ELSEVIER
Journal of Clinical Epidemiology xxx (xxxx) xxx
Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents

Kim Boesen[a,b,*], Karsten Juhl Jørgensen[b,c,d], Peter C Gøtzsche[e]

[a] *Meta-Research Innovation Center Berlin (METRIC-B), Berlin Institute of Health at Charité, QUEST Center for Responsible Research, Germany*
[b] *Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark*
[c] *Centre for Evidence-Based Medicine Odense (CEBMO) and Cochrane Denmark, Department of Clinical Research, University of Southern Denmark, Odense, Denmark*
[d] *Open Patient data Exploratory Network (OPEN), Odense University Hospital, Odense, Denmark*
[e] *Institute for Scientific Freedom, Copenhagen, Denmark*

Accepted 30 October 2021; Available online xxx

Abstract

Objectives: To assess whether drug regulatory agencies decided on applications for extended-release methylphenidate for use in adult ADHD based on select samples of trials.

Study design and setting: Case series of publicly available regulatory documents. We matched an index of extended-release methylphenidate trials for adult ADHD with trials appearing in regulatory documents of extended-release methylphenidate applications. Trials and regulatory documents were identified as part of this systematic review (https://doi.org/10.1002/14651858.CD012857). We sought to identify missing trials in the regulatory documents and to clarify regulatory submission requirements.

Results: We indexed 18 trials and matched those with 13 drug applications (11 approved, 2 rejected) published by 7 agencies. There were trials missing in 7 (54%) of 13 applications, median 4 trials (range 1-6). The median proportion of missing trial participants was 45% (range 23% - 72%). Regulators seemingly require that all trials must be included in new drug applications, but wording is ambiguous.

Conclusion: In this sample of extended-release methylphenidate drug applications for adult ADHD, 7 of 13 regulatory decisions were missing entire trials according to public documents, even though regulatory requirements seem to stipulate that all available trials should be included in drug applications.

Keywords: Drug authorisations; Drug regulatory agencies; Clinical trials; Psychiatry; ADHD; Methylphenidate

1. Background

Selective publication of trials [1,2] and selective outcome reporting [3,4] are common. For clinical trials published in medical journals, there can be important discrepancies compared to the raw trial data submitted to the drug regulators [5–7] and patient reported outcomes and harms seem to be particularly underreported in published reports [8,9].

In 2008, it was reported that 31% of trials of antidepressants included in new drug applications submitted to the US Food and Drug Administration (FDA) were never published in medical journals [10]. Most of these unpublished trials did not favour the antidepressant and were considered "negative" by the FDA [10]. The authors assumed that FDA's cohort of clinical trials was exhaustive and did not investigate whether the companies had conducted more clinical trials.

When pharmaceutical companies apply for marketing authorisation of a new drug, they must submit an application in the form of a Common Technical Document [11]. This is the international standard for all major drug regulatory agencies, and the document must contain information regarding quality assurance, non-clinical studies, e.g. pharmacokinetic and toxicology studies, and clinical trial data in the form of clinical study reports [12,13].

Comparative studies have found that clinical study reports of antidepressant trials obtained from the European

Conflict of interest: None.

* Corresponding author:
E-mail address: boesen.kim@gmail.com (K. Boesen).

https://doi.org/10.1016/j.jclinepi.2021.10.027

What is new?

What is already known on this topic

- Drug regulatory agencies base their decisions on clinical trials submitted by pharmaceutical companies.
- Little is known whether drug regulators are missing relevant clinical trials either sponsored by the applicants, publicly funded, or both, and thereby risk making decisions based on select samples of trials.

What this study adds

- It was difficult to identify which trials drug regulatory agencies based their decisions on to approve or reject extended-release methylphenidate applications.
- According to publicly available documents, drug regulatory agencies were missing clinical trials in 7 (54%) of 13 regulatory decisions regarding extended-release methylphenidate for ADHD in adults.
- Current regulatory submission requirements stipulate that applicants must submit all available trials, but ambiguous wording make them open to interpretation.

Medicines Agency (EMA) [14] and the UK regulator, Medicines and Healthcare products Regulatory Agency (MHRA), were incomplete [15,16] and internally inconsistent [17]. In a systematic review [5] of neuraminidase inhibitors for influenza based on clinical study reports, it was noted that the EMA and FDA "largely ignored" the largest oseltamivir trial, M76001, during the approval procedure (p. 28) [5].

To our knowledge, it has never been systematically assessed whether drug regulatory agencies may be missing entire clinical trials when they make decisions. Clinical study reports have generally not been easily accessible, but several drug regulatory agencies make documents publicly available about their authorised drugs [18].

Based on a cohort of regulatory documents obtained for a systematic review [19,20] of extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults, we wanted to systematically assess if drug regulatory agencies transparently report which trials they based their decisions on; are missing entire clinical trials prior to decision-making; and stipulate specific submission requirements that mandate the applicants to submit all trials in drug applications.

2. Methods

This is a case series based on publicly available drug regulatory documents. We obtained the documents during data collection for a systematic review on extended-release methylphenidate for adult ADHD [19,20]. Our systematic review was preregistered [19], but we did not publish a separate protocol for this analysis. Our results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [21]. See Supplement 1 for details on our methodology.

2.1. Step 1: Index of clinical trials

For our systematic review of extended-release methylphenidate for ADHD in adults [19,20], two authors (KB and ASP) systematically searched databases and trial registries (October 2017, March 2019, February 2021). In addition, one author (KB) searched pharmaceutical databases (May 2020), drug regulatory agency databases (May 2020, Aug 2021), and corresponded with trial authors (continuously from 2016 to 2021). Using this data, we created an index of randomised, placebo-controlled, extended-release methylphenidate clinical trials for ADHD in adults. For this analysis, we were interested in clinical trials sponsored by pharmaceutical companies or publicly funded trials with industry-involvement. We defined 'industry-involvement' as any type of collaboration and/or sponsorship with the pharmaceutical companies that market the relevant methylphenidate formulation, as stated in acknowledgement sections or declared in trial registries. Purely publicly funded trials rarely form the basis for new drug applications.

