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Process of drug registration in Israel: the correlation between the number of discussions within the Ministry of Health and postapproval variations by EMA and/or FDA

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ABSTRACT

Objectives US FDA and EMA allow facilitated regulatory pathways to expedite access to new treatments. Limited supportive data may result in major postapproval variations. In Israel, partly relying on Food and Drug Administration (FDA) and European Medicines Agency (EMA), clinical data are reviewed independently by the Advisory Committee of Drug Registration (ACDR). In this study, the correlation between the number of discussions at the ACDR and major postapproval variations is examined.

Design This is an observational retrospective comparative cohort study.

Setting Applications with FDA and/or EMA approval at time of assessment in Israel were included. The timeframe was chosen to allow a minimum of 3 years of postmarketing approval experience for potential major label variations. Data regarding the number of discussions at ACDR were extracted from protocols. Data on postapproval major variations were extracted from the FDA and EMA websites.

Results Between 2014 and 2016, 226 (176 drugs) applications, met the study criteria. 198 (87.6%) and 28 (12.4%) were approved following single and multiple discussions, respectively. A major postapproval variation was recorded in 129 (65.2%) compared with 23 (82.1%) applications approved following single and multiple discussions, respectively (p=0.002). Increased risk for major variation was found for medicines approved following multiple discussions (HR=1.98, 95% CI: 1.26 to 3.09) with a median time of 1.2 years, applications approved based on phase II trials (HR=2.58, 95% CI: 1.72 to 3.87), surrogate endpoints (HR=1.99, 95% CI: 1.44 to 2.74) and oncologic indications (HR=2.48, 95% CI: 1.78 to 3.45).

Conclusions Multiple ACDR discussions associated with limited supportive data are predictive for major postapproval variations. Moreover, our findings demonstrate that approval by the FDA and/or EMA does not pave the way to automatic approval in Israel. In a substantial per cent of the cases, submission of the same clinical data resulted in different safety and efficacy considerations, requiring additional supporting data in some cases or even rejection of the application in others.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study examined more than 200 applications approved in Israel between 2014 and 2016.
⇒ Analysis of various parameters with possible impact on the regulatory decisions such as clinical study phase, surrogate endpoints and others was included.
⇒ This study focused on the two leading regulatory authorities with publicly available and open online databases, and omitted drug applications submitted to other authorities.
⇒ Postapproval variations made by European Medicines Agency (EMA) and Food and Drug Administration (FDA) were pulled together into one database.
⇒ The pathways for submission, evaluation and approval of postapproval variations by EMA and FDA are different (eg, black box warning in FDA labelling, type II variation classification by EMA, etc), which could result in different outcomes.

BACKGROUND

The WHO (World Health Organization) states that part of each country's responsibilities for public health is the maintenance of an efficient regulatory system which assures strict standards for quality, efficacy, and safety of drugs.[1]

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are the world's leading regulatory authorities and have established the global landscape for drug regulation. According to these two authorities, the gold standard for clinical trials required as a basis for new drug application is two phase III comparative studies, one versus placebo and the other versus standard of care. In practice, many new drug applications and especially new indications for approved drugs are submitted with partial data, occasionally with phase II trial outcomes or results of an interim analysis.[1]

Regulatory authorities should enable the availability of new lifesaving and breakthrough therapies which can improve and even save patients' lives. On the other hand, in order to protect the health of the public, reliable scientific data are needed regarding safety and efficacy. There is a delicate balance between facilitated access and the need for ensuring the safety and efficacy of new drugs or indications.

In recent years, various regulatory pathways, aiming to expedite access to new drugs have become available. For example, FDA has several pathways, including priority review with a shortened assessment period of 6 months (instead of 10 months).[2–4] Other pathways allow the submission of partial results or results based on surrogate endpoints instead of mature and final clinical outcomes.[5] EMA, which is responsible for the evaluation of drugs applied through the Central procedure in European Union countries,[6–8] established an accelerated assessment pathway, reviewing the applications within 150 days (as opposed to the 210 day timeline for regular review).[9] In addition, similar to FDA, EMA permits the submission of partial data to support the safety and efficacy of orphan drugs or therapies targeting diseases with no available treatment. In these cases, the drugs will be approved for a limited period of time through the conditional marketing authorisation approval. As part of the conditions of such approval, sponsors are obliged to submit additional data supporting the safety and efficacy of the drug such that full marketing authorisation could be granted. For rare conditions, where additional information cannot be produced (eg, orphan diseases or other special indications), approval under exceptional circumstances can be granted.[10 11] Both in FDA and EMA, these accelerated pathways are reserved for new drugs, breakthrough therapies and orphan designations.

