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Licensing failure in the European decentralised procedure

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ABSTRACT

The majority of the licensing applications in the European Union are submitted via the decentralised procedure. Little is known about licensing failure (i.e. refusal or withdrawal of a marketing authorisation application) in the EU decentralised procedure compared to the EU centralised procedure and the approval procedure in the United States. The study aim was to determine the frequency of and determinants for licensing failure of marketing authorisation applications submitted via this procedure. We assessed procedures that failed between 2008 and 2012 with The Netherlands as leading authority and assessed the remaining major objections. In total 492 procedures were completed, of which 48 (9.8%) failed: 8 refused, 40 withdrawn. A wide variety of major objections was identified and included both quality (48 major objections) and clinical (45 major objections) issues. The low failure rate may be related to the regular interaction between competent authorities and applicants during the procedure. Some degree of licensing failure may be inevitable, as it may also be affected by the financial feasibility or willingness to resolve major objections, as well as other reasons to withdraw an application besides the raised major objections.

1. Introduction

Regulation of pharmaceutical products essentially covers two main categories: medicinal products with a new active substance and products with a known active substance that is generally not no longer patent protected. So-called generic medicinal products represent the majority of this second category. Previous research on licensing failure, i.e. a company has applied for a licence and the regulatory authorities have refused the application or the sponsor has withdrawn the application, focused on the regulatory fate of new active substances in the United States (US) (Sacks et al., 2014; Wang et al., 2013) and in the European Union (EU) centralised procedure (Borg et al., 2009; Pignatti et al., 2002; Putzeist et al., 2012; Regnstrom et al., 2010; Schneider and Schäffner-Dallmann, 2008). The latter procedure results in a single marketing authorisation for the entire EU. These studies indicate that approximately a fourth of the marketing authorisation applications fail. So far, however, little is known about the outcome of other regulatory pathways (Haraldsdóttir, 2010), like the decentralised procedure (DCP) in Europe, which is most commonly used for the second category of medicinal products (CMDh, 2014).

The DCP was introduced in 2005 and allows an applicant to file for a marketing authorisation in multiple, but not necessarily all, EU member states through a single procedure. The DCP accounted for the majority of applications for a marketing authorisation with 1052 procedures in 2013 (CMDh, 2014) compared to 80 procedures submitted through the centralised procedure (European Medicines Agency, 2014). Upon the application one member state acts as the Reference Member State and leads the procedure which includes performing the main benefit-risk assessment. For example, the Netherlands acted as the leading authority in over 25% of all finished DCP procedures in 2013 (CMDh, 2014). In the assessment of the submitted dossier the member states may raise major objections, which, if unresolved, are cause for refusal of the marketing authorisation application.

Licensing failure can be seen as a signature of robust regulatory control and protection of public health by preventing unsafe or inefficacious medicines reaching the patient. On the other hand, considerable resources are spent by both companies and regulatory authorities in navigating a dossier through a myriad of procedural steps raising the question of regulatory efficiency and preventable failure. Knowledge about the reasons for licensing failure could help pharmaceutical companies to identify deficiencies in their applications and to improve their drug development programs. Also, it may assist regulatory authorities to remove unnecessary hurdles for market approval.

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Our study aimed to determine the frequency of and determinants for licensing failure of marketing authorisation applications submitted via the DCP. We focussed our study on those applications where the Netherlands (i.e. the Dutch Medicines Evaluation Board) was the lead member state.

2. Material and methods

2.1. Data source

All marketing authorisation applications submitted between 1 January 2008 and 31 December 2012 in the DCP for which the Netherlands acted as the leading authority were extracted from the EU Communication and Tracking System in January 2014. Applications for the same medicinal product, but with different strengths or different product names, by the same (group of) applicant(s) were grouped into a single procedure. Subsequently, we selected the procedures in which all applications were completed and determined their outcomes. Licensing failure was defined as refusal of all applications within a procedure or withdrawal of all applications within a procedure by the applicant.

2.2. Data collection

For all completed procedures the Anatomical Therapeutic Chemical (ATC) code of the medicinal products and the legal basis (e.g. generic, hybrid or full dossier application Stegemann et al. 2011) were extracted from the Dutch Medicines Evaluation Board's documentation system. Next, for the failed procedures with at least an initial assessment report we extracted the remaining major objections from the last available assessment report – assessment reports are compiled at day 70, 120, 180 or 210 of the assessment procedure – in each procedure as documented by the Dutch Medicines Evaluation Board. So, no major objections were analysed for invalid applications and applications withdrawn before day 70 of the assessment procedure. For the failed procedures we also noted whether scientific advice was provided prior to the application.

