Transparency in SAHPRA – what should industry's position be?

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Outline

- The curious case of the persistent and untouchable “secrecy” clause
- International trends
- The particular demands of SAHPRA
  - The role of “advisory” committees
- A way forward

Many post-apartheid amendments

- Medicines and Related Substances Control Amendment Act (Act 90 of 1997)

- [South African Medicines and Medical Devices Regulatory Authority Act (Act 132 of 1998)]
- Medicines and Related Substances Amendment Act (Act 59 of 2002)
- Medicines and Related Substances Amendment Act (Act 72 of 2008)
- Medicines and Related Substances Amendment Act (Act 14 of 2015)

But, one section has remained as-is, untouched ….

“34. Preservation of secrecy.—No person shall, except for the purpose of the exercise of his powers or the performance of his functions under this Act, or for the purpose of legal proceedings under this Act, or when required to do so by any competent court or under any law, or with the written authority of the Director-General, disclose to any other person any information acquired by him in the exercise of his powers or the performance of his functions under this Act and relating to the business or affairs of any person, or use such information for self-gain or for the benefit of his employer.”

The impact ..

"reveal NOTHING and
that way you can
"NEVER be wrong …"

MEDICINES CONTROL COUNCIL

IKANSELE ELAWULA UKUSETSHENZISWA KWEMITHI

MEDISYNEBEHEERRAAD

KHANSELE TAOLO YA DIHLARE

MCC85 / 27-28 JULY 2017

THE 85th MEETING OF THE MEDICINES CONTROL COUNCIL WILL BE HELD IN THE **BOPHELO BOARDROOM**, PODIUM LEVEL, CIVITAS BUILDING, THABO SEHUME STREET, PRETORIA, ON THURSDAY AND FRIDAY: 27-28 July 2017

THE MEETING WILL COMMENCE AT: 09h00 ON 27 July 2017
08h00 ON 28 July 2017

THE **AGENDA (B1)** IS ATTACHED HERETO

.....

REGISTRAR OF MEDICINES

The information contained in this document is subject to a secrecy clause in terms of section 34 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965)

The post-1996 imperative

“32. Access to information.-

(1) Everyone has the right of access to -

(a) any information held by the state; and

(b) any information that is held by another person and that is required for the exercise or protection of any rights.

(2) National legislation must be enacted to give effect to this right, and may provide for reasonable measures to alleviate the administrative and financial burden on the state.”

CONSTITUTION OF THE REPUBLIC OF SOUTH AFRICA ACT NO. 108 OF 1996

But, there are limitations

“36(1) The rights in the Bill of Rights may be limited only in terms of law of general application to the extent that the limitation is reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom, taking into account all relevant factors, including -

(a) the nature of the right;

(b) the importance of the purpose of the limitation;

(c) the nature and extent of the limitation;

(d) the relation between the limitation and its purpose; and

(e) less restrictive means to achieve the purpose.”

National legislation

- Promotion of Access to Information Act (Act 2 of 2000)
- Balanced by chapter 4: Grounds for refusal of access to records, including
  - Section 36 “Mandatory protection of commercial information of third party”

International standards

- Article 39 of the World Trade Organization's Agreement on Trade-Related Aspects Intellectual Property Rights (TRIPS)
  - NMRA is under an obligation to protect undisclosed trial data against "unfair commercial use", "except where necessary to protect the public"

The African Union Model Law on Medical Products Regulation

- Article 34

"1) No person shall disclose to any other person or institution any information acquired by him in the exercise of his powers or the performance of his functions under this Law and relating to the business or affairs of any person, or use such information for self-gain or the benefit of his employer

A person may be permitted to disclose information:-

a) for the purpose of the exercise of his powers or the performance of his functions under this law with the written authority of the agency/authority"

b) when required to do so by any competent court or under any law, or

c) if it is in the public interest."

The US position

Enhancing Transparency at the US Food and Drug Administration
Moving Beyond the 21st Century Cures Act

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Laura and John Arnold Foundation, Houston, Texas.