Uncertainties related to the benefit–risk balance result in a higher incidence of postapproval major variations (addition of contraindication, warning or common or severe adverse events, indication or dosage restriction and drug withdrawal). Shepshelovich *et al* examined the postapproval variations in labelling for cancer drugs approved by FDA between 2006 and 2016 with and without supporting randomised controlled trials (RCTs), and came to the conclusion that drugs approved without supporting RCTs had a higher incidence of post-approval variations, related to common adverse events, Black Box Warnings and contraindications during postapproval follow-up.[12–14]

The Pharmaceutical Division at the Ministry of Health of Israel is responsible for the approval of new drugs and postapproval variations. The evaluation process is carried out simultaneously at the Drug Registration Department, assessing the data related to safety and efficacy, and at the Institute for Standardization and Control of Pharmaceuticals, responsible for the evaluation of the quality part of the dossier.

Most of the new drug applications are submitted in Israel following approval by health authorities in one of the recognised countries, which include the USA, the European Union, Japan, Australia, New Zealand, Canada, Switzerland, Norway and Iceland.[15] The evaluation of a drug application is usually done on the level of abridged assessment, relying on the pre-clinical data evaluation carried out by the health authority in one of the recognised countries.

The first stage of the drug application review is submission validation, during which assessors from the Drug Registration Department and the Institute for Standardization and Control of Pharmaceuticals verify that the file submitted meets the requirements. If accepted for assessment, the available clinical data supporting safety and efficacy are forwarded for a review of at least two external expert physicians, usually members of the Advisory Committee for Drug Registration (ACDR). The external experts are key opinion leaders in the scope of the application, and their participation in the ACDR is pending approval by the legal department of the Ministry of Health. The application is discussed in a scheduled meeting of the ACDR, where a recommendation regarding the approval of the application and conditions for approval is taken.[16] The ACDR's decision regarding the application could be either accepted, accepted with modifications, accepted with postapproval requirements, rejected or pending further data and clarifications.

In this study, we examined the correlation between the number of discussions per application at the ACDR in Israel, as an indicator for uncertainties regarding risk–benefit balance, and major post-approval variation by FDA or EMA.

METHODS

Identification of study drugs

Drug application files and protocols of the ACDR in Israel from 2014 to 2016, accessed via the Ministry of Health database, were reviewed by two researchers. Differences of opinion between the researchers were resolved by further discussion and additional data collection. Applications with FDA and/or EMA approval at the time of assessment in Israel were included in the analysis. The timeframe was chosen to allow a minimum of 3 years of postapproval experience for potential major label variations by EMA or FDA. Applications with negative benefit–risk balance as per local assessment, applications for

indication restriction, dosing regimen variations, applications for biosimilar drugs, drugs administered topically, ophthalmic drugs, coagulation factors and vaccines approved only by the FDA were excluded from this analysis to avoid confounders, as these types of applications constitute a minor and insignificant part of the ACDR work. New indications for approved drugs were considered a new drug application.

The number of discussions held for each drug application (single discussion vs multiple) was recorded.

Identification of major postpproval variations

The EMA and FDA online databases were scanned in order to confirm the regulatory pathway through which the drug was approved (regular or facilitated) and detect any major postapproval variations (date and type of variation). For drugs approved by the FDA, *Drugs@FDA*[17] database was scanned, as were data regarding regulatory approval[18–22] and the Drug Safety-related Labeling Changes page.[23] For drugs approved by the EMA, EMA's website[24] was scanned as was the European Commission database.[25] A major variation was defined as an addition of contraindication, warning or common or severe adverse event, indication or dosage restriction and drug withdrawal. The last version of each drug label available prior to drug approval in Israel was compared with the subsequent drug label versions. Drug survival was defined as the length of time from drug approval in Israel until documentation of first postapproval major variation by FDA or EMA.