2.2. Step 2: Drug regulatory documents

One author (KB) manually searched (May 2020, Aug 2021) drug regulatory databases of publicly available documents: The FDA's database of Drug Approval Packages, the Australian Therapeutic Goods Administration's (TGA) AusPAR Database and Register of Therapeutic Goods, Health Canada's Drug Product Database, EMA's database of Public Assessment Reports, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) database of drug reports and approved drugs, and national European drug regulatory agency databases. See Supplement 1 and our systematic review for details [19,20].

One author (KB) assessed each regulatory document and extracted information on all clinical trials appearing in the documents. They were categorised as '*pivotal trials*', i.e., the main trials used for approval, or '*other trials*', i.e., any other (identifiable) trial.

2.3. Step 3: Matching index trials with regulatory documents

We matched the index trials with those trials identified in the regulatory documents. We categorised any index trial not appearing in the regulatory documents as 'missing' if the trial was: (1) completed or ongoing at the time of decision-making, and (2) the trial was sponsored by

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

Table 1. Index of extended-release methylphenidate trials in adult ADHD.

Trial	Clinical trial registry	Formulation	Study start -stop	Sponsor	Industry-involvement
Biederman 2003	NCT00181571	OROS methylphenidate	June 2003 – Aug 2007	McNeil and Janssen[i]	Industry trial
Reimherr 2004	Not registered	OROS methylphenidate	Aug 2004 – Dec 2005	McNeil[ii]	Industry trial
Chronis-Tuscano 2004	NCT00318981	OROS methylphenidate	Dec 2004 – Dec 2006	McNeil[iii]	Industry trial
Medori 2005	NCT00246220	OROS methylphenidate	Mar 2005 – Nov 2006	Janssen	Industry trial
Winhusen 2005	NCT00253747	OROS methylphenidate	Nov 2005 – Mar 2008	University of Cincinnati	Ortho-McNeil Janssen listed as collaborator[iv]
Adler 2006	NCT00326391	OROS methylphenidate	Apr 2006 – Dec 2006	Janssen	Industry trial
Casas 2008	NCT00714688	OROS methylphenidate	Feb 2008 – Apr 2009	Janssen	Industry trial
Weisler 2009	NCT00880217	OROS methylphenidate	May 2009 – Jan 2010	Janssen	Industry trial
Goodman 2009	NCT00937040	OROS methylphenidate	July 2009 – Feb 2010	Janssen	Industry trial
Takahashi 2011	NCT01323192	OROS methylphenidate	March 2011 – April 2012	Janssen	Industry trial
Spencer 2003	Not registered	Dex-methylphenidate extended-release	Apr 2003 – Sep 2003	Novartis	Industry trial
Huss 2010	NCT01259492	Long-acting methylphenidate	Nov 2010 – Aug 2012	Novartis	Industry trial
Rösler 2004	NCT00619840	Extended-release methylphenidate	Nov 2004 – May 2006	Medice	Industry trial
Compas 2007	EUCTR 2006-000222-31	Extended-release methylphenidate	April 2007 – Aug 2011	German Ministry of Education and Research	Medice was involved in the trial design and data collection[v]
Retz 2008	NCT00730249	Extended-release methylphenidate	Sep 2008 – Jan 2010	Medice	Industry trial
Jain 2003	Not registered	Controlled-release methylphenidate	Oct 2003 – April 2004	Purdue	Industry trial
Wigal 2014	NCT02225639	Controlled release methylphenidate	Aug 2014 – May 2015	Purdue	Industry trial
Weiss 2014	NCT02139124	Controlled-release methylphenidate	Oct 2014 – Jan 2015	Purdue	Industry trial

[i] On ClinicalTrials.gov, Massachusetts General Hospital was listed as sponsor and McNeil as 'collaborator'. In published reports (Biederman et al. 2006, 2010, and 2011), McNeil and Janssen were listed as sponsors.
[ii] According to the published report, it was 'funded in part' by McNeil.
[iii] On ClinicalTrials.gov, University of Maryland was listed as sponsor and McNeil as collaborator. In the published report (Chronis-Tuscano et al, 2008) McNeil was listed as sponsor.
[iv] According to ClinicalTrials.gov.
[v] According to the published report [43].

the pharmaceutical company that had applied for drug approval, or (3) it was a publicly funded trial with 'industry-involvement' according to our definition.

2.4. Step 4: Enquiring with regulators on missing trials

For the applications with missing trials, we enquired with the regulators whether the applicants had submitted information on more trials than those appearing from the public documents. We did not enquire about applications with no missing trials.

2.5. Step 5: Clarifying regulatory requirements for new drug applications

One author (KB) searched the FDA, the TGA, Health Canada, and the EMA websites (April 2020) for guidelines and legislations regarding stipulated submission requirements of available clinical trial evidence. We did not assess individual European drug regulatory agency requirements, since clinical trial conduct, reporting, and marketing authorisation will be harmonised in the European Union,

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

Table 2. Publicly available regulatory documents.

eCase	Regulator	Application	Applicant	Regulatory documents	Decision
1	Health Canada	OROS methylphenidate	Janssen	Product Monograph [24]	Approved on 15 April 2008
2	FDA	OROS methylphenidate	Janssen	Drug Approval Package [25]	Approved on 27 June 2008
3	TGA	OROS methylphenidate	Janssen	Product Information [26]	Approved on 21 Jan 2009
4	MHRA	OROS methylphenidate	Janssen	Public Assessment Report [27]	Rejected on 14 July 2010
5	PMDA	OROS methylphenidate	Janssen	'Summary of Application' report [28]	Approved on 20 Dec 2013
6	BfArM	Extended-release methylphenidate	Medice	Public Assessment Report [29]	Approved on 18 July 2011
7	FDA	Dex-methylphenidate extended-release	Novartis	Drug Approval Package [30]	Approved on 26 May 2005
8	MEB	Long-acting methylphenidate	Novartis	Public Assessment Report [31]	Rejected on 20 Oct 2016
9	BfArM[i]	Long-acting methylphenidate	Novartis	Public Assessment Report [32]	Approved in 2017
10	TGA	Long-acting methylphenidate	Novartis	Product Information [33]	Approved in 2014
11	Health Canada	Controlled-release methylphenidate	Purdue	Product Monograph [34], Clinical Information Package [35]	Approved on 14 Dec 2017
12	FDA	Controlled-release methylphenidate	Purdue	Drug Approval Package [36]	Approved on 27 Feb 2019
13	Health Canada	Controlled-release methylphenidate	Purdue	Product Monograph [37]	Approved (unknown date)

[i] BfArM approved the drug but MHRA published the Public Assessment Report.

once the EU Clinical Trial Regulation is applied in the beginning of 2022 [22,23]. We did not search PMDA's website as it is mainly in Japanese. During our systematic review [19,20], we asked five regulatory agencies (FDA, TGA, Health Canada, MHRA, and BfArM) to clarify uncertainties in the publicly available documents and to specify whether submission of data from all existing trials, regardless of sponsorship, results, and trial status, was required for the drug approval process. During preparation of this manuscript, we additionally asked Health Canada, MHRA, and PMDA to clarify uncertainties related to three applications and we asked EMA about their submission requirements.