JAMA April 25, 2017 Volume 317, Number 16

The US Food and Drug Administration (FDA) has primary responsibility for oversight of every drug, biologic, and medical device sold in the United States. Yet the FDA is far more than a regulator. It is also an agency dedicated to public health, with the expertise of thousands of scientists and access to enormous amounts of information from clinical trials and other studies. Greater transparency can allow FDA not only to better meet its many obligations but also to advance the scientific enterprise needed to develop safe and effective medical products.

Blueprint for Transparency at the US FDA

- FDA Should Disclose More Information About Key Milestones in the Application Process

1. Disclose basic information about investigational notices, the filing of marketing applications, and the existence of clinical holds.

2. Include in disclosures the class of medication and mechanism of action, if known.

3. Include in disclosures the ClinicalTrials.gov numbers for all trials conducted or relied on as pivotal for marketing approval.

4. When FDA enters into a Special Protocol Assessment, release the text relevant to safety and efficacy after the study is completed.

5. When FDA has issued or released a clinical hold related to safety or efficacy, release a summary of the reasons within 10 days.

6. Disclose whether a marketing application has been designated for an expedited development or review program and, if so, provide the scientific basis for that designation.

7. Disclose written requests for pediatric studies at the time such requests are made, as well as other documents indicating agreement on changes to the initial request.

Blueprint for Transparency at the US FDA

- FDA Should Disclose More of Its Own Analysis and Decision Making

8. Disclose communications to companies when products are not approved.

9. Make public clinical and statistical reviews of products not approved or for which the marketing applications are abandoned or withdrawn.

10. Make pooled data sets, masked and deidentified as appropriate, and FDA's analyses of these data sets, available to the medical and research community through clinical data repositories.

Blueprint for Transparency at the US FDA

- FDA Should Disclose More About the Application and Review Process for Generic Drugs and Follow-on Biologics

11. Disclose basic information about the filing of generic drug applications.

12. Disclose those portions of Complete Response Letters to generic drug manufacturers that relate to bioequivalence.

13. Disclose the filing of abbreviated biologics licensing applications, including the name of the sponsor, the reference biologic product, and whether the application is for “biosimilarity” or “interchangeability.”

14. Disclose those portions of a Complete Response Letter with respect to an abbreviated biologics licensing application that relate to the biosimilarity to or interchangeability with the reference biologic product.

Blueprint for Transparency at the US FDA

- FDA Should Correct Misleading Information in the Market

15. Correct misleading information when there is the potential for substantial confusion about the safety or efficacy of the medical product for both approved and unapproved uses.

Blueprint for Transparency at the US FDA

- FDA Should Disclose Data From Scientific Studies to Enhance Understanding of Medical Products

16. Disclose Clinical Study Reports submitted in support of a marketing application.

17. Release the final reports that fulfill Postmarketing Requirements and Postmarketing Commitments at the time FDA considers the sponsor's obligation to conduct a study to be fulfilled.

18. When clinical trial data, including patient-level data, are not available to independent investigators through industry-sponsored websites, make data available through clinical data repositories, with policies on deidentification to protect patient privacy.

Important points

- "All of the blueprint's recommendations respect legal protections for trade secrets."
- "The mission of the FDA includes both protecting and advancing public health. Greater transparency is consistent with this mission and is a relatively inexpensive and promising strategy to accomplish much more than what is possible through thousands of individual regulatory actions."

What's in Your Medicine Cabinet?

Ensuring the Safety and Efficacy of Prescription Drugs, Biologics and Medical Devices in the United States

A Policy Paper

By the

Yale Collaboration for Research Integrity and Transparency

June 2017

C R I T

collaboration for research integrity and transparency

Problem	Lack of access by independent researchers to de-identified patient level data, summary level data and meta-data from clinical trials can obscure serious safety and efficacy problems with new and existing medical products. Lack of information about the basis for FDA regulatory actions and decision-making can harm medical decision-making.
Solution	The FDA should provide researchers access to de-identified clinical trial data submitted by drug and device manufacturers to support regulatory approval and post-marketing requirements. The FDA should enforce clinical trial registration and reporting requirements, and impose penalties for noncompliance. The FDA should adopt the recommendations of the FDA Transparency Working Group which will provide increased transparency of FDA regulatory actions and decision-making.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 October 2014
EMA/240810/2013

