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A review of clinical pharmacology deficiencies of European centralised drug marketing authorisation applications

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**Title** A review of clinical pharmacology deficiencies of European centralised drug marketing authorisation applications.

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**Abstract (189 words)**

The aim of this observational review was to review trends in deficiencies in clinical pharmacology dossiers by analysing the frequency and characteristics of major objections (MOs) related to clinical pharmacokinetics and dose-exposure-response (DER) relationships in assessment reports for medicinal products submitted in centralised procedures to the European Medicines Agency (EMA). Initial Assessor (Day 120) assessment reports between 2013 and 2018 were reviewed MOs and characterised with regards to ATC code, orphan status, legal basis and type of molecule, major objection topic and if scientific advice had been sought during development. 23% of the 551 identified Day 120 assessments contained at least one major objection related to clinical pharmacology. Most common topics identified were related to the pharmacokinetics in the target populations, analytical methods, dose-exposure-response relationships, absorption, distribution, metabolism, excretion, comparative bioavailability, and bioequivalence issues. The importance of a robust clinical PK dossier in the assessment of marketing authorisation applications was highlighted by the high frequency of major objections. This review should provide valuable insights to ensure that aspects of bioanalytical methods, comparative bioavailability, PK in the target population and DER relationships are thoroughly addressed in future marketing authorisation applications.

**Keywords** Clinical Pharmacology, Pharmacokinetics, Pharmacodynamics, Major Objections, Drug Development, Regulatory

**Abbreviations** ADME: Absorption, Distribution, Metabolism, Excretion; ATC: Anatomical Therapeutic Chemical; CHMP: Committee for Medicinal Products for Human Use; DER: Dose-exposure-response; EMA: European Medicines Agency; MAA: Marketing authorisation application; MHRA: Medicines and Healthcare products Regulatory Agency; MO Major Objection; PBPK: Physiologically based pharmacokinetic; PKMO: Pharmacokinetic Major Objection; PK/PD: Pharmacokinetic/Pharmacodynamic; SmPC: Summary of product characteristics; WHO: World Health Organisation.

## 1. Introduction (2541 words)

Regulatory agencies hold a wealth of knowledge and this lends itself to overviews of the submitted data in applications. The concise, high-level learnings from information contained in assessment reports from the European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) could potentially benefit future applicants for marketing authorisation by identifying trends and measures which can then assist in efficient regulatory approvals. Previously, work has been published on the topics of rationale and factors influencing withdrawal or refusal of a centralised European drug application (Putzeist et al., 2012b; Tafuri et al., 2013) or of applications via mutual recognition and decentralised procedures (Ebbers et al., 2015). The grounds for approval of a specific drug category (i.e. orphan medicines) was further investigated by Putzeist and colleagues (Putzeist et al., 2012a); who highlighted that essential success factors are related to achievement of clinical outcomes and to powerful evidence of clinical relevance and benefits, but also to previous company experience with orphan medicines approval. Additionally, two studies have investigated the role of scientific advice in drug development, either related to company size (Putzeist et al., 2011) or to measurable effects of compliance with scientific advice (Hofer et al., 2015). Balancing the desirable effects and undesirable effects of drugs is the core task of drug regulatory agencies when conducting a benefit-risk assessment. As part of this benefit-risk assessment a multidisciplinary team is required to assess quality, non-clinical, clinical pharmacology, clinical efficacy, and safety aspects of the dossier submitted as part of marketing authorisation applications (MAAs). The clinical pharmacology section of the dossier addresses many aspects including (where appropriate) analytical methods, pharmacokinetic (PK) data analysis, absorption, distribution, metabolism and excretion (ADME), PK in the target and special populations, drug- and food-interactions and clinical pharmacodynamics including exposure-response (DER) relationship analyses. The clinical efficacy section of the dossier establishes dose selection and efficacy results. The pharmacokinetic information needs to be sufficiently reflected in the summary of product characteristics (SmPC) together with adequate precautions and restrictions in case there is a lack of information or where data warrants it.