3. Results

3.1. Index of clinical trials

We identified 16 industry-sponsored trials and 2 publicly funded trials with 'industry involvement', Table 1. Six different extended-release methylphenidate formulations were tested: Osmotic-controlled release oral delivery system (OROS) methylphenidate (Janssen, Concerta; 10 trials), extended-release (ER) methylphenidate (Medice, Medikinet;three trials), controlled-release (CR) methylphenidate (Purdue, Foquest/Adhansia;two trials), controlled-release (CR) methylphenidate (Purdue, Biphentin;one trial), long-acting (LA) methylphenidate (Novartis, Ritalin LA/XL;one trial), and dex-methylphenidate extended-release (Novartis, Focalin XR;one trial). All trials assessed benefits and harms. 12 trials had similar trial characteristics and six trials had particular design characteristics: Reimherr 2004 and Jain 2003 used a cross-over design; Chronis-Tuscano 2004 included women with ADHD who also had daughters with ADHD; Winhusen 2005 (publicly-funded but with industry involvement) also assessed smoking-cessation related outcomes; COMPAS 2007 (publicly-funded but with industry involvement) used a factorial design to also assess the impact of clinical management or group psychotherapy; and Wigal 2014 used a 'simulated work environment' in a cross-over trial design. See key trial characteristics in Supplement 1, eTable 2.

3.2. Public drug regulatory documents

We included drug regulatory documents related to 13 drug applications [24–37], Table 2. They were published by seven different agencies: The FDA (three applications), Health Canada (three), the TGA (two),

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

Table 3. Included and missing participants in regulatory documents.

eCase	Regulatory agency	Application	Included participants (%)	Missing participants (%)	Total participants [i]
1	Health Canada	OROS methylphenidate	402 (28%)	1057 (72%)	1459
2	FDA	OROS methylphenidate	631 (44%)	828 (56%)	1459
5	PMDA	OROS methylphenidate	1194 (53%)	1048 (47%)	2242
6	BfArM	Extended-release methylphenidate	521 (55%)	433 (45%)	954
4	MHRA	OROS methylphenidate	1204 (61%)	754 (39%)	1958
3	TGA	OROS methylphenidate	910 (63%)	549 (37%)	1459
10	TGA	Long-acting methylphenidate	725 (77%)	221 (23%)	946
8	MEB	Long-acting methylphenidate	946 (100%)	0	946
9	BfArM	Long-acting methylphenidate	946 (100%)	0	946
11	Health Canada	Controlled-release methylphenidate[ii]	435 (100%)	0	435
12	FDA	Controlled-release methylphenidate[ii]	435 (100%)	0	435
7	FDA	Dex-methylphenidate extended-release	221 (100%)	0	221
13	Health Canada	Controlled-release methylphenidate[iii]	50 (100%)	0	50

[i] Ongoing trials at time of regulatory decision-making were included with their final sample size.
[ii] The formulation Foquest/Adhansia
[iii] The formulation Biphentin

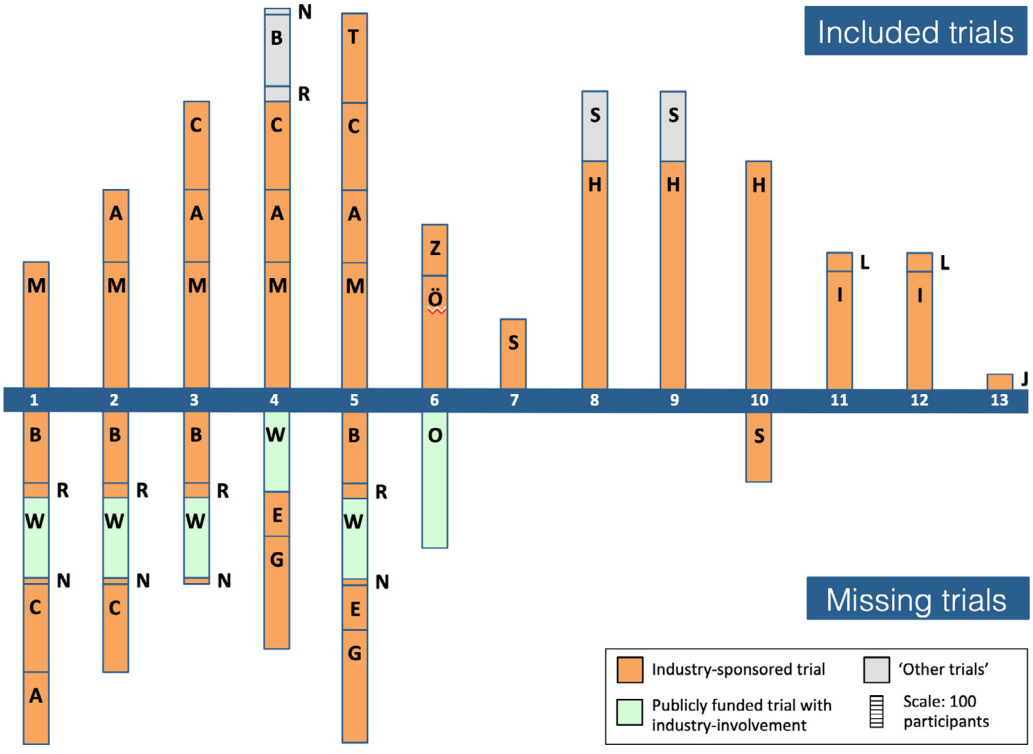

Fig. 1. Included and missing trials according to publicly available documents. Numbers correspond to the 13 drug applications (see also Supplement 1, eTable 4).
A= Adler 2006, B= Biederman, 2003, C= Casas 2008, E= Weisler 2009, G= Goodman 2009, H= Huss 2010, I= Weiss 2014, J= Jain 2003, L= Wigal 2014, M= Medori 2005, N= Chronis-Tuscano 2004, O= COMPAS 2007, Ö=Rösler 2004, R= Reimherr 2004, S= Spencer 2003, T= Takahashi 2011, W= Winhusen 2005, Z= Retz 2008.