European Medicines Agency policy on publication of clinical data for medicinal products for human use

POLICY/0070
Status: Adopted
Effective date: 1 January 2015
Review date: No later than June 2016
Supersedes: Not applicable

The justification

- “The aim of the European Medicines Agency ('the Agency') is to protect and foster public health. Transparency is a key consideration for the Agency in delivering its service to patients and society.”
- “Although the Agency since its creation has launched several initiatives to increase transparency of information on medicinal products, there is growing demand from stakeholders for additional transparency, **not only about the Agency's deliberations and actions, but also about the clinical data on which regulatory decisions are based.** The Agency is committed to continuously extend its approach to transparency and has, therefore, taken the initiative to develop a policy on publication of clinical data, in accordance with article 80 of Regulation (EC) No 726/2004”.

An important *caveat*

- **Protecting commercially confidential information (CCI):**
- The Agency respects and will not divulge CCI. **In general, however, clinical data cannot be considered CCI**. The Agency acknowledges that there are limited circumstances where information could constitute CCI.

Right from the start

Regulating medicines in Europe: the European Medicines Agency, marketing authorisation, transparency and pharmacovigilance

Govin Permanand, Elias Mossialos and Martin McKee

Clin Med 2006;**6**:87–90

"The US Food and Drug Administration (FDA) has traditionally been more open and accessible …. Notwithstanding recent accusations that the FDA may have suppressed information about several drugs, notably Vioxx®, the EMEA's new transparency provisions are playing catch-up."

Responses…

"A further point to consider is that EMA plans to release CSRs only on request. We would suggest making these documents routinely available on the EMA website after marketing authorization. This could be done by including a link to the CSRs of studies considered in the authorization process and listed in the European Public Assessment Reports (EPAR)."

Wieseler *et al. Systematic Reviews* 2012, **1**:50
http://www.systematicreviewsjournal.com/content/1/1/50

SYSTEMATIC REVIEWS

COMMENTARY Open Access

Access to regulatory data from the European Medicines Agency: the times they are a-changing

Beate Wieseler*, Natalie McGauran, Michaela F Kerekes and Thomas Kaiser

Abstract

Systematic reviewers are increasingly trying to obtain regulatory clinical study reports (CSRs) to correct for publication bias. For instance, our organization, the Institute for Quality and Efficiency in Health Care, routinely asks drug manufacturers to provide full CSRs of studies considered in health technology assessments. However, since cooperation is voluntary, CSRs are available only for a subset of studies analysed. In the case of the inhaled insulin Exubera, the manufacturer refused to cooperate and in 2007 we asked the European Medicines Agency (EMA) to provide the relevant CSRs, but EMA denied access. Other researchers have reported similar experiences.

In 2010 EMA introduced a new policy on access to regulatory documents, including CSRs, and has also undertaken further steps. The new policy has already borne fruit: in 2011, by providing additional sections of relevant CSRs, EMA made an important contribution to a review of oseltamivir (Tamiflu).

Unfortunately, speedy implementation of the new policy may be endangered. We define a CSR following the International Conference on Harmonisation (ICH) E3 guideline. Although this guideline requires individual patient data listings, it does not necessarily require that these listings be made available in a computer-readable format, as proposed by some regulators from EMA and other agencies. However, access to raw data in a computer-readable format poses additional problems; merging this issue with that of access to CSRs could hamper the relatively simple implementation of the EMA policy. Moreover, EMA plans to release CSRs only on request; we suggest making these documents routinely available on the EMA website.

Public access to regulatory data also carries potential risks. In our view, the issue of patient confidentiality has been largely resolved by current European legislation. The risk of other problems, such as conflicts of interest (CoIs) of independent researchers or quality issues can be reduced by transparency measures, such as the implementation of processes to evaluate CoIs and the publication of methods and protocols.