Major objections were grouped into domains and subdomains: (1) Quality — Drug products and Drug substance; (2) Non-clinical — Pharmacodynamics, Pharmacokinetics and Toxicology; and (3) Clinical — Benefit-Risk and Equivalence. Within the subdomains the major objections were grouped into issue categories and subsequently specific issues were identified.

2.3. Data analysis

The number of procedures and the number of major objections per domain, subdomain, issue category and specific issues were entered into a database. We used descriptive statistics to present characteristics of the completed procedures, licensing failure rates and frequencies of specific major objections. Risk ratios were calculated using MedCalc (www.medcalc.org/calc/relative_risk.ph). To assess potential differences in reasons for failure at different points in time during the procedure an additional analysis was performed comparing early termination of a procedure (latest report is from day 70 or day 120) with late termination (latest report is from day 180 or day 210) of a procedure using a chi-square test.

3. Results

3.1. Characteristics of the analysed procedures and licensing failure rates

During the study period 2482 marketing authorisation applications were submitted that constituted a total of 519 procedures. Of these, 492 procedures including 188 active substances were completed by January 2014, of which 48 (9.8%) procedures including 40 active substances resulted in licensing failure: 8 (1.6%) by refusal and 40 (8.1%) by withdrawal.

Table 1 shows the general characteristics of all 492 completed procedures and the 48 failed procedures. The procedures were evenly distributed between 2008 and 2012. Generic and hybrid procedures accounted for the far majority of the procedures with 80.5% and 9.8% respectively. The procedures were about as often withdrawn or refused after day 70 (n = 12) as after day 120 (n = 7), 180 (n = 12) or 210 (n = 10). In 7 procedures the applications were withdrawn before the initial assessment was finalised (i.e. at day 70). The licensing failure rate was the highest in medicinal products acting on the alimentary tract and metabolism and especially low for medicinal products acting on the cardiovascular system (risk ratio 0.06 (95% confidence interval (CI) 0.00–0.49) compared to products acting on the alimentary tract and metabolism. Hybrid applications were twice as likely to fail as generic applications (risk ratio 2.18, 95% CI 1.12–4.24).

3.2. Number and nature of the major objections

For 7 procedures no day 70 assessment report was available, leaving 41 procedures for analysis of the major objections. The total number of major objections and the numbers per domain, subdomain and issue category are shown in Table 2. A total of 93 major objections were identified in 34 of the procedures (see supplementary table for a detailed description of the individual major objections). In 7 (17%) procedures the application for a marketing authorisation was withdrawn by the applicant despite the absence of any (remaining) major objection. In most procedures there were one (n = 9) or two (n = 9) remaining major

Table 1
Characteristics of all procedures and failed procedures

	All 492 completed procedures	Failed 48 procedures		Risk ratio (95% CI)
Year of submission				
2008	81	5	(6.2%)	Ref.
2009	89	8	(9.0%)	1.46 (0.50–4.27)
2010	93	11	(11.8%)	1.92 (0.69–5.28)
2011	124	17	(13.7%)	2.22 (0.85–5.78)
2012	105	7	(6.7%)	1.08 (0.36–3.28)
Most recent report available in the procedure				
Day 70	–	12	N/A	N/A
Day 120	–	7	N/A	N/A
Day 180	–	12	N/A	N/A
Day 210	–	10	N/A	N/A
No report	–	7	N/A	N/A
ATC code				
A/Alimentary tract & metabolism	47	10	(21.3%)	Ref.
C/Cardiovascular system	73	1	(1.4%)	0.06 (0.00–0.49)
G/Genito-urinary system and sex hormones	34	4	(11.8%)	0.54 (0.18–1.57)
J/Antiinfectives for systemic use	51	3	(5.9%)	0.28 (0.08–0.94)
L/Antineoplastic and antineoplastic and immunomodulating agents	77	7	(9.1%)	0.43 (0.17–1.06)
M/Musculo-skeletal system	35	2	(5.7%)	0.27 (0.06–1.15)
N/Nervous system	109	14	(12.8%)	0.60 (0.29–1.26)
R/Respiratory system	25	4	(16.0%)	0.75 (0.26–2.16)
S/Sensory organs	20	2	(10.0%)	0.47 (0.11–1.95)
Other	21	1	(4.8%)	0.22 (0.03–1.64)
Legal basis				
Generic application	396	34	(8.6%)	Ref.
Hybrid application	48	9	(18.8%)	2.18 (1.12–4.27)
Full dossier application	12	1	(8.3%)	0.97 (1.14–6.51)
Well established use application	18	3	(16.7%)	1.94 (0.66–5.73)
Fixed dose combination application	4	0	(0.0%)	N/A
Other[a] and combinations[b]	14	1	(7.1%)	0.83 (0.12–5.65)
Scientific advice				
Yes	–	3	N/A	N/A
No	–	45	N/A	N/A