During assessment concerns can be raised for the applicant to address. A Major Objection (MO) is defined as a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health. Identification and reduction of major deficiencies would translate into a more efficient approval process by reducing the number of questions raised and lead to less resources being invested in the assessment process, especially if these deficiencies can be prevented (Ebbers et al., 2015). The clinical pharmacology and clinical efficacy sections of the dossier are critical sections of a

MAA as they support the dose rationale in the target population and special populations in addition to providing information on drug interactions.

This observational review is focused on determining trends in MOs raised in the clinical pharmacology section of assessment reports in the initial list of questions. These findings should improve the understanding of pharmacokinetics requirements in the MAAs. Additionally, the knowledge should reduce the identification of major deficiencies in future drug authorisation submissions and would limit the number of potential concerns that raise uncertainties, potentially resulting in higher approval rates for therapies and faster patient access to relevant treatments. For this observational review two objectives were formulated. The first objective was to determine the frequency of MOs related to clinical pharmacology. The second objective was to characterise the pharmacokinetic major objections (PKMOs) in terms of type of Anatomical Therapeutic Chemical (ATC) code, orphan status, legal basis and type of molecule, PKMO issue and if scientific advice had been sought during development.

## 2. Methods

### *2.1. Study design and marketing authorisation characteristics*

A list of products for the specified period, 2013-2018, were retrieved from the Medicines and Healthcare products Regulatory Agency's (MHRA's) database for centralised procedures. Duplicate reports (i.e. the same products, indication and data, but different marketing authorisation numbers) were excluded in order to avoid double quantification of the same product and PKMOs.

Subsequently, the adopted Day 120 overviews (including list of questions) were retrieved from CHMP's Meeting Documents repository. The Day 120 reports were chosen to be analysed as they represent the official response of the CHMP to the applicant following assessment by the rapporteurs in the Day 80 assessment reports and review by all other national member agencies and the EMA.

The following information was retrieved for each product for which PKMOs were identified: anatomical main group of the ATC classification, legal basis of marketing authorisation application (i.e. new substance – article 8(3), generic – article 10(1), hybrid – article 10(3), etc.) and type of molecule (small molecules or biological substance), orphan status (i.e. if designated as EMA orphan medicine) and if scientific advice had been sought from a regulatory agency (EMA and/or European national agency) during development.

### *2.2. Data collection and PKMOs characteristics*

The PKMOs found in the clinical sections of the report were extracted and analysed in a standardised manner. Where the MO was raised under general clinical aspects (e.g. multidisciplinary, efficacy or safety), but it included deficiencies related to PK or DER relationship, the MO was still considered to be a PKMO.

In order to limit the risk of interpretation and subjectivity, 4 researchers (JH, ARI, SC and EK) independently assessed the PKMOs and categorised them according to Table S1; disagreement was resolved by discussion and consensus. Categories were based on the PK topics/headings used in the Day 80 assessment report (Clinical template rev.10.16), extra categories were added where further granularity was required. Each identified PKMO was categorised according to the topics raised, therefore if one PKMO referred to more than one category, quantification in two or more categories was allowed.

### *2.3. Data analysis*

All data were entered into a spreadsheet (MS Excel) and all analyses were descriptive.

## 3. Results

A total of 551 Day 120 assessments/products were identified in the years 2013-2018, with 120 (23%) of these containing at least one PKMO. The trend over the years is shown in Figure 1.

Of the products with PKMOs, half (50%) were non-orphan small molecules with the other half comprised of non-orphan biological (21%), orphan small molecules (16%) and orphan biological (13%) products (Figure S1). A graphical summary of products categorised by ATC code is shown in Figure S2.

The number of topics identified are summarised by the legal basis the application was submitted under (Figure 2) and by year (Figure S3). For products with PKMOs in all years (2013-2018), the proportion of products were submitted under the following legal basis: 8(3): New active substance (57%), 10(1): Generic (17%), 10(3): Hybrid (9%), 10(4): Biosimilar (11%), 10(a): Well-established use (2%), 10(b): Fixed combinations (4%), 10(c): Informed consent (0%). The proportion of topics identified by regular (non-orphan) or orphan product are presented in Figure S4. The number of products with a PKMO by type of scientific advice received by year and legal basis are presented in Figures S5 and S6, respectively. For products with a PKMO, scientific advice (EMA and/or national) was received for biologicals (88%), small molecules (61%), orphan products (83%) and non-orphan products (65%), respectively.