In conclusion, regulatory data are an indispensable source for systematic reviews. Because of EMA's policy change, a milestone for data transparency in clinical research is within reach; let's hope it is not unnecessarily delayed.

Keywords: Systematic reviews, Publication bias, Regulatory authorities, European Medicines Agency, Clinical study reports, Individual patient data listings, Raw data

"The EMA is the only regulator in the world that is routinely releasing part of its holdings, but our experience shows that document release can take considerable time to occur and often only after a lengthy correspondence. Despite the problems, the EMA's unique efforts should not be undermined."

Doshi and Jefferson *Trials* (2016) 17:78
DOI 10.1186/s13063-016-1194-7

Trials

RESEARCH Open Access

Open data 5 years on: a case series of 12 freedom of information requests for regulatory data to the European Medicines Agency

Peter Doshi[1*] and Tom Jefferson[2]

Abstract

Background: Clinical trial (and other) data from the European Medicines Agency (EMA) offers the best available opportunity to address the extensive reporting bias in pharmaceutical trial literature. Data are requested via freedom of information requests, but 5 years on, little is known about how the system is working.

Methods: Case series of 12 requests for regulatory data (clinical study reports and other regulatory data) relating to 29 different compounds. We logged start and end dates for correspondence with and data releases from the EMA, the need for additional correspondence and appeal of initial negative decisions, and inspected data releases for redaction. We measured: time from initial request to first substantive response from the EMA, to final decision from the EMA (in case of appeal), to initial receipt of documents, and to completion of request; number of data transmission batches generated; number of pages received for each request; average number of pages per batch over time (for releases in multiple batches); judgment as to whether the request was satisfied.

Results: We found great variability in time to receive an initial decision from the EMA (1 to 13 weeks). Additional correspondence with the EMA was necessary in 10 of 12 requests. Four of 12 were initially refused but 3 of 4 were allowed on appeal after 3 to 33 additional weeks. One request was denied despite appeal. Time to final decision was 1 to 43 weeks. We received data for 11 of 12 requests in 98 batches. While two requests remain outstanding as at June 2015 the remaining nine requests took a median 43 weeks to completion (range: 17 to 186 weeks). Despite redaction in 10 of 11 releases (mainly of researcher and participant identifying information), 8 requested were wholly satisfied.

Conclusions: The EMA is the only regulator in the world that is routinely releasing original clinical trial data, but release can take considerable time to occur and often only after a lengthy correspondence. Given its importance for research and significance for transparency we suggest ways in which the process could be made more efficient.

Keywords: Freedom of information act, Freedom of information, Access to documents, CSR, European medicines agency, Clinical study report, EMA, Regulatory science, Systematic reviews, Cochrane collaboration, Reporting bias, Evidence synthesis, Publication bias

"EMA stands out among regulators in providing information on non-approved applications for marketing authorization. In the USA, the decision not to approve and why are considered commercially confidential."

British Medical Bulletin, 2015, **116**:43–53
doi: 10.1093/bmb/ldv042
Advance Access Publication Date: 21 October 2015

Clinical trial transparency: many gains but access to evidence for new medicines remains imperfect

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Abstract

Background: Although selective and incomplete publication is widely acknowledged to be a problem, full access to clinical trial data remains illusive.

Sources of data: Authors' personal files, key documents from Food and Drug Administration and European Medicines Agency and focussed searches of PubMed.

Areas of agreement: Existing sources of information provide an incomplete overview of scientific research.

Areas of controversy: Persistent arguments about commercial confidentiality and the potential difficulties in de-identifying raw data can block important progress. Current industry efforts are voluntary and only partially satisfy the need for complete data.

Growing points: Requirements for trial registration are increasing. Important regulatory changes in particular in Europe have the potential to result in the release of more information.

Areas timely for developing research: Documenting the effects of prospective trial registration and requirements for proactive clinical trial publication on healthcare decisions, public health and rational resource allocation.

TRANSPARENCY POLICIES OF THE EUROPEAN MEDICINES AGENCY: HAS THE PARADIGM SHIFTED?