Statistical analysis

The correlation between drug characteristics and duration of approval (single vs multiple discussion) was explored using the χ^2 test or Fisher's exact test. Associations between single versus multiple discussions as well as drug characteristics and occurrence of postapproval major variation during the follow-up period were explored using log-rank test. Hazard ratios (HRs) were described, as were their respective 95% CIs, for both univariate and multivariate analyses using Cox regression. Data analyses were conducted using SPSS Statistics for Windows, V.25.0 (IBM Corp). All statistical tests were two-sided, and statistical significance was defined as p<0.05.

Patient and public involvement

No patient involved

RESULTS

Drug characteristics

Between 1 January 2014 and 31 December 2016, 292 applications, previously approved by the FDA and/or EMA, were discussed in the ACDR meetings. Among these, 226 applications which included 176 drugs, met the study criteria (figure 1).

Twenty-eight (12.4%) applications were approved following multiple discussions and 198 (87.6%) were approved following a single discussion. Characteristics of the drug applications are presented in table 1.

Most of the applications were for drugs in the field of oncology (31.0%) followed by haematology (14.6%), and infectious disease (14.6%). The majority of the applications were for drugs administered orally (43.8%), intravenously (25.2%) and subcutaneously (19.0%). The number of applications for new drug registration was 115 and 99 for new indications. One hundred (44.2%) applications were for biologic drugs.

All applications analysed in this study were previously approved by the FDA and EMA (169 and 167, respectively); of these 59 (34.9%) of 169 were approved only by FDA and 57 (34.1%) of 167 only by EMA. Eighty-nine (out of 169) drug applications were approved via one of the FDA facilitated regulatory approval pathways (52.7%), while only 25 (out of 167) were approved via EMA's facilitated pathways (15.0%). Most of the applications were approved based on phase III clinical trials (80.1%) and 40.3% were approved based on surrogate endpoints.

Single versus multiple discussions and major postapproval variations

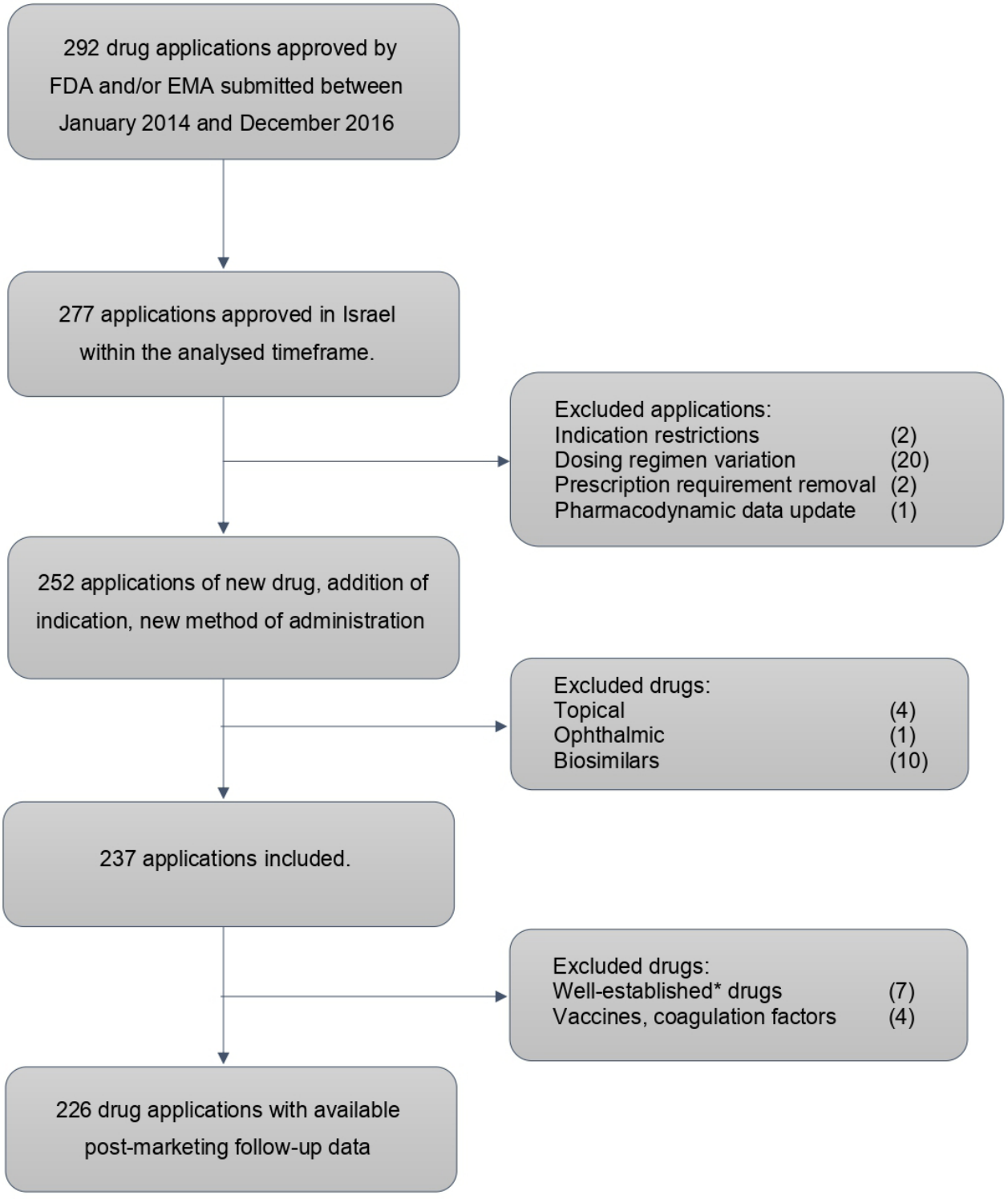
The median follow-up time for postapproval major variations by FDA and/or EMA was 4.3 years (95% CI: 11 days to 5.5 years). Out of 198 applications approved following a single discussion, for 129 (65.2%) applications, a postapproval major variation was recorded during the follow-up, as opposed to 23 (82.1%) out of 28 applications approved following multiple discussions (p=0.002). The median time from the approval of the application in Israel to the first recorded major variation was 2.4 years (95% CI: 1.9 to 3.0). The median time for major variation for drugs approved following a single discussion was 2.8 years (95% CI: 2.2 to 3.4) versus 1.2 years (95% CI: 0.6 to 1.8) for drugs approved following multiple discussions (p=0.002), as shown in figure 2.