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

Table 4. Regulatory submission requirements.

Regulatory agency	Submission requirements
FDA	**FDA's guideline on New Drug Applications** [46] "All controlled clinical studies, including incomplete or abandoned studies, and all pertinent data, whether developed with support of the sponsor or obtained from any other source should be presented in this section" (section D, 1, c) **US Electronic Code of Federal Regulation** [47] "A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study" (Title 21, part 314)
Health Canada	**Submission Certificate for a New Drug Submission**[48] "[…] a) all pivotal studies included in the submission are complete and final comprehensive analyses provided; b) all pivotal data necessary to support the proposed indications, doses and formulations have been provided […]"
EMA and TGA[i]	**EMA's guideline on the Common Technical Document** [50] "The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative […]. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered"(section 2.5.4) **EU Clinical Trial Directive (2001/83/EC)** [51] "Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable" (Annex I, section 5.2)

[i] TGA follows the EMA standards [52,53].

MHRA (two), PMDA (one), the Dutch Medicines Evaluation Board (MEB) (one), and the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (one). 11 applications were approved and two were rejected, OROS methylphenidate by MHRA [27] and long-acting methylphenidate by MEB [31].

The documents varied in length and content. FDA's Approval Packages reported detailed results and summaries of the scientific discussions and Health Canada's Clinical Information Package included parts of the clinical study reports, whereas Health Canada and the TGA's prescriber documents reported sparse clinical trial data and did not include scientific discussions. The European drug regulators' Public Assessment Reports varied from BfArM's 7-page report [30] on extended-release methylphenidate to MHRA's 130-page report [27] on OROS methylphenidate. We describe key document characteristics in Supplement 1, eTable 3.

3.3. Matching index trials with regulatory documents

We identified missing trials in 7 (54%) of the 13 drug applications. The median number of missing trials was 4 (range 1 to 6). In Fig. 1, we depict the included and missing trials and they are tabulated in Supplement 1, eTable 4. The median proportion of missing trial participants of the total population was 45%, ranging from TGA's approval of long-acting methylphenidate (23%) to Health Canada's approval of OROS methylphenidate (72%), Table 3.

In Box 1, we illustrate the potential impact of missing trials (Cases 1 and 2), and how a pharmaceutical company was involved in a publicly funded trial, which was not assessed in the initial application (Case 3). We describe all drug applications in Supplement 1, eCase 1 to eCase 13.

3.4. Inquiring with regulators on missing trials

We contacted the responsible agencies, i.e., FDA, TGA, Health Canada, BfArM, and MHRA, for the applications with missing trials (Supplement 1 eTable 5 and Supplement 2). We asked them whether they had received information on more trials than those appearing from the public documents. We did not contact PMDA, as the tabulated lists in their 'Summary of Application' document [28] resembled Clinical Study Report tables and seemed exhaustive.

The FDA, TGA, and Health Canada abstained from directly addressing our questions on the missing trials, whereas BfArM confirmed that they had not assessed the missing COMPAS 2007 trial. The FDA referred us to their Drug Approval Database website and Health Canada sent us Module 2.7 from the OROS methylphenidate clinical study report, which contains a list of all clinical trials submitted as part of the application. After our manuscript was accepted for publication, Health Canada responded to an inquiry about controlled-release methylphenidate. Health Canada released a Clinical Information Package after we had searched their database in May 2020. The disclosed clinical study report documents unveiled a discrepancy with other publicly available documents (see Discussion and Supplement 1 for details). Finally, TGA asked us to request specific documents, such as clinical study report modules.

Box 1

Case 1. FDA's internal disagreement on the authorisation of OROS methylphenidate

The FDA [25] approved OROS methylphenidate in June 2008 on the basis of the two Janssen sponsored trials, Medori 2005 (5 weeks; 402 participants)

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

[38], and Adler 2006 (7 weeks; 229 participants) [39]. FDA's medical reviewer raised concerns regarding the drug's harms, particularly cardiovascular safety, and recommended the conduct of a third trial as a condition for approval (p. 72) [25]. The FDA Team Leader and the Division Director did not agree, among other reasons, because they believed it was not feasible, nor ethical, to conduct more clinical trials. The Division Director, Thomas Laughren stated, "The study proposed by Dr. Mannheim is simply not feasible. It would need to involve hundreds of thousands of patients, would need a placebo arm, and would take years to complete. In the meantime, the labels for Concerta and other drugs in this class already have very strong warning language that alerts prescribers to possible cardiovascular risks. Thus, I do not agree with the need for the study proposed by Dr. Mannheim, and I will not suggest it to the sponsor" (p. 43) [25]. At the time of decision-making, five clinical trials were ongoing or completed that did not appear from the FDA Review [25]. Furthermore, the applicant submitted information on four placebo-controlled trials, but the FDA did not ask for these trials, "The source papers have not been reviewed at the time of this review" (p. 125) [25]. See also Supplement 1, eCase 2.

Case 2. The missing Casas 2008 trial across OROS methylphenidate authorisations

Health Canada approved OROS methylphenidate for adult ADHD in April 2008 [24] on the basis of one trial, Medori 2005 [38]. In June 2008, FDA approved the drug [25] on the basis of two trials, Medori 2005 [38] and Adler 2006 [39]. In January 2009, the TGA [26] approved the drug based on the same two trials, but they also listed harms' data from a third study, Casas 2008 (13 weeks; 279 participants) [40]. This trial was conducted between February 2008 and April 2009 and (seemingly) ongoing at the time of FDA, Health Canada, and TGA's decisions, despite only appearing in TGA's documents.

In June 2010, the British regulator, MHRA [27], rejected the OROS methylphenidate application on the basis of all three Janssen trials [38–40]. Taking into account dropouts as 'treatment failures', the MHRA reviewer commented, "The totality of the data is therefore weak, with one successful, one borderline failure, and one clearly failed trial" (p. 106) [27]. The Casas 2008 [40] trial was the "clearly failed trial". It can be speculated whether the FDA and Health Canada had decided differently, if the Casas 2008 trial had appeared in their public documents. See also Supplement 1, eCases 1 to 4.

Case 3. BfArM's approval of extended-release methylphenidate and the COMPAS trial

The German drug regulator, BfArM, approved the drug for use in adults in April 2011 [30,41] on the basis of two pivotal trials, Rösler 2004 (24 weeks; 359 participants) [42] and Retz 2008 (8 weeks; 162 participants) [43]. These trials were conducted between 2004 to 2006 and 2008 to 2010, respectively, and sponsored by the applicant, Medice. A German publicly funded trial, COMPAS 2007 (52 weeks, 433 participants) [44], was conducted in the same period (2007 to 2011) and it finished in August 2011 [44], four months after BfArM's approval. The applicant, Medice, was involved in COMPAS' trial design and outcome collection [44], but the trial did not appear from the Public Assessment Report [30]. We asked BfArM whether they were informed about the COMPAS trial prior to approval, to which they responded that the study was ongoing at the time of decision-making (Supplement 1 eTable 6 and Supplement 2). BfArM further informed us that Medice included data from COMPAS in a subsequent 'Type II variation' submission, which was an extension of the indication to also include initiation of treatment in adults that have not previously been treated. The type II variation was approved in November 2017 [45]. See also Supplement 1, eCase 6.

3.5. Regulatory requirements for new drug applications

In general, the FDA, TGA, Health Canada, and EMA seemed to require all trials to be submitted but there were important uncertainties in their wording, see Table 4. We enquired with the agencies (Supplement 1 eTable 5 and Supplement 2), and we also sought information on the agency websites (Supplement 1 eTable 6).

The FDA guideline [46] and the US legislation [47] specified that all clinical trials "*pertinent*" to the proposed indication should be included. Health Canada requires applicants to submit a certificate stating, "all pivotal trials necessary to support the proposed indications […] have been provided " [48], but their guideline [49] on the Common Technical Document did not clarify this further. EMA's guideline [50] on the Common Technical Document specified that all "*pertinent*" data should be submitted, whereas the EU Trial Directive 2001/83 [51], which formed the legal basis for the content of the Marketing Authorisation Dossier, was more broad and stated, "*all clinical trials should be communicated*". Subsequent EU Regulations have seemingly not elaborated on the submission requirements (Supplement 1 eTable 7). The TGA has adopted the European Common Technical Document standards [52,53].

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

4. Discussion

4.1. Summary of findings

To our knowledge, this may be the first report to systematically investigate whether drug regulatory agencies make decisions based on complete or select samples of clinical trials. In our cohort of 13 extended-release methylphenidate applications for ADHD in adults, we identified missing trials in 7 (54%) applications. Previously, it has been reported [5] that the EMA and FDA approved oseltamivir for influenza but "largely ignored" the largest oseltamivir trial. Our findings therefore raise the concern that missing trials in drug applications may constitute a general issue.

There may be several explanations why some clinical trials did not appear in the public documents: First, the companies may deliberately not include all trials in their applications. Second, the drug regulatory agencies do not unequivocally request that the applicants submit all trials. Third, the agencies do not conduct their own systematic searches of clinical trial registries and databases of published literature but rely on the material submitted by the applicant. Fourth, the agencies apparently do not always check that everything listed in the index has been submitted. Our research group has previously found that appendices were only included for 32 of 70 trials of antidepressants [15] and in FDA's medical review of OROS methylphenidate [25], they even noted they had not reviewed all 'bibliographic references' submitted by the applicant, see Case 1. Fifth, drawing on a case study of depot aripiprazole's authorisation [54], regulatory agencies may exclude clinical trials from public documents depending on their own assessments. In TGA's Public Assessment Report of depot aripiprazole [55] two pivotal trials were assessed but the agency discarded one of these trials due to outcome switching. In the corresponding Product Information [56], the discarded trial did not appear in the 'Clinical Trials' section, whereas the discarded trial's data appeared under 'Adverse Events'. This seems similar to TGA's Product Information on OROS methylphenidate [26] as described in Case 2. Also here, one of the trials, Casas 2008 [40], appeared only in the 'Adverse Events' section. One might therefore speculate that TGA discarded the Casas 2008 results, which also seems supported by MHRA's classification of it as "a clearly failed trial" [27].

The regulatory submission requirements seemingly stipulate that all available evidence should be submitted. However, the devil may lie in the detail. FDA and EMA (and subsequently TGA) label the required submitted material as "*pertinent*" and Health Canada defines them as "all pivotal trials", Table 4. Whether this means that all data from all available trials must be submitted, or only those trials that the regulatory agency and the applicant have already agreed on during pre-authorisation meetings, seems unclear. This uncertainty may stem from the International Council for Harmonisation's (ICH) guideline [57] on the Common Technical Document Module 5, which all four agencies rely on. The guideline uses the same terminology and labels the included trials, "pertinent to the efficacy of the medicinal product" [57].

We noted that most drug regulatory agencies did not directly address our questions regarding the extent of missing trials. The exception was Health Canada who sent us a clinical study report module 2.7 (eCase 1) and referred us to publicly disclosed clinical study report material (eCase 11), which fully addressed our questions. We understand that regulatory staff does not have authority, or perhaps insight, to explain former decisions made by their superiors. However, our questions regarding the availability of specific trials prior to decision-making seem to constitute basic information that, in our view, should already be in the public domain.

4.2. Limitations

We did not register a protocol for this analysis. It was an exploratory project related to our systematic review on extended-release methylphenidate for adult ADHD [19,20], for which a protocol is available [19]. This analysis is based on documents obtained through our predefined systematic search, and we therefore do not believe the lack of an additional protocol affected the results.

It is important to reiterate that our analysis was based on public documents and, with the exception of Health Canada's (and probably PMDA's) approval of OROS methylphenidate and Health Canada's approval of controlled-release methylphenidate, we do not know whether the agencies had access to more data. Critically, the listed evidence in Health Canada's publicly available OROS methylphenidate Product Monograph matched the corresponding clinical study report (eCase 1), whereas the controlled-release methylphenidate Product Monograph did not match the clinical study report material (eCase 11). We would therefore need access to clinical study reports from all drug applications to confirm our results, which could take years to obtain.