[Figure 1]

[Figure 2]

## 4. Discussion

From 2013 to 2015 there was a steady number of PKMOs (approximately 10-13%) on a background of an increasing number of products being assessed, while from 2016 to 2018 there was a decreasing trend in the total number of assessments, but the number of PKMOs increased (31-38%) (Figure 1). This pivot point (2014/2015) with an increasing number of PKMOs probably reflects a greater focus on dose selection and establishing dose-exposure-response relationships (also shown in Figure S3) in regulatory agencies and industry, which was highlighted in the EMA/EFPIA workshop in December 2014 (Musuamba et al., 2017). Furthermore, it reflects the greater emphasis that PK and especially Pharmacokinetic/Pharmacodynamic (PK/PD) modelling has in in drug development. During 2016, the EMA's guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation was issued for public consultation, with the guideline adopted in 2018. It should be noted that this increase correlates with the number of procedures referred to the EMA's modelling and simulation working party, which steadily increased (activity reports 2013-2016 (European Medicines Agency, 2019)) from 59 procedures in 2013 to 105 procedures in 2016. These trends are also reflected in the number of topics identified each year (Figure S3) with a general increasing trend in the number of topics identified for pharmacokinetics in the target populations and DER relationships. The only other topic where there was an increasing trend was for analytical methods, possibly reflecting a recognition of more stringent criteria for bioanalytical method validation. For many other PK topics (e.g. ADME, bioavailability, and bioequivalence) trends remained stable over the sampling period.

Over the period sampled, there was a higher proportion of orphan products with PKMOs (29%, Figure S1) compared with the proportion of products with orphan designation (approximately 21%) submitted for marketing authorisation to the EMA (European Medicines Agency, 2018a) and the proportion of orphan medicines authorised (approximately 14%) (European Medicines Agency, 2020) for the same period. Further analysis indicates that a higher proportion of orphan drugs had PK issues related to analytical methods, characterising the PK in target populations, impact of immunogenicity, drug-interactions and characterising DER relationships (Figure S4). This undoubtedly reflects the complexity of drug development in orphan drug development, with many of these topics reflecting the scarcity of patients, limiting clinical studies but also the limited knowledge about the rare diseases the medical products are aiming to treat (Bouwman et al., 2020).

In terms of therapeutic areas, there were proportionally more PKMOs for nervous system products (Figure S2). This was partly driven by bioequivalence issues with several generic applications, but in addition many of the PKMOs for this therapeutic area were due to issues with adequately describing DER relationships or justifying the selected dose, reflecting the difficulties in quantifying drug at the site of action in the CNS. Conversely, there were proportionally fewer PKMOs for general anti-infectives for systemic use reflecting the improved understanding of PK/PD in this area. For many regulatory agencies, the clinical guidelines for anti-infectives are extensive and quite descriptive of the data requirements especially with regard to defining PK/PD relationships and the clinical trials required to support specific indications (European Medicines Agency, 2018b; Metlay et al., 2006).

The number of topics identified by legal basis of the application were generally as expected (Figure 2). Nearly all bioequivalence issues related to quality Biopharmaceutics Classification System (BCS) biowaivers were attributed to generic applications and biosimilarity issues were attributed to biosimilar applications. Other bioequivalence issues (e.g. study design, statistical issues) were attributed to generics and fixed combination, PKMOs for comparable bioavailability were generally related to comparing formulations used during the clinical development and the final commercial formulation therefore these were attributed to new active substance, hybrid and biosimilar applications. Issues related to DER relationships and PK in the target population were almost exclusively attributed to new active substances. All PKMO topics related to interactions (primarily drug and food interactions) were linked to new active substances.