After 4 years follow-up, a major variation was recorded for all drugs approved following multiple discussions vers 60% of drugs approved following a single discussion.

Correlations between drug characteristics and major variations are described in tables 2 and 3. Based on univariate analysis (table 2), a significant correlation was found for applications approved following multiple discussions, oncologic drugs, PO or SC administration, approvals based on phase II trials and applications based on surrogate endpoints.

In multivariate analysis, only oncologic drugs, PO administration and FDA (but not EMA) facilitated pathways were found to be statistically significant predictive factors correlated with postapproval major variations (table 3).

Since approval by FDA and/or EMA was found to be a significant predictive factor, a subcomparison was performed for each regulatory authority including three subgroups (application rejected, approved via the regular pathway and approved via facilitated pathway). For FDA approvals, a statistically significant correlation was found



* Well-established drugs are drugs that fulfill all the following criteria
1. A drug that was registered and marketed in Israel in the past or a similar drug (active substance, strength, and pharmaceutical form) marketed in a recognized country for more than 10 years.
2. The active substance is included in the Israeli National Health Services and there is no product registered in Israel with same active substance.
3. The safety profile of the drug is known, and the benefits outweighs the risks.
4. The drug or similar drug (same active substance, strength, and pharmaceutical form), is imported to Israel according to regulation 29C due to authorized drug marketing termination.

Figure 1 Flowchart of applications included in the dataset. EMA, European Medicines Agency; FDA, Food and Drug Administration.

Table 1 Characteristics of drugs within the dataset and comparison between approval following single versus multiple discussions

Characteristics	All applications	Applications approved following single discussion	Applications approved following multiple discussions	P*
Number of applications	226	198 (87.6%)	28 (12.4%)	
Indication, N (%)				
Autoimmune	22 (9.7%)	21 (10.6%)	1 (3.6%)	0.326
Dermatology	17 (7.5)	16 (8.1%)	1 (3.6%)	0.702
Cardiology	12 (5.3%)	11 (5.6%)	1 (3.6%)	>0.999
Oncology	70 (31.0%)	53 (26.8%)	17 (60.7%)	**<0.001**
Haematology	33 (14.6%)	24 (12.1%)	9 (32.1%)	**0.01**
Infectious disease	33 (14.6%)	28 (14.1%)	5 (17.9%)	0.573
Gastroenterology	24 (10.6%)	22 (11.1%)	2 (7.1%)	0.747
Nephrology	2 (0.9%)	2 (1.0%)	0 (0.0%)	>0.999
Pulmonology	20 (8.8%)	18 (9.1%)	2 (7.1%)	>0.999
Ophthalmology	9 (4.0%)	9 (4.5%)	0 (0.0%)	0.606
Endocrinology	29 (12.8%)	26 (13.1%)	3 (10.7%)	>0.999
Psychiatry	6 (2.7%)	6 (3.0%)	0 (0.0%)	>0.999
Rheumatology	15 (6.6%)	14 (7.1%)	1 (3.6%)	0.701
Urology	6 (2.7%)	6 (3.0%)	0 (0.0%)	>0.999
Neurology	6 (2.7%)	6 (3.0%)	0 (0.0%)	>0.999
Gynaecology	7 (3.1%)	6 (3.0%)	1 (3.6%)	>0.999
Medical Genetics	9 (4.0%)	7 (3.5%)	2 (7.1%)	0.309
Method of administration, N (%)				
PO	99 (43.8%)	87 (43.9%)	12 (42.9%)	0.914
Intravenous	57 (25.2%	47 (23.7%)	10 (35.7%)	0.172
Intramuscular	13 (5.8%)	11 (5.6%)	2 (7.1%)	0.667
SC	43 (19.0%)	39 (19.8%)	4 (14.3%)	0.488
Inhalation	4 (1.8%)	4 (2.0%)	0 (0.0%)	>0.999
Intravitreal	7 (3.1%)	7 (3.5%)	0 (0.0%)	0.601
Intrauterine	1 (0.4%)	1 (0.5%)	0 (0.0%)	>0.999
Intrabuccal	1 (0.4%)	1 (0.5%)	0 (0.0%)	>0.999
Previous approval, N (%)				
Regular approval by FDA Facilitated approval by FDA	80 (35.4%) 89 (39.4%)	72 (36.4%) 73 (36.9%)	8 (28.6%) 16 (57.1%)	0.106
Regular approval by EMA Facilitated approval by EMA	142 (62.8%) 25 (11.1%)	129 (65.2%) 21 (10.6%)	13 (46.4) 4 (14.3%)	0.15
Facilitated approval	61 (27.0%)	48 (24.2%)	13 (46.4%)	**0.013**
Approved based on phase II trial	33 (14.6%)	22 (11.1%)	11 (39.3%)	**<0.001**
Approved based on phase III trial	181 (80.1%)	165 (83.3%)	16 (57.1%)	**0.001**
Approved based on surrogate endpoint	91 (40.3%)	72 (36.4%)	19 (67.9%)	**0.001**
Type of application, N (%)				
New drug registration	115 (50.9%)	104 (52.5%)	11 (39.3%)	0.19
Addition of indication	99 (43.8)	85 (42.9%)	14 (50.0%)	0.48
New method of administration	12 (5.3)	9 (4.5%)	3 (10.7%)	0.174
Other characteristics, N (%)				
Biologic drug	100 (44.2%)	85 (42.9%)	15 (53.6%)	0.289

Values in bold are statistically significant at p<0.05.
*P value for comparison between the per cent with single versus multiple discussions.
PO, per os; SC, subcutaneous; FDA, Food and Drug Administration; EMA, European Medicines Agency.