Since our findings were largely based on publicly available documents, this may also be an indicator of the current level of transparency. If our estimates of missing trials are incorrect, it may be due to the regulatory agencies' lack of disclosure. One could argue it is reasonable to include only those trials supporting the authorised indications in public documents. However, it obscures transparency when excluded trials are not listed, and it can give a distorted impression of the submitted evidence and of the drug's benefits and harms.

It is important to highlight the variation in the available documents. FDA's Drug Approval Packages and the European Public Assessment Reports are lengthy documents with detailed scientific discussions. Health Canada's Clinical Information Package contains part of the clinical study

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

report, but no regulatory discussions. PMDA's report was largely composed of other agencies' documents. The Canadian Product Monographs and the Australian Prescriber Information are summaries of product characteristics and not scientific reports.

Our sample of 13 applications related to one drug is small and it is an important limitation to the generalisability across indications, fields, and drug regulators. We also do not know if we have missed additional rejected applications. We were surprised to find reports related to two rejected applications. EMA publishes information on rejected applications, called 'refusal assessment reports' [58]. To our knowledge, this is not common and other regulators, e.g., the FDA, publishes reports of authorised drugs only [59].

We may have missed some publicly funded trials with industry-involvement. Selective reporting of publicly funded trials is particularly pronounced [60,61], and sometimes the industry-involvement has not been declared in publications, even when the trial was later used in a registration application [62].

4.3. Suggestions for improvements

We identified limitations in the current drug regulatory system with potentially serious consequences for the reliability of drug approvals. Despite our lengthy investigation, we are still not certain on what basis most drugs were approved. It is therefore regrettable that for instance the FDA plans to weaken transparency by phasing out the publication of medical, statistical, and other reviews and substituting them with less informative 'integrated reviews' [63].

Drug regulators need to ensure that their decisions are based on all data from all relevant trials and not just a selection of them. The current gaps could be addressed on several levels: It is highly recommendable that regulatory agencies conduct their own systematic searches of trial registries and databases of published literature. According to FDA's manual on how to conduct clinical reviews (section 9.1) [64], reviewers are not obliged to systematically search for evidence; the submission requirements need to be clarified to avoid loopholes and these requirements must be enforced; the pharmaceutical companies need to be held accountable if they fail to submit relevant data or trials, or fail to inform about ongoing or planned trials; finally, it would be sensible to increase collaboration between regulatory agencies. Health Canada and the TGA have already initiated projects on shared drug review assessments with the Singaporean and Swiss authorities [65]. Our recommendations are summarised in Box 2. The European Commission recently solicited input to the revision of the EU general pharmaceutical legislation [66]. This may be an opportunity to address some of the issues we highlight in this paper, including clarification of submission requirements and better overviews of assessed clinical trials in drug applications [67].

Box 2

Recommendations to improve the completeness and transparency of regulatory decisions

1. Regulatory agencies should systematically search clinical trial registries and databases of published literature prior to decision-making to avoid missing clinical trials.
2. Regulatory agencies should clearly disclose all trials (not just the favourable ones) they assessed prior to decision-making in publicly available documents.
3. Regulatory submission requirements regarding available clinical trials should be made clearer to avoid loopholes in interpretation.
4. Regulatory agencies should consider establishing an international website with basic information on drug authorisations (e.g. assessed pivotal and supporting trials, regulatory discussions, concerns raised, and final decision) to enable comparisons, reduce redundancy, and increase transparency.
5. Pharmaceutical companies should be held accountable if they fail to inform regulatory agencies about all available evidence.

On a general note, our method for indexing clinical trials based on published reports and clinical trial registries and our identification of publicly available regulatory documents can be applied across drugs and indications. Our research group used a similar approach to map clinical trials of the HPV vaccines [68]. Our method also highlights potential solutions to address the current loopholes in drug regulation, Box 2. However, this project should also be considered a 'work-in-progress' and it will be updated if new information emerges.

5. Conclusion

Based on publicly available regulatory documents, we found that 7 (54%) of 13 regulatory decisions regarding extended-release methylphenidate for adult ADHD were made based on a select sample of clinical trials, although current requirements seem to state that all available trials should be included in drug applications. It will be important to assess larger cohorts of drug approvals to better estimate the prevalence of missing trials in new drug applications. Similarly, drug regulatory agencies may consider employing new protocols to avoid missing clinical trials prior to decision-making.

Availability of data and material

All data underlying this project are available from, or referred to, in the supplements. It was an exploratory analysis related to our systematic review and we did not publish a separate protocol for this project.

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

Funding

METRIC-B (KB) is funded by grants from the Einstein Foundation and Stiftung Charité.

Author contributions

KB coined the idea, collected the data, drafted the letters to the drug regulators, and wrote the first draft of the paper. KJ and PCG supervised the correspondence with the drug regulators and critically revised the manuscript. All authors approved the final manuscript. KB is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgements

Asger Sand Paludan-Müller (ASP) extracted data for our systematic review on methylphenidate for adult ADHD, which formed the basis for this analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.10.027.

References

[1] Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan A-W, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLOS One 2008;3:e3081.
[2] Dwan K, Gamble C, Williamson PR, Kirkham JJ, the Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias — an updated review. PLoS ONE 2013:e66844.
[3] Chan AW, Hrobjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA 2004;291:2457–65.
[4] Goldacre B, Drysdale H, Dale A, Milosevic I, Slade E, Hartley P, et al. COMPare: a prospective cohort study correcting and monitoring 58 misreported trials in real time. Trials 2019;20:118.
[5] Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuroaminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database Syst Rev 2014;4:CD008965.
[6] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: comparison of trial data from clinical study reports with corresponding trial register entries and journal publications. Syst Rev 2020;9:42.
[7] Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the evidence of antidepressants for depression: a reanalysis of a network meta-analysis. BMJ Open 2019;9:e024886.
[8] Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P, et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. PLOS Medicine 2013;10:e1001536.
[9] Noury JL, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 2015;351:h4320.
[10] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358:252–60.
[11] International Council for Harmonisation of technical requirements for pharmaceuticals for human use. organisation of the common technical document for the registration of pharmaceuticals for human use. M4. Current step 4 version. 15 June 2016. Available from: https://database.ich.org/sites/default/files/M4_R4__Guideline.pdf (accessed 5 Dec 2021).
[12] European Medicines Agency. ICH M4 Common technical document for the registration of pharmaceuticals for human use – efficacy. Revision 2. July 2016. Available from: https://www.ema.europa.eu/en/ich-m4e-common-technical-document-registration-pharmaceuticals-human-use-efficacy (accessed 5 Dec 2021).
[13] Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open 2013;3:e002496.
[14] Gøtzsche PC, Jørgensen AW. Opening up data at the European medicines agency. BMJ 2011;342:d2686.
[15] Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016;352:i65.
[16] Paludan-Müller AS, Sharma T, Rasmussen K, Gøtzsche PC. Extensive selective reporting of quality of life in clinical study reports and publications of placebo-controlled trials of antidepressants. Int J Risk Saf Med 2021;32:87–99.
[17] Maund E, Tendal B, Hrobjartsson A, Jørgensen KJ, Lundh A, Schroll J, et al. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. BMJ 2014;348:g3510.
[18] Restoring invisible and abandoned trials. Regulatory resources. Not dated. Available from: https://restoringtrials.org/regulatory-resources/ (accessed 5 Dec 2021).
[19] Boesen K, Danborg PB, Gøtzsche PC, Jørgensen KJ. Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults (protocol). Cochrane Database Syst Rev 2017;11:CD012857.
[20] Boesen K, Paludan-Müller AS, Gøtzsche PC, Jørgensen KJ. Extended-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults (review). Cochrane Database Syst Rev (In press).
[21] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296.
[22] Regulation No. 536/2014 of the European Parliament and of the Council. Official J Euro Union 2014:L158/1. 27 May 2014. Available from: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf (accessed 5 Dec 2021).
[23] European Medicines Agency. Clinical Trial Regulation. Not dated. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation (accessed 5 Dec 2021).
[24] Health Canada. Concerta Product Monograph. Submission control no. 224296. 17 April 2019. Available from: https://pdf.hres.ca/dpd_pm/00050777.PDF (accessed 5 Dec 2021).
[25] Center for Drug Evaluation and Research. Drug Approval Package. 21-121/S-017. 27 June 2008. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021121s017.pdf (accessed 5 Dec 2021).
[26] Therapeutic Goods Administration. Concerta extended release tables. CCDS181023. Date of revision 21 Oct 2021. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/

pdf?OpenAgent&id=CP-2009-PI-00919-3&d=202005111016933 (accessed 5 Dec 2021).
[27] Medicines and Healthcare Products Regulatory Agency. Public Assessment Report. Concerta XL 27 mg prolonged-release tablets. UK/H/0544/004/MR. Available from: https://mhraproductsproduction.blob.core.windows.net/docs/e16cca8676c72aff9c51ed19f93314a251e61a05 (accessed 5 Dec 2021).
[28] Pharmaceuticals and Medical Devices Agency. Summary of application materials. 17 January 2014. Available from: https://www.pmda.go.jp/drugs/2013/P201300158/index.html (accessed 5 Dec 2021).
[29] Bundesinstitut für Arzneimittel und Medizinprodukte. Public Assessment Report Summary [Öffentlicher Bewertungsbericht]. Medikinet Adult. 18 July 2011. Available from: https://portal.dimdi.de/amispb/doc/2011/07/25/2163890/OBFMBD5B836E01CC4AAA.rtf (accessed 5 Dec 2021).
[30] Center for Drug Evaluation and Research. Drug Approval Package. Focalin XR. 26 May 2005. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021802s000TOC.cfm (accessed 5 Dec 2021).
[31] Medicines Evaluation Board. Public Assessment Report Ritalin LA. NL License RVG 2021;116377:116379–82. 20 October 2016. Available from: https://www.geneesmiddeleninformatiebank.nl/Pars/h116382.pdf (accessed 5 Dec 2021).
[32] Medicines and Healthcare products Regulatory Agency. Public Assessment Report. Ritalin XL. UK License 2018. No: 00101/0973-0977. March 2018. Available from: https://mhraproductsproduction.blob.core.windows.net/docs/4781baf366b1fafd0ea203962ccb54faadcdcfcc (accessed 5 Dec 2021).
[33] Therapeutic Goods Administration. Australian Product Information. Ritalin 10/Ritalin LA. Latest amendment 14 Aug 2020. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03175-3 (accessed 5 Dec 2021).
[34] Health Canada. Product Monograph. Foquest. Submission Control No: 214860. 1 March 2019. Available from: https://pdf.hres.ca/dpd_pm/00049955.PDF (accessed 5 Dec 2021).
[35] Health Canada. Clinical Information. Foquest – submission control no. 187330. Release date 29 May 2020. Available from: https://clinical-information.canada.ca/ci-rc/item/187330. [Accessed 5 Dec 2021].
[36] Center for Drug Evaluation and Research. Drug Approval Package. Adhansia XR. 27 Feb 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212038Orig1s000TOC.cfm (accessed 5 Dec 2021).
[37] Health Canada. Product Monograph. Biphentin. Revision 14 January 2020. Available from: https://pdf.hres.ca/dpd_pm/00054671.PDF (accessed 5 Dec 2021).
[38] NCT00246220. A study of the effectiveness and safety of prolonged-release methylphenidate hydrochloride in adult patients with attention deficit/hyperactivity disorder. Last updated 17 May 2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00246220 (accessed 5 Dec 2021).
[39] NCT00326391. A safety and effectiveness study of methylphenidate hcl extended-release tablets in adults with attention deficit hyperactivity disorder. Last updated 24 May 2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00326391 (accessed 5 Dec 2021).
[40] NCT00714688. A study to evaluate effectiveness and safety of prolonged release OROS methylphenidate in adults with attention deficit hyperactivity disorder. Last updated 8 May 2014. Available from: https://clinicaltrials.gov/ct2/show/NCT00714688 (accessed 5 Dec 2021).
[41] BfArM Presse. Methylphenidat auch für Erwachsene: BfArM erweitert Zulassung. 15 April 2011. Available from: https://web.archive.org/web/20110901054212/http://www.bfarm.de/DE/BfArM/Presse/mitteil2011/pm02-2011.html?nn=1009636 (accessed 5 Dec 2021).
[42] NCT00619840. Placebo-Controlled Multi-Centre Double-Blind Trial for Adults With Extended-Release Methylphenidate for ADHD (EMMA). Last updated 21 Feb 2008. Available from: https://clinicaltrials.gov/ct2/show/NCT00619840 (accessed 5 Dec 2021).
[43] NCT00730249. Quality Assurance of Administering Methylphenidate in Adults With Attention Deficit Hyperactivity Disorder (ADHD) - QUMEA (QUMEA). Last updated: 13 January 2010. Available from: https://clinicaltrials.gov/ct2/show/NCT00730249 (accessed 5 Dec 2021).
[44] Philipsen A, Jans T, Graf E, Matthies S, Borel P, Colla M, et al. Effects of group psychotherapy, individual counseling, methylphenidate, and placebo in the treatment of adult attention-deficit/hyperactivity disorder: A randomized clinical trial. JAMA Psychiatry 2015;72:1199–210.
[45] Bundesinstitut für Arzneimittel und Medizinprodukte. Public Assessment Report. Methylphenidate hydrochloride. DE/H/0690/001-007/MR . Updated 19 January 2018. Available from: https://www.geneesmiddeleninformatiebank.nl/Pars/h34030.pdf (accessed 5 Dec 2021).
[46] Center for Drug Evaluation and Research. Guideline for the Format and Content of the Clinical and Statistical Sections of an Application. July 1988. Available from: https://www.fda.gov/media/71436/download (accessed 5 Dec 2021).
[47] Electronic Code of Federal Regulation. Title 21, chapter 1, subchapter d, part 314, subpart B, §314.50. Updated 2 April 2020. Available from: https://www.ecfr.gov/cgi-bin/text-idx?SID=6d2c00e689dbe39f96cc4fe77ce33908&mc=true&node=se21.5.314_150&rgn=div8 (accessed 5 Dec 2021).
[48] Health Canada. Submission certificate for a NDS, SNDS, SANDS, ANDS, or NC. In effect 1 April 2020. Available from: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/forms/certnds_attpdn-2020-eng.doc (accessed 5 Dec 2021).
[49] Health Canada. Guidance document: guidance document: preparation of drug regulatory activities in the common technical document (CTD) format. 22 June 2012. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/preparation-drug-regulatory-activities-common-technical-document-format.html (accessed July 2021).
[50] European Medicines Agency. ICH M4 Common Technical Document for the registration of pharmaceuticals for human use – efficacy. Revision 2. July 2016. Available from: https://www.ema.europa.eu/en/ich-m4e-common-technical-document-registration-pharmaceuticals-human-use-efficacy (accessed 5 Dec 2021).
[51] European Commission. Directive 2001/83/EC. 6 November 2001. Available from: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf (accessed 5 Dec 2021).
[52] Therapeutic Goods Administration. Mandatory requirements for an effective application. Feb 2018. Available from: https://www.tga.gov.au/publication/mandatory-requirements-effective-application (accessed 5 Dec 2021).
[53] Therapeutic Goods Administration. International scientific guidelines adopted in Australia. 5 Aug 2020. Available from: https://www.tga.gov.au/ws-sg-index (accessed 5 Dec 2021).
[54] Boesen K, Naudet F, Ioannidis JPA. Depot aripiprazole: subverted trials and authorisation of a best-selling drug. Available as a preprint at SSRN 18 March 2021:1–31 (accessed 5 Dec 2021). doi:10.2139/ssrn.3805790.
[55] Therapeutic Goods Administration. Australian Public Assessment Report for Aripiprazole Monohydrate. November 2014. Available from: https://www.tga.gov.au/sites/default/files/auspar-aripiprazole-monohyrate-141125.pdf (accessed 5 Dec 2021).
[56] Therapeutic Goods Administration. Product Information. Abilify Maintena. 25 Nov 2014. Available from: https://www.tga.gov.au/