[a] i.e. informed consent applications.
[b] i.e. generic and hybrid applications combined in one procedure or generic and an informed consent application combined in one procedure.

objections at the time of refusal or withdrawal. The highest number of major objections in one procedure was eight. This concerned an inhalation combination product for the treatment of asthma. It had six major objections regarding methodology and design of the bioequivalence study and demonstration of therapeutic equivalence, e.g. choice of patient category and choice of endpoints, and one safety concern due to insufficient measurements of blood concentrations levels.

3.2.1. Quality

The identified major objections were about equally distributed between quality and clinical concerns. No major objections with regard to the non-clinical aspects of the application dossier were identified. Quality major objections more often concerned the *drug product* than the *drug substance* (Table 2). The major objections concerning the *drug product* related to insufficient control of impurities, insufficient control of the manufacturing process, insufficient pharmaceutical development and insufficient pharmaceutical equivalence with the innovator product. The latter constituted quality major objections because quality data may need to be provided in support of bioequivalence or therapeutic equivalence studies or to substantiate a biowaiver (i.e. permission not to submit bioequivalence studies). This may include, for example, data to demonstrate similarity of dissolution profiles of the generic product and the innovator product. An example of a major objection on the insufficient control of impurities is the lack of a proper explanation for brown spots observed on the tablets. Therefore the shelf life of the tablets could not be guaranteed.

All major objections about the *drug substances* concerned the Active Substance Master File[1] (ASMF) (Table 2). In particular, the identified major objections concerned insufficient control of impurities, inadequate definition of starting material, concerns about the validation of analytical methods and a violation of Good Manufacturing Practice. For example, in one procedure the starting material of the active substance had an alkylating structure that could be genotoxic. Therefore the manufacturer had to demonstrate that the amount of this potential genotoxic impurity was within the acceptable limit. The applicant withdrew the application immediately after the major objection was raised in the day 70 assessment report.

3.2.2. Clinical

Clinical major objections related to the benefit-risk profile of the product and the equivalence of the product with the reference product (Table 2). In the benefit-risk subdomain 12 of the 16 major objections concerned the demonstration of efficacy, while only 4 major objections were raised on safety issues. The majority of the clinical major objections related to the demonstration of equivalence with an innovator product as part of the substantiation of its efficacy and safety. In more detail the major objections regarding equivalence related to a wide variety of specific issues (Supplementary Table).

Fig. 1 compares the number of procedures with clinical or quality major objections and the number of clinical and quality major objections between early (after day 70 and day 120) terminated procedures and late (after day 180 or day 210) terminated procedures. A slight, but not significant, shift towards more clinical than quality major objections was observed for late versus early termination.

In 3 of the 48 (6%) procedures scientific advice was given. This concerned one full application for oral contraceptive pills and two hybrid applications for a combination inhalation product for the treatment of COPD and for a tablet for the treatment of colitis ulcerosa, respectively.

[1] Note: The Active Substance Master File (ASMF) contains all information about the active substance to assess the quality of the active substance. It is submitted by the manufacturer of the active substance under confidentiality.

Table 2
Major objections and related procedures per domain, subdomain and specific issue.

	Major objections		Procedures	
Total	93	100%	41	100%
Quality	42	52%	22	54%
Drug product	**32**	***34%***	**17**	***42%***
Insufficient control of impurities	9		6	
Insufficient control of manufacturing process	4		4	
Insufficient pharmaceutical development	3		2	
Insufficient pharmaceutical equivalence with reference product	15		9	
Drug substance	**16**	***17%***	**7**	***17%***
Active substance master file	16		7	
Clinical	**45**	**48%**	**22**	**54%**
Benefit-Risk	**16**	***17%***	**8**	***20%***
Efficacy not demonstrated	12		6	
Safety concerns	4		3	
Equivalence with reference product	**29**	***31%***	**15**	***37%***
Bioequivalence not demonstrated	23		14	
Therapeutic equivalence not demonstrated	7		3	

*No major objections with regard to the non-clinical aspects of the application dossier were identified.
The significance of bold indicate the main categories.

4. Discussion

Of all the DCP procedures in the period 2008 to 2012 with the Netherlands as lead European authority, one out of 10 procedures failed. Important remaining deficiencies regarded both quality and clinical aspects. We observed a wide variety of specific deficiencies leading to refusal or withdrawal of applications. Clinical major objections mainly concerned the equivalence with the innovator product. Quality major objections concerned the medicinal products and the active substances, e.g. the amount of impurities. In addition, a substantial share of the quality major objections concerned substantiation of the equivalence to the innovator product by pharmaceutical characteristics.

The licensing failure rate of the procedures in our study (9.8%) is low when compared to the applications via the EU centralised procedure (27.1%) (Regnstrom et al., 2010) and approval procedures for new molecular entities in the US (26.5%) (Sacks et al., 2014). The lower failure rate may be attributed to the large proportion of generics and hybrid applications in our study, for which the development is relatively straightforward as the efficacy and safety of the active moiety is already known and not to be re-established. Interestingly, in our study hybrid applications failed twice as often as generic applications. Licensing applications for hybrid products refer to efficacy and safety date of an innovator product, such as generic products. In contrast to generic applications, in hybrid applications equivalence to the innovator product cannot be determined by bioequivalence. For instance, locally applied and locally acting products, such as eye drops, to which blood levels are of no meaning, are authorised by hybrid applications. Moreover the product in a hybrid application may differ essentially from the innovator product in terms of, for example, therapeutic indications or formulation. Therefore, hybrid applications may require more advanced tests or clinical studies to demonstrate equivalence with the innovator product than generic applications and as a result may fail more often.

The relative high approval rate may be the outcome of an interaction and learning-curve between the regulators and pharmaceutical companies. Early in the assessment more major objections may have been present than identified in our study in which we assessed major objections in the latest assessment report. Regulators assess the submitted data and point out the deficiencies at different points in time during the process, allowing the applicant to submit additional data and argumentation to resolve the raised objections. For that purpose a 'clock-stop' period of up to six months is included after day 105 of the assessment. This allows the applicant to prepare its response to the major objections and, if necessary, to conduct additional studies (European

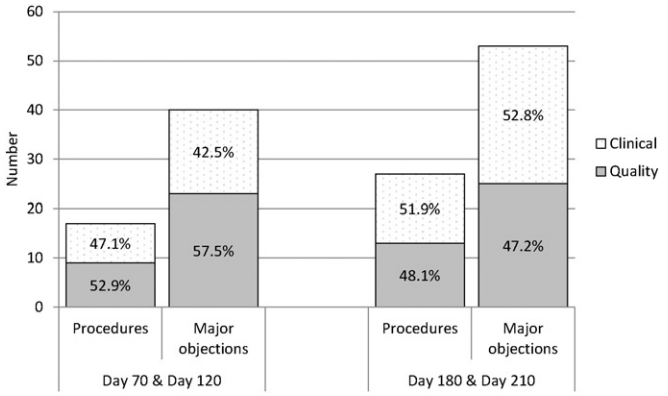

Fig. 1. Comparison of the number of procedures with quality and/or clinical major objections and the nature of the major objections between early (latest report available day 70 or 120) and late (latest report available day 180 or 210) termination of the marketing authorisation application.

Commission, 2007). Also after the distribution of the report at day 120 and 180 the applicants is provided with an opportunity to respond to the major objections (CMDh, 2013a; European Commission, 2007). At about 195 days after start of assessment a break-out session may take place in which the applicant can discuss the remaining major objections with the leading member state and the concerned member states (CMDh, 2013a,b). So, at regular intervals the authorities and applicants interact in order to resolve major objections. The process of interaction and the accompanying relatively high approval rate should not be misunderstood for negligence of the regulatory authorities to thoroughly assess the applications or to make sound judgements. The assessment procedure in the DCP, including for generics and hybrids, is as rigorous as for new chemical entities in the EU centralised procedure.

In terms of the variety of specific deficiencies leading to refusal or withdrawal, our study results do not differ from previous studies on licensing failure in the US or the EU centralised procedure (Pignatti et al., 2002; Sacks et al., 2014; Wang et al., 2013). The considerable number of quality concerns, as well as concerns regarding equivalence, could have been expected considering the dominance of generic products in the DCP. Their established benefit-risk profile substantially eliminates efficacy and safety as points for concerns. In addition, a specific reason for the high number of quality issues might be related to the use of contract manufacturers by generic companies, for example, to manufacture active substances. Such manufacturers often produce the same active substance for multiple generic companies and might not be willing to resolve a specific issue for one generic company. Instead, innovative companies often have full control over the manufacturing process, as they tend to manufacture their new chemical entity active substance themselves.