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MEDICAL LAW REVIEW *2017*

"Whereas in the European Ombudsman's opinion 'public health should always trump commercial interests', in the case of access to clinical trial reports, it was 'not obvious' to the General Court whether, as a result of weighing up of interests, 'the balance will clearly be in favour of the public interest defended by the EMA'. While the Ombudsman asserted that 'the public interest in disclosure will generally defeat any claim of commercial sensitivity', the General Court held that disclosure requires a 'delicate assessment' of the interests involved."

One of the key challenges is expedited or conditional approval

Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review

Alison M Pease,[1] Harlan M Krumholz,[2,3,4,5] Nicholas S Downing,[6] Jenerius A Aminawung,[7] Nilay D Shah,[8] Joseph S Ross[3,4,5,7]

BMJ 2017;357:j1680

"The quantity and quality of postapproval clinical evidence varied substantially for novel drugs first approved by the FDA on the basis of limited evidence, with few controlled studies **published** after approval that confirmed efficacy using clinical outcomes for the original FDA approved indication."

The data

“For 117 novel drugs approved by the FDA for 123 indications on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease, or both, the quantity and quality of post-approval clinical evidence varied substantially

After a median period of 5.5 years after approval, the median total number of post-approval clinical studies of the same indication for which the drug was first approved by the FDA was 1 (interquartile range 0-2), 3 (1-8), or 1 (0-2) for drugs approved on the basis of a single pivotal trial, surrogate markers of disease, or both, respectively.”

Major comparisons

Current MCC model

- Decision-making power vested in the Council
- Council members chair each of the Expert Committees, which make recommendations to the Council
- Secretariat implements the decisions of Council

SAHPRA model

- Decision-making power vested in the CEO, with oversight by the Board
- CEO will be able to appoint advisory committees
- CEO will delegate certain decisions to the secretariat

Major comparisons

Current MCC model

- Expert Committee recommendations are not binding on the Council
- Public cannot compare/contrast Council decisions with expert recommendations, UNLESS on the basis of a PAIA application

SAHPRA model

- Advisory committee recommendations will not be binding on the CEO and staff
- Should such recommendations be made public, to enhance accountability of the CEO and staff?

Major comparisons

Current MCC model

- No publicly-accessible medicines register
- No equivalent to EPARs/AusPARs
- No basis disclosed for decisions (whether P&A, Clinical, Names and Scheduling or final Council)

SAHPRA model

- Plans for a publicly-accessible register
- Should the basis for ALL regulatory decisions be documented, and publicly-accessible?

Should SAPRAA have an opinion?

VIEWPOINT

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1603

Published online 18 October 2013 in Wiley Online Library

European Federation of Statisticians in the Pharmaceutical Industry's position on access to clinical trial data

Christine Fletcher,[a*] Stefan Driessen,[b] Hans Ulrich Burger,[c] Christoph Gerlinger,[d,e] and Egbert Biesheuvel[f] on behalf of the EFSPI

The European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) believes access to clinical trial data should be implemented in a way that supports good research, avoids misuse of such data, lies within the scope of the original informed consent and fully protects patient confidentiality. In principle, EFSPI supports responsible data sharing. EFSPI acknowledges it is in the interest of patients that their data are handled in a strictly confidential manner to avoid misuse under all possible circumstances. It is also in the interest of the altruistic nature of patients participating in trials that such data will be used for further development of science as much as possible applying good statistical principles. This paper summarises EFSPI's position on access to clinical trial data. The position was developed during the European Medicines Agency (EMA) advisory process and before the draft EMA policy on publication and access to clinical trial data was released for consultation; however, the EFSPI's position remains unchanged following the release of the draft policy. Finally, EFSPI supports a need for further guidance to be provided on important technical aspects relating to re-analyses and additional analyses of clinical trial data, for example, multiplicity, meta-analysis, subgroup analyses and publication bias.

Can SA learn, or must it first repeat?

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Opinion | Health | Dec 11, 2013

Learning from the FDA's Plan B Fiasco

Lisa Heinzerling

100%

Thanks!