharmaceutical companies simultaneously.[28] This feedback can help pharmaceutical companies to stay informed about currently pressing issues and prevent delays in clinical trial development or negative decisions on marketing authorization applications. To improve the quality of the BPMs, it is important to both communicate the meeting's objectives clearly and provide a framework for the discussions beforehand. One approach could be to group query topics into general BPM themes, for example, the theme "EMA internal affairs" to summarize regulatory pathways, PRIME, and pediatric development, and the theme "study protocols" for trial design, RWE, and end points. By sharing these general query themes and underlying topics in a preset framework, companies can more easily categorize their queries and be prompted to bring forward other relevant topics for BPMs, while allowing the EMA to make better use of its expertise and further update relevant published guidelines and Q&As. Additional research is necessary to address the companies' vantage points on the efficiency of BPMs, and the availability of information requested during these BPMs. This follow-up research can be executed by sending evaluation questionnaires to all participating pharmaceutical companies. Other topics of interest would be the possible overlap of oncology-related recurrent queries with recurrent queries from other therapeutic fields, and with recurrent queries from small and medium-sized enterprises (SMEs) which submit their queries to the SME office instead of via BPMs.[8]

In conclusion, during the 5-year period, targeted therapy, CDx, institutional collaboration, trial design, and regulatory pathways/guidelines were the most discussed topics in oncology BPMs, with molecular developments being the common denominator. The EMA provided information for 80% of queries, and 43 queries were recurrent between BPMs. Creating Q&A documents, publishing new guidelines, providing a framework for discussions, and questionnaire-based follow-up research can improve the quality of BPMs, and the accessibility of the information requested during the BPMs.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed the research, performed the research, and analyzed the data.

DISCLAIMER

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the author(s) is/are employed/affiliated.

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