Several of the identified major objections in the DCP may have been resolvable, e.g. during the clock-stop, by submitting readily available or obtainable quality data or additional bioequivalence data. However, non-innovator pharmaceutical companies might be less willing, or able, to resolve deficiencies considering the investments at low profit margins. In some cases, companies may have tried to obtain approval with minimal investments while accepting a refusal. This may explain the minimal number of quality concerns in previous studies on licensing failure for new chemical entities and biologicals, since innovator companies might be more driven to resolve outstanding quality major objections during the assessment, given the prospect of substantial profits (Pignatti et al., 2002; Sacks et al., 2014).

We expected that quality related major objections would cause earlier termination of marketing authorisation applications, because quality issues might be more pronounced early in the assessment, while clinical issues could be more susceptible to debate with the regulators. However, only a slight shift in type of major objection between early and late termination of procedures was found, not constituting a clear difference.

Various major objections concerned deviations from scientific or regulatory guidelines, as can be observed in the Supplementary Table. Regulatory and scientific guidelines are intended to provide pharmaceutical companies with a clear course of the assessment procedure. Drug development in conformity with those guidelines may reduce the licensing failure rate. In case of doubts on the applicability or interpretation of guidelines, companies may apply for scientific and/or regulatory advice, preferably in an early stage of the development. In 6% of the failed procedures such advice was requested prior to the application. From internal Medicines Evaluation Board documents we know that scientific advice was given for 11% of the medicinal products approved between September 2011 and September 2013 through the DCP with the Netherlands as leading authority. Compliance with scientific advice has been associated with marketing approval in the centralised procedure (Regnstrom et al., 2010).

Furthermore, it should be noted that licensing failure may be due to other reasons than the major objections in the assessment procedure. In our study, 7 procedures were withdrawn without any major objections remaining. Some applicants explicitly mentioned such reasons, such as the withdrawal of an application because the company changed the development focus from generics to new medicinal products. Another applicant withdrew its application because of an overlap in product portfolio after a recent merger.

Our study has several limitations. First, we only included the remaining major objections of failed procedures. As mentioned before multiple major objections may have been resolved throughout the assessment. Future studies may assess in greater detail how initial major objections changed or are resolved throughout the assessment procedure. This may provide regulatory authorities insight in the major objections which initially constitute hurdles, but do not lead to refusal. It may also help pharmaceutical companies to submit better applications, which may save valuable time in the assessment procedure. Second, the present study only concerned procedures with the Netherlands as leading authority and EU member states may differ in their specialities and preferences regarding therapeutic areas, which may affect the licensing failure rate. However, as mentioned before the Netherlands acts as the leading authority for a substantial share of all application through the DCP (CMDh, 2014). In addition, the DCP is by nature a combination of assessments by multiple member states. Hence, we believe that our data may provide a comprehensive representation of major objections in the DCP in general. Finally, it should be noted that the major objections are often of a multidisciplinary nature. They may include aspects of multiple different, but related deficiencies. Therefore the assessment of the major objections is subject to interpretation of the researchers, although this has been prevented as much as possible by consultation of senior assessors and regulators of the Dutch Medicines Evaluation Board to determine the key point of the major objections.

5. Conclusions

In the best interest of public health, it is the regulators' task to prevent ineffective and unsafe medicines from entering the market, and to contribute to patients' access to beneficial medicines. Our study showed that approximately one out of 10 procedures in the DCP with the Netherlands as leading authority failed, which was due to a wide variety of determinants, both quality and clinical related. The low failure rate may be related to the regular interaction between authorities and pharmaceutical companies throughout the assessment. However, given the wide variety of major objections there might not be a magic button to prevent the deficiencies in the submitted dossiers. In addition, the success of an application may to some extent depend on the financial feasibility and willingness to resolve major objections, especially for off patent generic medicinal products. Besides, pharmaceutical companies may withdraw their marketing authorisation applications due to

reasons other than the raised major objections. Overall, some degree of licensing failure may thus be inevitable.

Conflict of interest

The authors declared no potential conflicts of interest that are directly relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejps.2015.10.014.

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