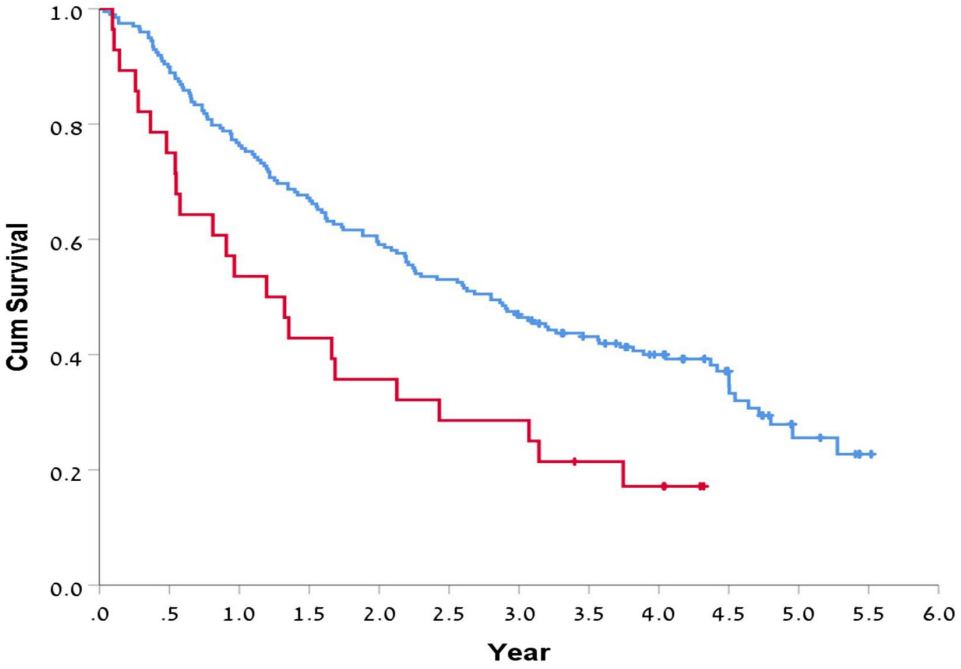


Figure 2 Survival of drug applications. Approved following single (blue) versus multiple (red) discussions, without recorded major variations.

for applications approved via facilitated pathway versus regular pathway (p<0.001) as well as versus applications rejected (p=0.023). Comparable findings were demonstrated for EMA approvals with a statistically significant correlation in applications approved via facilitated pathway versus regular pathway (p=0.001).

Higher risk for occurrence of postapproval major variation was associated with drug applications approved following multiple discussions (HR: 1.98; 95% CI: 1.26 to 3.09), as well as applications in the field of oncology (HR: 2.48; 95% CI: 1.78 to 3.45) and applications of drugs administered Per Os (PO) (HR: 1.79; 95% CI: 1.29 to 2.46). Higher risk for postapproval major variation was also associated with applications not approved by FDA, but approved by EMA (HR: 1.35; 95% CI: 0.88 to 2.09), applications approved via a facilitated pathway by the FDA (HR: 2.21; 95% CI: 1.52 to 3.21), as well as applications not approved by EMA but approved by FDA (HR: 1.41; 95% CI: 0.98 to 2.03) and applications approved via a facilitated pathway by the EMA (HR: 2.18; 95% CI: 1.35 to 3.51). An additional association was found for applications approved based on phase II clinical trial (HR: 2.58; 95% CI: 1.72 to 3.87) and applications approved based on a surrogate endpoint (HR: 1.99; 95% CI: 1.44 to 2.74). Lower risk for occurrence of major variation was found for applications approved based on phase III clinical trials (HR: 0.5; 95% CI: 0.32 to 0.67).

DISCUSSION

To our knowledge, this is the first study which examines the association between the number of discussions as part of the application assessment process in countries partly relying on FDA and EMA assessment and the variations imposed by those same authorities' postapproval. The assessment process for new drug applications and post-authorisation variations in Israel is mainly an abridged one, focusing on quality and the clinical data supporting safety and efficacy, while relying on the evaluation of preclinical data by FDA, EMA and regulatory authorities of other recognised countries. However, approval by the FDA and/or EMA does not pave the way to automatic approval in Israel. Indeed, this study found that from 2014 to 2016, 17.0% of the applications discussed in the ACDR were not approved or approved with limitation of use (conditions for approval and/or major variations) compared with the approval by FDA and/or EMA. This finding, as well as the rate of drug applications approved following multiple discussions (12.4%), indicate that in a substantial percentage of the cases, submission of the same clinical data resulted in a different safety and efficacy considerations, requiring additional supporting data in some cases or even rejection of the application in others.

Dörr *et al*, compared between the approvals of new drug applications made by Swissmedic versus FDA and EMA. The authors reported that Swissmedic did not approve 7% of the applications approved by EMA.[26] As opposed to Israel, prior approval by FDA and/or EMA are not required for drug applications submitted to Swissmedic and each application is subjected to a full assessment process.

In our study, we found that among drug applications approved following multiple discussions, in which objections regarding the efficacy and safety were raised during the assessment process, the incidence of postapproval major variations was higher compared with

Table 2 Univariate analysis of predictive factors for drug label major variation

Characteristics	Major variation not documented*	Major variation documented*	P
Number of applications	74	152	
Approved following multiple discussions	5 (6.8%)	23 (15.1%)	**0.002**
Indication, N (%)			
Autoimmune	7 (9.5%)	15 (9.9%)	0.548
Dermatology	5 (6.8%)	12 (7.9%)	0.559
Cardiology	4 (5.4%)	8 (5.3%)	0.515
Oncology	11 (14.9%)	59 (38.8%)	**<0.001**
Haematology	7 (9.5%)	26 (17.1%)	0.06
Infectious disease	12 (16.2%)	21 (13.8%)	0.947
Gastroenterology	5 (6.8%)	19 (12.5%)	0.137
Nephrology	1 (1.4%)	1 (0.7%)	0.705
Pulmonology	8 (10.8%)	12 (7.9%)	0.415
Ophthalmology	8 (10.8%)	1 (0.7%)	**0.007**
Endocrinology	11 (14.9%)	18 (11.8%)	0.423
Psychiatry	2 (2.7%)	4 (2.6%)	0.774
Rheumatology	4 (5.4%)	11 (7.2%)	0.844
Urology	1 (1.4%)	5 (3.3%)	0.231
Neurology	1 (1.4%)	5 (3.3%)	0.748
Gynaecology	4 (5.4%)	3 (2.0%)	0.246
Medical Genetics	5 (6.8%)	4 (2.6%)	0.392
Method of administration, N (%)			
PO	21 (28.4%)	78 (51.3%)	**<0.001**
IV	19 (25.7%)	38 (25.0%)	0.492
IM	6 (8.1%)	7 (4.6%)	0.134
SC	19 (25.7%)	24 (15.9%)	**0.036**
Inhalation	1 (1.4%)	3 (2.0%)	0.529
Intravitreal	6 (8.1%)	1 (0.7%)	**0.021**
Intrauterine	1 (1.4%)	0 (0.0%)	0.209
Intrabuccal	0 (0.0%)	1 (0.7%)	0.718
Previous approval, N (%)			
Regular approval by FDA Facilitated approval by FDA	33 (44.6%) 20 (27.0%)	47 (30.9%) 69 (45.4%)	**<0.001**
Regular approval by EMA Facilitated approval by EMA	56 (75.7%) 4 (5.4%)	86 (56.6%) 21 (13.8%)	**0.003**
Facilitated approval	10 (13.5%)	51 (33.6%)	**<0.001**
Approved based on phase II trial	3 (4.1%)	30 (19.7%)	**<0.001**
Approved based on phase III trial	67 (90.5%)	114 (75.0%)	**<0.001**
Approved based on surrogate endpoint	17 (23.0%)	74 (48.7%)	**<0.001**
Type of application, N (%)			
New drug registration	38 (51.4%)	77 (50.7%)	0.638
Addition of indication	33 (44.6%)	66 (43.4%)	0.702
New method of administration	3 (4.1%)	9 (5.9%)	0.841
Other characteristics, N (%)			
Biologic drug	41 (55.4%)	59 (38.8%)	**0.023**

Values in bold are statistically significant at p<0.05.
*The percentage was calculated out of total applications for which major variation was or was not documented. The percentage was calculated out of total applications approved according to the number of discussions.
EMA, European Medicines Agency; FDA, Food and Drug Administration; PO, per os; SC, subcutaneous.

Table 3 Multivariate analysis of predictive factors for drug label major variation (Including regulatory authorities)*

Characteristics†	Hazard ratio	Confidence interval	P*
Approved following multiple discussions	1.26	0.73-2.16	0.404
Oncology	1.91	1.20-3.02	**0.006**
PO administration	2.04	1.20-3.46	**0.009**
SC administration	1.13	0.65-2.01	0.664
Biologic drug	1.15	0.66-2.01	0.627
Facilitated approval by FDA	1.65	1.09-2.49	**0.019**
Facilitated approval by EMA	1.6	0.94-2.72	0.087
Approved based on phase II trial	0.92	0.39-2.17	0.853
Approved based on phase III trial	0.78	0.37-1.64	0.509
Approved based on surrogate endpoint	1.04	0.68-1.60	0.846

Values in bold are statistically significant at p<0.05.
*Variables found significant in univariate analysis were included.
†In rare events, cox regression does not converge so not all significant variables were included.
PO, per os; SC, subcutaneous.

drug applications approved following a single discussion. Furthermore, the time for first major variation by EMA and/or FDA for applications approved following multiple discussions was much shorter (1.2 vs 2.8 years) as compared with applications approved following single discussion.

Most of the applications approved following multiple discussions were in the field of oncology and haematology. An oncologic indication was found to be a predictive factor for major variations. Additionally, we found that applications based on phase II clinical trials and/or on surrogate endpoints were approved following multiple discussions and were predictive factors for major variations. Previous studies have shown that drugs indicated for oncologic and haematologic diseases are frequently approved through facilitated pathways,[27] and comprise the majority of drugs approved without supporting RCTs.[28] Typically in these cases, the primary outcome is based on a surrogate endpoint (such as overall response rate (ORR)) as opposed to the gold standard clinical outcome of overall survival (OS).[13] Approval using surrogate endpoints justifies the requirement for additional efficacy and safety data, in light of the possibility of a negative risk–benefit balance.

It is a well-established fact that clinical trials are limited in their ability to detect many of the long-term adverse events in the postmarketing phase.[29 30] Most of the new drug applications, especially in the field of oncology and haematology, are submitted based on limited reports, sometimes without RCTs, and include only common and very common adverse events.[31] The limited number of participants and follow-up time underestimate less common serious and non-serious adverse events. Furthermore, in many cases, the adverse events of the coadministered drugs and the manifestations of the disease, can potentially mask the adverse events of the drug, even in RCTs, resulting in limited knowledge regarding the safety profile at the time of approval.[31] For drugs approved through conditional or accelerated pathways, post-marketing confirmatory trials are needed for further establishing safety and efficacy.[32 33]

We found a correlation between major postapproval variations and approval of an application via a facilitated pathway specifically by FDA and approval following multiple discussions in Israel. In our study, approval via FDA's facilitated pathways was found as a predictive factor for major variations in multivariate analysis. According to previous studies, facilitated drug approval is more frequent in FDA compared with EMA.[28 34] EMA's conditional marketing authorisation is limited to new drug applications, while in the USA, both new drug applications and variations in indications can be submitted for accelerated approval, thus contributing to the higher number of facilitated pathway applications in USA. Furthermore, differences in the approved indications between EMA and FDA, based on similar safety and efficacy data, reflect the differences in the approach of each regulatory authority and the diversion in the benefit–risk balance evaluation. These differences could be the basis for postapproval variations in labelling, in view of the discrepancies in the approval between these two authorities.[35 36]

It is noteworthy, that besides Israel, other regulatory authorities also have approval pathways which rely on approvals by major regulatory authorities, like EMA and FDA. Singapore, for example, has abridged approval process for applications approved by one reference authority and a verification approval process for applications approved by at least two reference authorities.[37] In Australia, the Therapeutic Goods Administration (TGA) has a special pathway for approval of prescription medicines based on assessments from comparable overseas regulators.[38] In cases relying on EMA and/or FDA accelerated drug approvals, there is probably a need for thorough evaluation of the basis for approvals made by the EMA and/or FDA.

STUDY LIMITATIONS

This study focused on the two leading regulatory authorities with a publicly available and open online database, omitting drug applications submitted to other authorities. Postapproval variations made by EMA and FDA were pulled together into one database. The pathways for submission, evaluation and approval of postapproval variations by EMA and FDA are different (eg, black box warning in FDA labelling, type II variation classification by EMA, etc),[39 40] which could result in different outcomes.

CONCLUSIONS

The higher incidence of postapproval major variations found in drugs approved following multiple discussions

suggests that the issues raised during those repeat discussions were justified. Multiple discussions are often done following requests for additional efficacy and/or safety information or due to further consultation with experts in the field. These findings reinforce the actions of the Drug Registration Department and its Advisory Committee as an independent decision-making process. For regulatory authorities relying on EMA and/or FDA accelerated drug approvals, a further evaluation should be considered.

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