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Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes

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Q3 **Small and medium-sized enterprises (SMEs) are an important source of innovative medicines. Compared with their larger counterparts, they experience challenges as a result of insufficient human and financial resources that can hamper drug development and regulatory compliance. This analysis reviews the profile of major objections raised in applications for medicines for human use submitted by SMEs to the European Medicines Agency between 2011 and 2015 and their impact on the outcome of applications. It showed that SMEs experience challenges in the quality (e.g., manufacturing process validation and on control and/or characterisation data of drug substance or drug product) and the clinical sections of marketing authorisation applications (e.g., analysis or robustness of pivotal data or selection of submitted studies, study design issues and marginal or no clinical relevant efficacy), with deficiencies in demonstrating clinical efficacy representing the major eventual hurdles to authorisation.**

Introduction

Small and medium-sized enterprises (SMEs) are an important source of innovative medicines [1]. Compared with their larger counterparts, they experience challenges caused by insufficient human and financial resources that can hamper drug development, regulatory compliance and clearance. Previous analyses have looked into the deficiencies of marketing authorisation applications [2–5]. This paper reports on a specific analysis of applications submitted by SMEs to the European Medicines Agency (EMA). It analyses the most frequently encountered hurdles, factors correlated to authorisation and the regulatory strategies Q4 used to address them.

The assessment of a marketing authorisation application in the EU consists of various milestones, the first of which is the so-called 'Day 120 List of Questions', which provides a preliminary assessment of the benefit:risk profile of a medicinal product by the EMA's scientific committee: the Committee for Medicinal Products for Human use (CHMP). This preliminary assessment identifies questions that can include major objections, which preclude a marketing authorisation. These objections relate to quality (chemical, pharmaceutical and biological testing), non-clinical (toxicological and pharmacological testing) and/or clinical efficacy and safety documentation submitted in support of the application. The major objections in the different sections of the application provide insights into the regulatory and scientific challenges encountered during drug development by SMEs.

In subsequent phases of the assessment of the application, the applicant must provide clarifications, additional analyses or further data to address these questions. This additional information further supports the regulatory decision making, based on the evaluation of the strengths and uncertainties in the evidence related to benefits and risks, and any proposals for post-authorisation data generation and risk management strategies. Not all applications have major objections. However, for those that do, if left unresolved they will lead to an unfavourable conclusion on the benefit:risk profile of the medicinal product in the claimed indication. This report analyses the profile of major objections in applications for medicines for human use submitted

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by SMEs to the EMA with a positive or negative outcome (negative opinion or withdrawal) between 2011 and 2015, and their impact on the outcome. The type of product (chemical and biological), the orphan drug status of the medicine, the therapeutic indication and the type of application (full or abridged) were also analysed (see Supplementary material online).

Analysis

Out of the 64 applications, 42 (66%) had a positive outcome (positive CHMP opinion), whereas 22 (34%) had a negative one (18 applications were withdrawn and four had a negative CHMP opinion). Twenty-four (37.5%) of the 64 applications were for orphan medicines, 16 (25%) contained biologicals and 23 (36%) were abridged applications. Of the 64 applications, antineoplastic and immunomodulating agents represented the largest group (11/64, 17%), followed by agents intended for alimentary tract and metabolism (10/64, 15%) and nervous system (8/64, 12.5%) diseases. The percentage of SME applications for which a major objection was raised in the quality, nonclinical and/or clinical documentation and its subsections were analysed.

Major objections in clinical efficacy, clinical safety and quality were observed in 80% (51/64), 48% (31/64) and 73% (47/64) of the applications, respectively (Fig. 1). Fewer dossiers had nonclinical deficiencies (19%). Nonclinical objections were reported more frequently in dossiers for biologicals than those for chemical entities [i.e., 38% (6/16) vs 13% (6/48)], whereas only minor differences were observed in the quality and clinical sections. Within each section of the dossier, major objections were categorised using a granular classification of types of quality, nonclinical or clinical objections (Figs 2 and 3). The average number of types of major objections was 7 ± 6 (range 0–24), with higher figures observed for those dossiers with a negative outcome than those with a positive outcome [averages of 10 ± 7 (range 2–24) vs 5 ± 4 (range 0–18), respectively]. Applications for biologicals had on average more objections than those for chemical entities 11 ± 8 (range 0–24) versus 5.5 ± 4 (range 0–17). Minor differences were observed between the respective figures for orphan vs non-orphan medicines and full vs abridged applications.

