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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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 marketing authorisation applications for medicines for human use submitted by SMEs to the European Medicines Agency (EMA) 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 control and/or characterisation data of drug substance or drug product) and 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. It analyses the most frequently encountered hurdles, factors correlated to authorisation and the regulatory strategies 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 by SMEs to

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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, non-clinical 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 non-clinical deficiencies (19%). Non-clinical 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, non-clinical 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, non-clinical or clinical documentation at 'Day 120 List of Questions' and dossier outcome (Table 1). The odds of non-approval of SME applications were 2-times higher when at least a major objection was raised in quality, 5.3-times higher in non-clinical, 3.5-times higher in clinical efficacy and 4.7-times higher in clinical safety documentation. The odds of non-approval 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

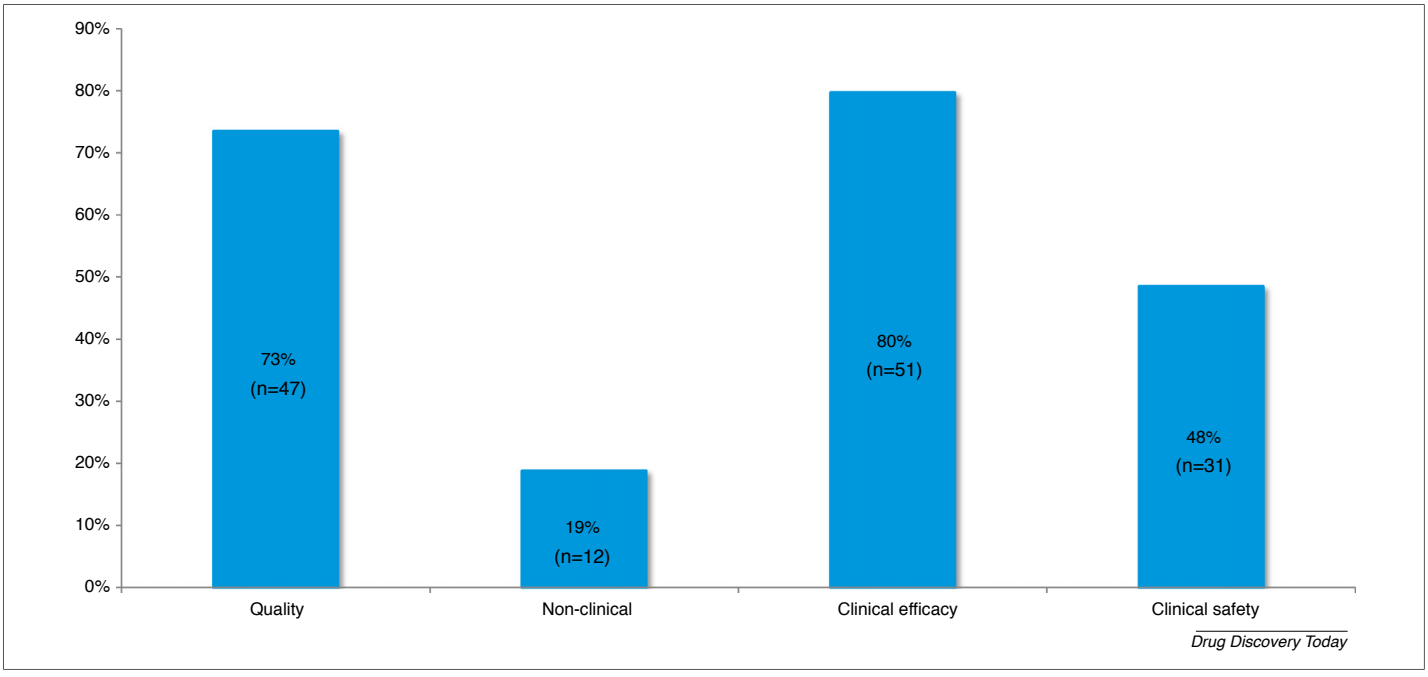

FIGURE 1

Percentages of dossiers with major objections on quality, non-clinical, 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.

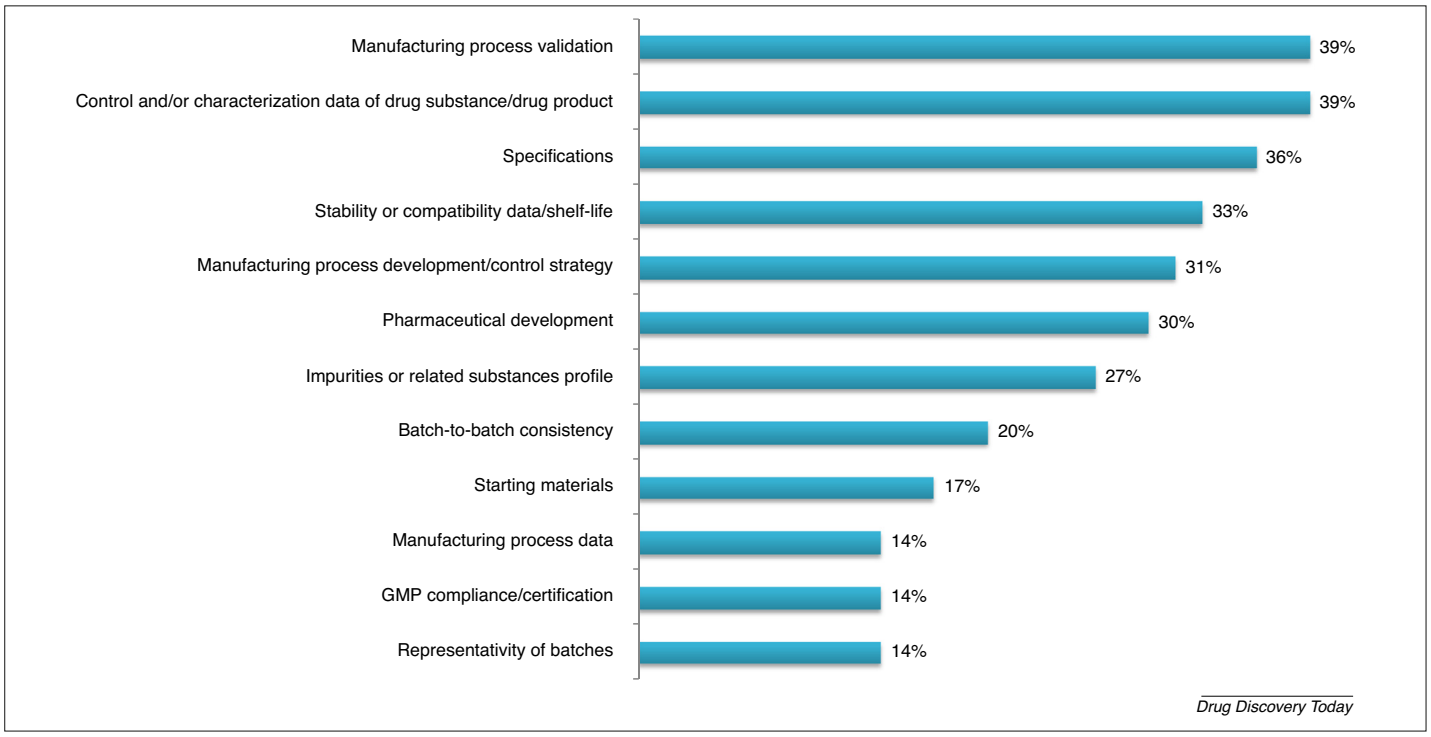

FIGURE 2

Percentages of dossiers with subtypes of quality major objections raised 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 (n = 64) (major objections in >10% of the dossiers are shown).

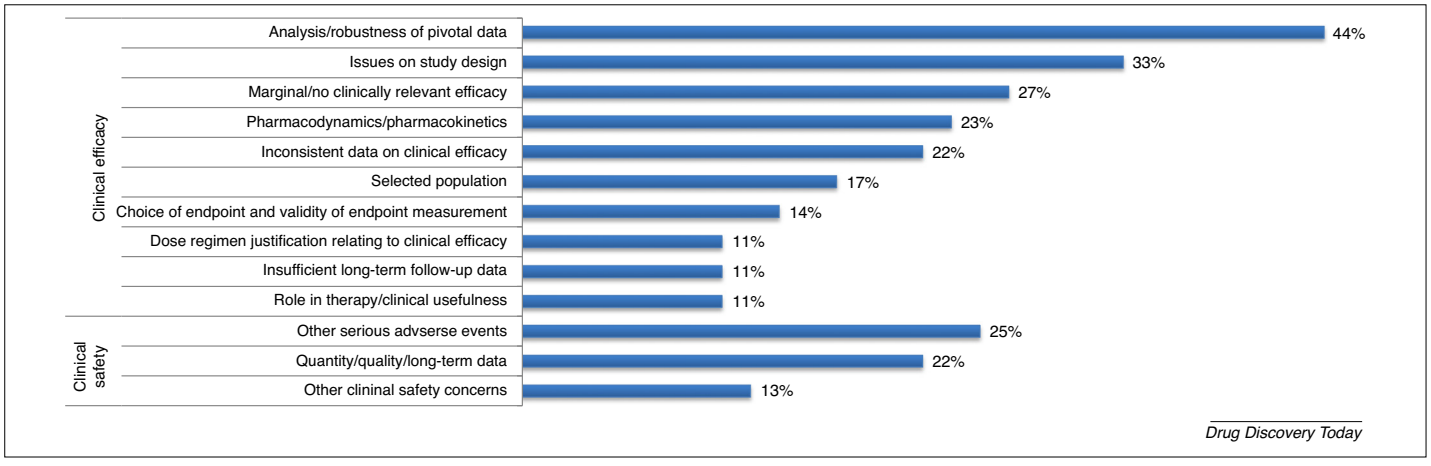

FIGURE 3

Percentages of dossiers with subtypes of clinical efficacy and safety major objections raised 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 (n = 64) (major objections raised in >10% of the dossiers are shown).

related to 'control and/or characterisation data of drug substance/drug product' [75% (12/16) vs 27% (13/48), respectively], specifications [69% (11/16) vs 25% (15/48)] and 'impurities or related substances profile' [56% (9/16) vs 17% (8/48)]. No notable differences between orphan and non-orphan medicines or between abridged and full applications were observed.

Analyses were performed to identify associations between specific types of objections raised in each section of the dossier and outcome. For quality major objections, those associated with unfavourable outcomes related to demonstration of 'batch-to-batch consistency' (69%, 9/13 of dossiers with such objections had a negative outcome vs 25%, 13/51 of dossiers without such objections had a negative outcome; OR = 6.4).

Major objections in the non-clinical and clinical sections of the applications

A limited number of applications (n = 12) experienced major objections in the non-clinical documentation. The objection raised in >10% of the dossiers related to toxicity study design. The most frequent objections raised in the clinical efficacy docu-

TABLE 1

Overview of major objections on quality, non-clinical, clinical efficacy and clinical safety in the 'Day 120 List of Questions' assessment milestone and outcomes of European Union human use marketing authorisation applications by small and medium-sized enterprises (SMEs) between 2011 and 2015 (n = 64)

Major objections	Non approved (n = 22)	Approved (n = 42)
Quality		
+	18 (38%)	29 (62%)
–	4 (24%)	13 (76%)
Non-clinical		
+	8 (67%)	4 (33%)
–	14 (27%)	38 (73%)
Clinical efficacy		
+	20 (39%)	31 (61%)
–	2 (15%)	11 (85%)
Clinical safety		
+	16 (52%)	15 (48%)
–	6 (18%)	27 (82%)

Positive (+) refers to SME applications for which a major objection was raised in the quality, non-clinical or clinical documentation. Negative (–) refers to SME applications for which no major objection was raised in the quality, non-clinical or clinical documentation. Approved refers to a positive opinion. Non approved refers to a negative opinion or withdrawal.

mentation related to 'analysis/robustness of pivotal data/selection of submitted studies', 'issues on study design' and 'marginal/no relevant clinical efficacy' (Fig. 3).

Notable differences in the proportions of major clinical objections were observed between abridged vs full dossiers on 'inconsistent data and related to clinical efficacy' [43.5% (10/23) vs 10% (4/41)] and 'pharmacodynamics/pharmacokinetics' [39% (9/23) vs 15% (6/41), respectively]. Other notable differences were observed between biologicals and chemical entities on 'insufficient long-term follow-up efficacy data' [31% (5/16) vs 4% (2/48)], 'other serious adverse events (unrelated to increased mortality)' [44% (7/16) vs 19% (9/48)] and 'other clinical safety concerns' [25% (4/16) vs 2% (1/48)].

Major objections associated with unfavourable outcomes were those relating to the 'choice of endpoints' (78%, 7/9 of dossiers having such objections had a negative outcome vs 27%, 15/55 of dossiers without such objections had a negative outcome; OR = 9), 'clinical safety concerns' [80% (4/5) vs 31% (18/59); OR = 8.8] and 'pharmacodynamics/pharmacokinetics' [67% (10/15) vs 24% (12/49); OR = 6].

Concluding remarks

The analysis provided a comprehensive review of major objections raised by the EMA's scientific committee (the CHMP) on the quality, non-clinical and clinical documentation in applications from SMEs over the period 2011–2015, having either a positive or a negative outcome. It showed that SMEs experience challenges at the stage of marketing authorisation application particularly within the quality and clinical sections. Approximately 80% of applications had objections on clinical efficacy, 73% on quality and 48% on clinical safety documentation. A limited number of applications (19%) had major objections raised on the non-clinical documentation. SMEs experienced more challenges for biologicals than chemical entities. The figures for quality major objections were higher than those reported in a previous analysis of major objections for all types of applicants (SMEs and larger companies). Comparisons are, however, limited by the different methodologies used for categorising major objections in both analyses [2].

Major objections identified in the 'Day 120 List of Questions' provide a preliminary assessment of the benefit-risk profile of the product and bring to the fore hurdles experienced during development, regulatory compliance issues and a company's readiness for marketing approval. As a result, analysing such major objections as factors impacting nonapproval could be misguided. The findings on the non-clinical documentation are, in this respect, of relevance. Although the odds of non-approval of SME applications were 5.3-times higher when at least a major objection was raised in the non-clinical documentation at 'Day 120 List of Questions', only 5% of negative outcome applications had unresolved major objections on the non-clinical documentation. Most companies eventually resolve major objections through clarifications, additional analysis and supplementary data that become available during subsequent phases of the application review or handled in the post-approval setting. Conversely, outstanding major objections, which remain unresolved, hinder drug approval.

Within that context, an analysis of the outstanding major objections in the 22 negative dossiers, after clarifications and supplemental data were provided by the companies, showed that deficiencies in demonstrating clinical efficacy represented the major hurdle to marketing authorisation. Ninety-one percent (20/22) of these applications had unresolved objections on clinical efficacy, 50% (11/22) on clinical safety, 36% (8/22) on quality and 5% (1/22) on non-clinical safety. Clinical efficacy objections relating to 'analysis/robustness of pivotal data' were raised in 68% of negative dossiers (15/22), 'study design' in 32% (7/22), with 'marginal/no clinical relevant efficacy' reported for 27% (6/22) of them. Serious adverse events and 'quantity/quality/long-term safety data' were raised in 18% (4/22) of dossiers and clinical safety concerns in 14% (3/22) of them.

Reasons for regulatory failure are multiple and ways to improve the R&D engine and approval rates through funding and alliances have been highlighted [6,7]. Accordingly, the figures reported in this review should be viewed in the context of deal-making of drug candidates initially developed by SMEs and subsequently in-licensed by big or mid-size biopharmaceutical companies prior to filing [1]. Furthermore, analyses of factors impacting drug approval could account for non-evidentiary factors (e.g., product or indication profile, company experience or strategy, social factors), which contribute to the multifactorial nature of regulatory decision making [8].

At time of development, applicants can prospectively seek regulatory and scientific advice on their development programme for approval with a view to minimising the most frequent hurdles (e.g., 'analysis/robustness of pivotal data', 'study design'). Conversely, the less frequently raised issues (e.g., 'marginal/no clinical relevant efficacy', serious adverse events) are dependent on the safety and efficacy data of the drug candidate emerging from the development programme and subject to review and analysis by regulators.

When looking at the role of regulators during drug development, enabling tools such as regulatory and scientific advice and dedicated small business financial incentives have been implemented with success [9]. These tools now also allow applicants to prospectively discuss pre- and post-approval evidence-generation plans to support approval and patient access, with regulators and market access authorities [10–13]. Clearly, encouraging the uptake of scientific advice by SMEs should remain a priority. Compliance with scientific advice has been shown to correlate with a positive outcome of marketing authorisation applications, particularly for orphan medicines, which are often developed by SMEs [14–16]. Financial fee reductions for seeking scientific advice are, in in this respect, particularly relevant for SMEs [17]. Such regulatory due diligence should help SMEs to address evidence gaps and bridge drug development strategies with regulatory expectations – eventually translating into programmes generating data for approval packages less likely to lead to major objections and regulatory setbacks.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2018.06.018.

References

1 Lincker, H. *et al.* (2014) Regulatory watch: where do new medicines originate from in the EU? *Nat. Rev. Drug Discov.* 13, 92–93http://dx.doi.org/10.1038/nrd4232
2 Pignatti, F. *et al.* (2002) The review of drug applications submitted to the European Medicines Evaluation Agency: frequently raised objections, and outcome. *Eur. J. Clin. Pharmacol.* 58, 573–580
3 Borg, J.J. *et al.* (2009) Where is industry getting it wrong? A review of quality concerns raised at Day 120 by the Committee For Medicinal Products for Human Use during European Centralised Marketing Authorisation Submissions for Chemical Entity Medicinal Products. *J. Pharm. Pharm. Sci.* 12, 181–198
4 Putzeist, M. *et al.* (2012) Factors influencing non-approval of new drugs in Europe. *Nat. Rev. Drug Discov.* 11, 903–904
5 Schneider, C.K. *et al.* (2008) Typical pitfalls in applications for marketing authorization of biotechnological products in Europe. *Nat. Rev. Drug Discov.* 7, 893–899
6 Czerepal, E.A. *et al.* (2008) Drug approvals and failures: implications for alliances. *Nat. Rev. Drug Discov.* 7, 197–198. https://www.nature.com/articles/nrd2531
7 O'Connell, K.E. *et al.* (2014) The premium of a big pharma license deal. *Nat. Biotechnol.* 32, 617–619
8 Liberti, L. *et al.* (2017) Factors related to drug approvals: predictors of outcome? *Drug Discov. Today* 22, 937–946
9 Report on the 10th anniversary of the SME initiative. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/05/WC500206029.pdf
10 EMA early Research & Development Advice Services. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001768.jsp&mid=WC0b01ac0580b18a3a
11 General principles EMA-FDA parallel scientific advice (human medicinal products). Available at: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OfficeofInternationalPrograms/UCM557100.pdf
12 Parallel consultation with regulators and health technology assessment bodies. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001857.jsp&mid=WC0b01ac0580a11c96
13 Managing Access, Value and Sustainability. *New Health Technologies*. Available at: https://doi.org/10.1787/9789264266438-en
14 Regnstrom, J. *et al.* (2010) Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur. J. Clin. Pharmacol.* 66, 39–48
15 Hofer, M.P. *et al.* (2015) Regulatory watch: impact of scientific advice from the European Medicines Agency. *Nat. Rev. Drug Discov.* 14, 302–303
16 Hofer, M.P. *et al.* (2018) Marketing authorisation of orphan medicines in Europe from 2000 to 2013. *Drug Discov. Today* 23, 424–433
17 European Medicines Agency SME incentives. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&mid=WC0b01ac05800240cc