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027

sites/default/files/auspar-aripiprazole-monohyrate-141125-pi.pdf (accessed 5 Dec 2021).

[57] ICH Harmonised Guideline. Revision of M4E guideline on enhancing the format and structure of benefit-risk information in ICH efficacy M4E(R2). Step 4 version. 15 June 2016. Available from: https://database.ich.org/sites/default/files/M4E_R2__Guideline.pdf (accessed 5 Dec 2021).

[58] European Medicines Agency. Procedural advice on publication of information on negative opinions and refusals of marketing authorization applications for human medicinal products. 2 May 2013. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-publication-information-negative-opinions-refusals-marketing-authorisation_en.pdf (accessed 5 Dec 2021).

[59] US Food and Drug Administration. Drugs@FDA: FDA approved drugs. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/ (accessed 5 Dec 2021).

[60] Goldacre B, DeVito NJ, Heneghan C, Irving F, Bacon S, Fleminger J, et al. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource. BMJ 2018;362:k3218.

[61] Wieschowski S, Riedel N, Wollmann K, Kahrass H, Müller-Ohlraun S, Schürmann C, et al. Result dissemination from clinical trials conducted at German university medical centers was delayed and incomplete. J Clin Epidemiol 2019;115:37–45.

[62] Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. BMJ 2004;328:879–83.

[63] Herder M, Morten CJ, Doshi P. Integrated drug reviews at the US Food and drug administration - legal concerns and knowledge lost. JAMA Intern Med 2020;180:629–30.

[64] Center for Drug Evaluation and Research. Manual of policies and procedures. Good review practice: clinical review template. Effective date 10 Dec 2010. Available from: https://www.fda.gov/media/72472/download (accessed 5 Dec 2021).

[65] Health Canada. Improving the regulatory review of drugs and devices. 26 April 2020. Available from: https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html (accessed 5 Dec 2021).

[66] European Commission. Revision of the EU general pharmaceutical legislation. Not dated. Available from: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en (accessed 5 Dec 2021).

[67] Boesen K, Paludan-Müller AS. Feedback from: meta-research innovation center berlin (METRIC-B). 27 April 2021. Available from: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation/F2253796_en (accessed 5 Dec 2021).

[68] Jørgensen L, Gøtzsche PC, Jefferson T. Index of the human papillomavirus (HPV) vaccine industry clinical study programmes and non-industry funded studies: a necessary basis to address reporting bias in a systematic review. Syst Rev 2018;7:8.

Please cite this article as: K. Boesen, K.J. Jørgensen and P.C. Gøtzsche, Clinical trials were missing from regulatory documents of extended-release methylphenidate for ADHD in adults: a case study of public documents, Journal of Clinical Epidemiology, https://doi.org/10.1016/j.jclinepi.2021.10.027