The EMA has provided scientific advice since 1996 (Hofer et al., 2015) with approximately half of MAAs being preceded by scientific advice (European Medicines Agency, 2009) and it has previously been shown that compliance with scientific advice correlates with MAA success (Regnstrom et al., 2010). In this study only products with PKMOs were characterised with regards to the type of scientific advice received, and limited conclusions can be made as data for all applications (i.e. applications without PKMOs) was not investigated. Results showed that from 2013-2014 approximately half of products with PKMOs had received scientific advice (Figure S5). However, from 2016-2018, the proportion of products with a PKMO obtaining scientific advice was approximately 75%; this advice was mostly obtained from the EMA either solely or also from European national agencies (Figure S5). For products with PKMOs, 88% of products submitted as a new active substance had received scientific advice (Figure S6); while this research cannot elucidate what any of the received scientific advice was about (or if it regarded PK issues), it does confirm that applicants had contact with regulatory agencies, however it may also suggest that companies may need to seek more nuanced advice on

pharmacokinetics and DER relationships. On the other hand, nearly all generics and well-established use products with PKMOs did not receive any scientific advice, this likely reflects the scientific evidence required to support a MAA for these products and that product specific bioequivalence guidance is available for many generic products. In contrast, scientific advice was received for most biological and orphan products, reflecting their complex and specialised drug development programs. Nonetheless, previous research has indicated that compliance with scientific advice is associated with a reduction in total number of MOs (Hofer et al., 2015) and applicants are encouraged to start dialogue with the competent regulatory agencies early in the product and process development and get as much scientific advice as possible.

Limitations of this research are recognised. Even though the assessment method of the PKMOs was highly standardised, there is a risk of interpretation and subjectivity, this was minimised by consensus agreement with a panel of PK assessors. Furthermore, only centralised procedures were investigated. This analysis therefore only focuses on drugs that require mandatory or optional submission via the centralised route. It is known that most drugs in Europe are licensed via other routes (i.e. national, decentralised procedures). Other outcomes would be expected if data sets from these other procedures were considered, as these procedures tend to be used for other medicinal products such as generics or products intended for a local market. Furthermore, only MOs listed at Day 120 were included. It is acknowledged that other PKMO may be raised at later stages of the centralised procedure through the upgrading of 'other concerns' (OCs) and/or the addition of new MOs. Lastly, the focus of this research was to investigate MOs, therefore issues that would normally be considered OCs, such as issues in certain special populations e.g. patients with hepatic impairment or in vitro drug interaction studies, would not be identified. Similar to previous research (Putzeist et al., 2012a; Putzeist et al., 2012b), further studies are needed to investigate what impact PKMOs have on the ultimate approval, withdrawal or refusal of MAAs.

## 5. Conclusion

This study identified and characterised PKMOs in Day 120 assessment reports for medicinal products submitted in centralised procedures to the EMA between 2013 and 2018. The high frequency of MOs highlights the importance of a robust clinical pharmacology dossier in the assessment of MAAs. This includes ensuring that issues related to analytical methods, comparative bioavailability, PK in the target population and DER relationships are thoroughly addressed in MAAs. Regulatory agencies hold a wealth of experience and information that can be utilised by stakeholders by seeking scientific advice. This may provide more innovative approaches to drug development and should limit the number of MOs raised during regulatory assessment.

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**Disclaimer**

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or organisations with which the authors are employed/affiliated.

**Conflict of Interest**

The authors declare that they have no conflicts of interest.

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**Author Contributions**

All authors contributed to the design of the research, data collection and analysis as well as writing, reviewing and approving the final manuscript. The contribution of JOS to this article relates to the period of employment in the Specialised Scientific Disciplines Department at the European Medicines Agency.

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259

**Figure Captions**

**Fig. 1** Number of products per year with/without a PKMO at day 120 of assessment

**Fig. 2** Number of PKMO topics at day 120 of assessment identified by article it was submitted under. Only showing topics where total count was 5 or more across all years (2013-2018). No products with PKMOs were submitted under article 10(c): informed consent

**Supplementary material captions**

**Table S1** List of study inclusion and exclusion criteria and PK topics

**Fig. S1** Proportion of products at day 120 of assessment (all years: 2013-2018) with PKMO at day 120 characterised by orphan status (orphan vs non-orphan) and type of product (small molecule vs biological)