Analyses were performed to identify associations between major objections raised in the quality, nonclinical or clinical documentation at 'Day 120 List of Questions' and dossier outcome (Table 1). The odds of nonapproval of SME applications were 2-times higher when at least a major objection was raised in quality, 5.3-times higher in nonclinical efficacy, 3.5-times higher in clinical efficacy and 4.7-times higher in clinical safety documentation. The odds of Q5 nonapproval of SME applications were 2.4-times higher for biologicals as compared with chemicals, 1.3-times higher for full dossiers as compared with abridged ones and 0.7-times lower for orphan medicines as compared with non-orphan medicines. The analysis of applications by therapeutic indication was inconclusive owing to limited sample sizes.

Major objections in the quality section of the applications

The most frequent major objections on quality compliance are presented in Fig. 2. Thirty-nine percent (25/64) of applications experienced objections on 'manufacturing process validation' and on 'control and/or characterisation data of drug substance/drug product'. Other frequently raised objections related to 'specifications', 'stability or compatibility data/shelf life', 'manufacturing process development/control strategy', pharmaceutical development and 'impurities or related substances profile'.

Notable differences in the proportions of major quality objections were observed between biologicals and chemical entities and

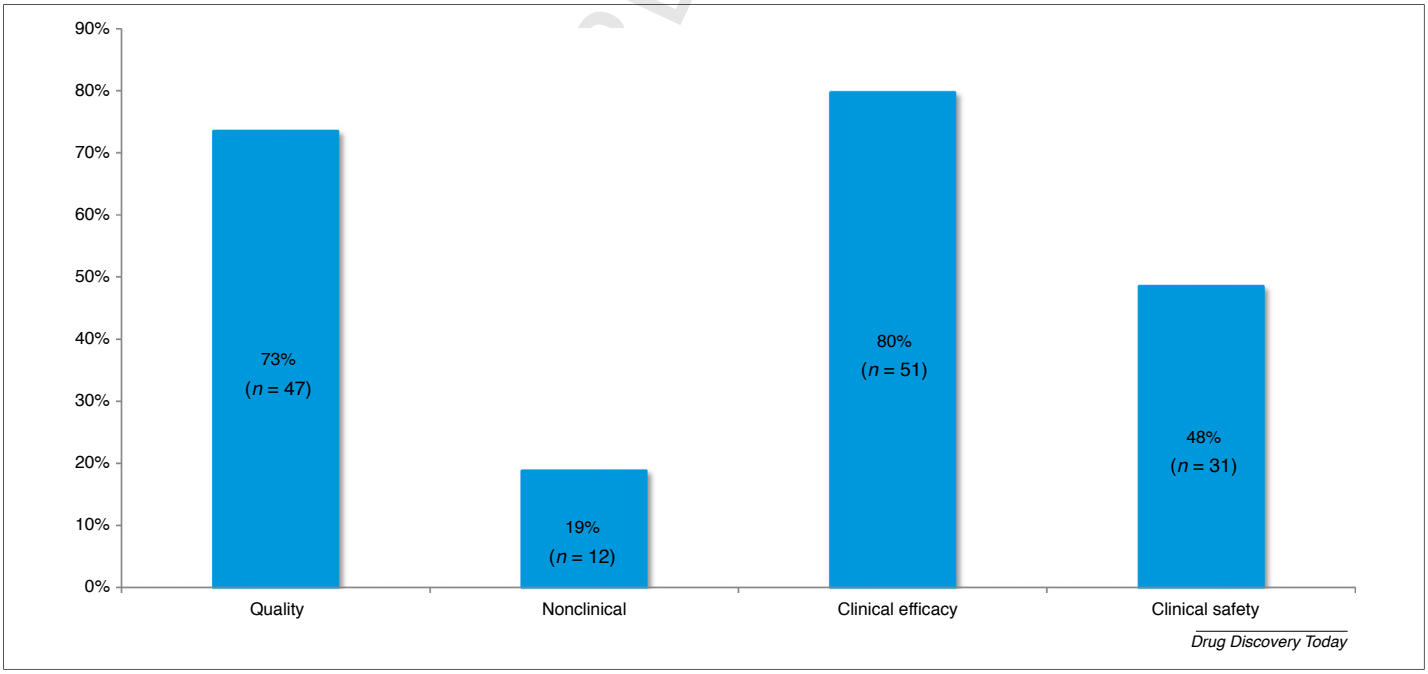

FIGURE 1

Q9 Percentages of dossiers with major objections on quality, nonclinical efficacy, clinical efficacy and clinical safety in the 'Day 120 List of Questions' assessment milestone of European Union human use marketing authorisation applications by small and medium-sized enterprises (SMEs) between 2011 and 2015.

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