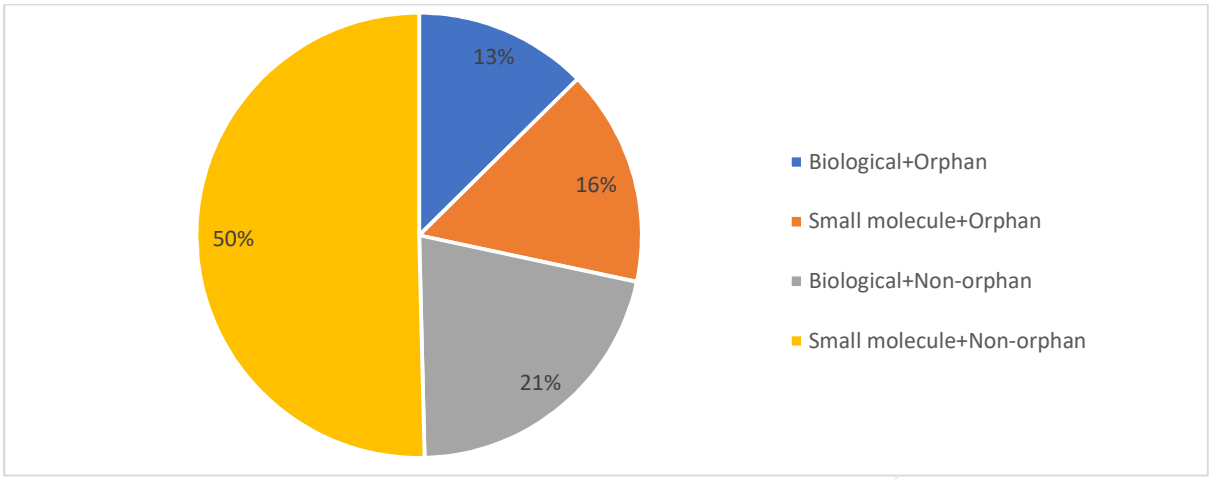
**Fig. S2** Percentage of products at day 120 of assessment with or without a PKMO categorised by ATC code

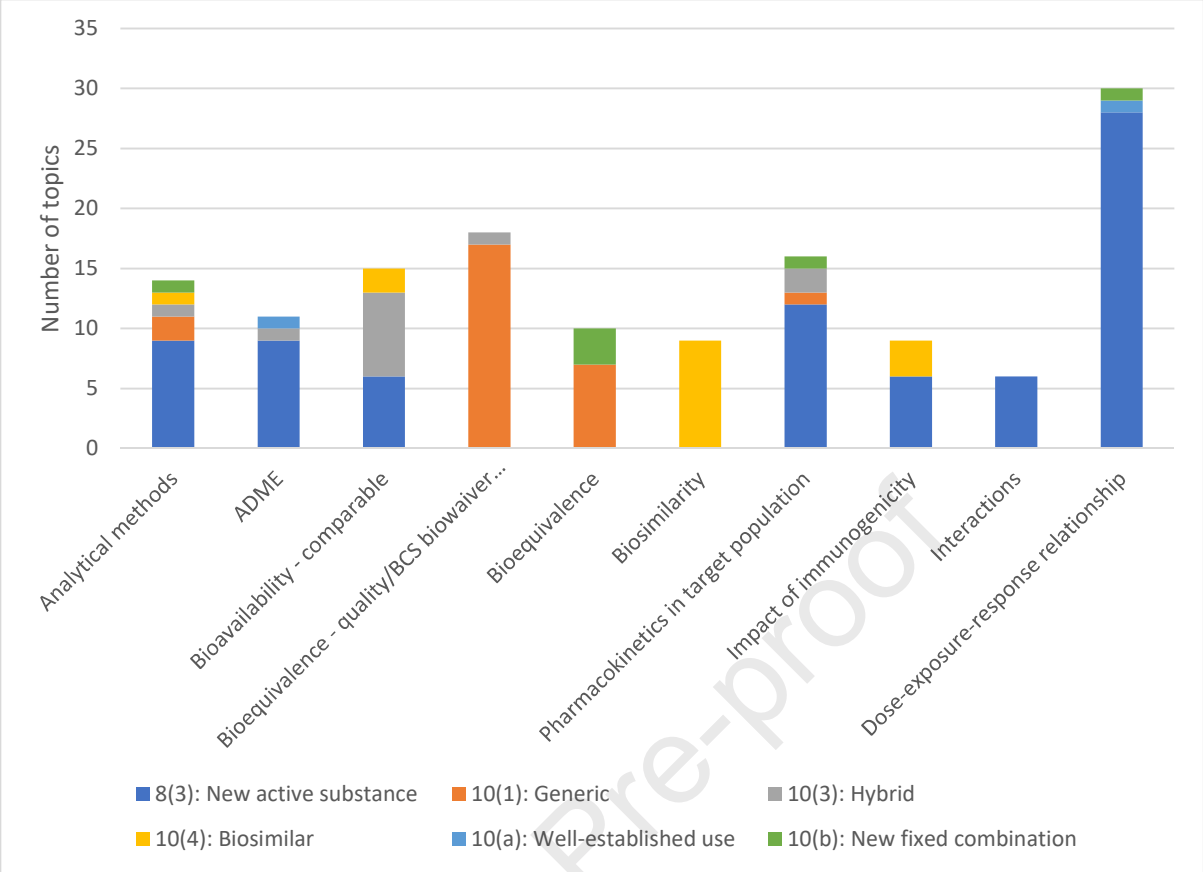
**Fig. S3** PKMO topic trends by year (2013-2018). Only showing topics at day 120 of assessment where total count was 5 or more across all years (2013-2018)

**Fig. S4** Proportion of PKMO topics (total of all years (2013-2018)) at day 120 of assessment by orphan status. Only showing topics where proportion was 5% or more for at least one product type

**Fig. S5** Number of products with PKMOs at day 120 of assessment categorised by type of scientific advice received prior to the marketing authorisation application and year of assessment

**Fig. S6** Number of products with PKMOs at day 120 of assessment categorised by type of scientific advice received and legal basis





| **Study inclusion/exclusion criteria** | |
|---|---|
| Inclusion criterion:<br><br>Centralised procedures with D120 assessment report dated between January 2013 and December 2018, inclusive.<br><br>List of questions contain at least one major objection related to PK or DER relationship deficiencies. | Exclusion criterion:<br><br>Duplicate reports (i.e. the same products, indication and data, but different marketing authorisation numbers) were excluded in order to avoid double quantification of the same product and major objections. |

| **PK topics** | |
|---|---|
| 1. Methods | 5. Dose proportionality and time dependency |
| 1.1 Analytical methods | 5.1 Dose proportionality |
| 1.2 Pharmacokinetic data analysis | 5.2 Time dependency |
| 1.3 Evaluation and Qualification of Models | 6. Intra- and inter-individual variability |
| 1.4 Statistical methods* | 7. Pharmacokinetics in target population |
| 2. ADME - Absorption | 8. Special populations |
| 2.1 Bioavailability | 8.1 Impaired renal function |
| 2.2 Bioavailability – comparable (non-generics) | 8.2 Impaired hepatic function |
| 2.3 Bioequivalence - quality/BCS biowaiver justification | 8.3 Gender (sex) |
| 2.4 Bioequivalence (generics/fixed combinations) | 8.4 Race |
| 2.4 Biosimilarity (biologics) | 8.5 Weight |
| 2.5 Influence of food | 8.6 Elderly |
| 3. ADME – Distribution* | 8.7 Children |
| 4. ADME - Elimination | 9. Interactions |
| 4.1 Excretion | 9.1 In vitro |
| 4.2 Metabolism | 9.2 In silico |
| 4.3 Inter-conversion | 9.3 In vivo |
| 4.4 Pharmacokinetics of metabolites | 10. Exposure relevant for efficacy and safety evaluation |
| 4.5 Consequences of possible genetic polymorphism | 10.1 Dose-exposure -response (DER) relationship |
| | 10.2 Impact of immunogenicity* |
| Categories were based on the PK topics/headings used in the Day 80 assessment report (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/assessment-templates-guidance) with categories added for greater granularity marked with an asterisk (*). | |

**Highlights**

- PK/PD aspects of procedures submitted to the EMA were reviewed.
- 23% of assessments contained at least one major objection related to clinical pharmacology.
- A wide variety of clinical pharmacology issues were identified.
- Indicates the importance of a robust clinical pharmacology dossier for applications.

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**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: