Institution: University College London

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Accelerating the international development of medicines for children through an open access excipient database

Period when the underpinning research was undertaken: 2012-2015

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Catherine Tuleu	Professor, Paediatric Pharmaceutics	2003-present
Smita Salunke	Research Associate; EuPFI Chief Scientific Officer	2009-present

Period when the claimed impact occurred: 2014-present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Excipients are critical formulation components, yet for paediatric medicines their safe inclusion and use remains a true challenge in drug development. The Safety and Toxicity of Excipients for Paediatrics (STEP) database, developed by Tuleu, Salunke and colleagues at UCL, is a unique, freely accessible global resource that compiles toxicity information of excipients for paediatric medicines. It was developed through a collaborative venture between the UCL-led European Paediatric Formulation Initiative and the United States Pediatric Formulation Initiative. Since its launch in 2014, the STEP database has rapidly grown into an essential resource, as evidenced by the circa 3000 registered users in 44 countries across 6 continents, and has demonstrably influenced the development of numerous paediatric treatment programmes and products.

2. Underpinning research (indicative maximum 500 words)

Professor Catherine Tuleu is an internationally renowned expert in the field of paediatric formulation, ranked 2nd in the 2016 Medicine Maker list of the 100 most influential international scientists in drug development. Her research focuses on the safety of excipients (materials that are included in medicines but are not the specified active ingredient) in paediatric medications. The inhomogeneity of children, particularly with regard to age and size, alongside marked differences in physiology compared to adults, means that safety data must be considered specifically for this group. Since 2007, the European Medicines Agency (EMA) has required justification of the excipients included in paediatric medicines for Paediatric Investigation Plans. Tuleu realised that no specialised database was then available to support the development of paediatric formulations, resulting in not only increased workload for medicines developers but also a higher risk of error and inconsistency.

Consequently, a UCL-led consortium chaired by Tuleu was formed in 2007, named the European Paediatric Formulation Initiative (EuPFI). One of the key ambitions of EuPFI was the creation of a database that would collate and openly share safety and toxicology data on excipients and make this freely available to safely facilitate the development of new drugs for children. This strategic aim was shared by the USA, which led to a collaboration with the United States Pediatric Formulation Initiative (under the auspices of the Eunice Kennedy Shriver National Institute of Child Health and Human Development).

The outcome of this cooperation was the STEP database, launched in 2014. This is a freely accessible database relating to specific excipients for use in paediatric medicines with particular emphasis on safety and toxicity data for children. The basic principles involved are summarised

in Figure 1 [**R1**]. The STEP database research was funded mostly by the EU GRiP (Global Research in Paediatrics) Network of Excellence and partly by EuPFI. The European Medicines Agency was a partner of the GRiP consortium; hence the regulator has been directly involved in the database development.

Figure 1: Basic principles and benefits of the STEP database

The development and evaluation of the database is described over three research papers [**R2**, **R3**, **R4**]. Firstly, a needs analysis was performed [**R2**] (2012) whereby a global survey was conducted of stakeholders (n=247) to identify the database content and structure that was required by the end users. This demonstrated that there was indeed a clear need for such a database, with 97% of respondents supporting the initiative. The second paper [**R3**] (2013) describes the pilot study, involving data from over 2000 references covering 10 excipients, presenting preclinical, clinical, regulatory information and toxicological reviews, with references and source links. The information generated during the pilot study was used to define the data entry guidelines to ensure consistency among the curators entering the data. This pilot formed the basis of a broader data gathering exercise which is outlined below. The third paper [**R4**] (2015) describes a systematic evaluation of the STEP database from the perspective of end users. The data searching, led by Salunke, interrogates ~150 sources (public and private) including various government databases. A key component of the development of STEP was to develop a suitable methodology for the data searching and evaluation process and this is summarised in Figure 2.

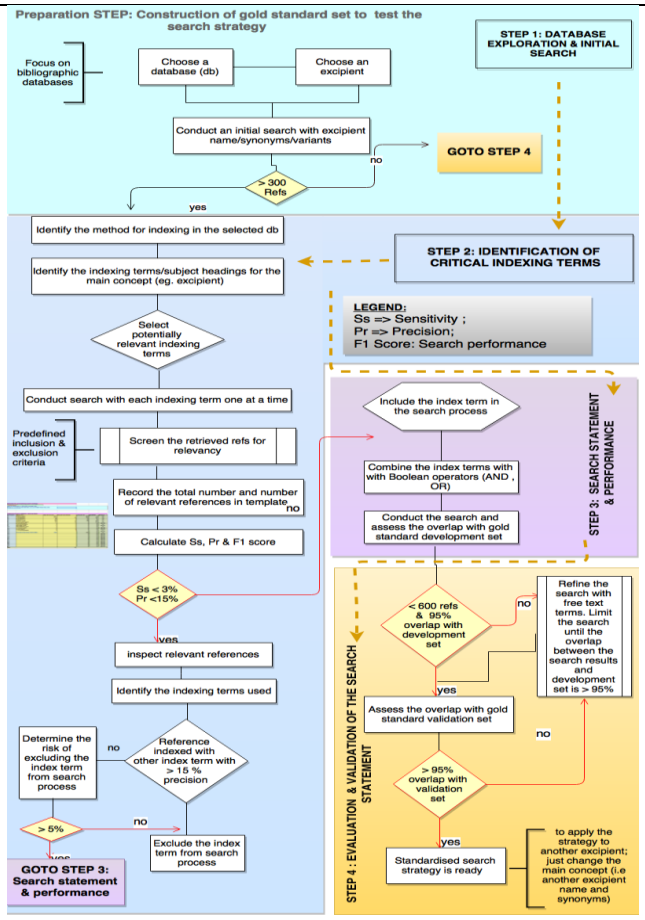

Figure 2: Summary of search methodology used for the STEP database (http://www.eupfi.org/step-database-info/)

3. References to the research (indicative maximum of six references)

[R1] http://www.eupfi.org/step-database-info/

[R2] Salunke S, Giacoia G, Tuleu C. The STEP (safety and toxicity of excipients for paediatrics) database. Part 1-A need assessment study. Int J Pharm. 2012;435(2):101-111. doi:10.1016/j.ijpharm.2012.05.004

[R3] Salunke S, Brandys B, Giacoia G, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) database: part 2 - the pilot version. Int J Pharm. 2013;457(1):310-322. doi:10.1016/j.ijpharm.2013.09.013

[R4] Salunke S, Tuleu C; European Paediatric Formulation Initiative (EuPFI). The STEP database through the end-users eyes-usability study. Int J Pharm. 2015;492(1-2):316-331. doi:10.1016/j.ijpharm.2015.06.016

4. Details of the impact (indicative maximum 750 words)

The STEP database was launched in 2014 with 10 excipients listed; it currently contains 75 excipients. Uniquely in such projects, key stakeholders (pharmaceutical companies, regulators from the European Medicines Agency (EMA), academics and health care professionals) have played a proactive and vital role in the selection and prioritisation of excipients that were progressively included in the database. Additionally, several companies have sponsored inclusion of excipients of interest in the database, while the Bill and Melinda Gates Foundation have provided funds to support a further 10 excipients for inclusion.

The database is globally accessible via the website through an intuitive search interface [**S1**]. Registration data shows that currently more than 3000 users from 44 countries on 6 continents are registered and use the STEP database, with the pharmaceutical industry representing ~70% of users, followed by hospital, government, regulatory agencies and academia. Across the EU and increasingly worldwide, the database has accelerated development of products, reduced staff time and costs in repetitive searches, provided a consistent approach to excipient selection and a reliable source of safety data that reduces the risk to the patient.

Several major pharmaceutical manufacturing companies, such as Eli Lilly [**S2**], Sanofi, Pfizer, Roche, AbbVie, GSK and Novartis have cited the STEP database in their published information. For example, the Senior Research Advisor, Eli Lilly and Company, Indianapolis, comments [TEXT REDACTED FOR PUBLICATION] [**S2**].

The Chief Executive Officer of Proveca (a pharmaceutical company specialising in the research, development, licensing and commercialisation of medicines for children) states that the STEP database underpinned the company's excipient minimisation and safety strategy and has created savings not only in monetary expense, but also in terms of development efficiency. Throughout 2013-2020, STEP was used to screen out over 50 excipients in 12 formulation development programmes, reducing initial investment in candidate excipients that would not meet regulatory approval. In doing so, this created an associated saving to the company of approximately GBP1,000,000, 12 months of development time, plus the facilitation of the justification of excipient inclusion to the EMA. As an example of how STEP has contributed to Proveca's regulatory authority interactions, it facilitated the approval of 6 Paediatric Investigation Plans since 2013, including Sialanar, a glycopyrronium bromide paediatric formulation for the treatment of severe sialorrhoea (drooling). This product has a patient base of over 3500 children across the EU [TEXT REDACTED FOR PUBLICATION]. Proveca's CEO describes the STEP database as being "*central to our work"* and states that STEP "*enables a formulation 'right first time' approach, informed by sound science and peer reviewed research*", which ultimately "*enables paediatric medicines licensing which is a quantifiable return on investment for industry, but most importantly, enables the safe and effective treatment of children with licensed medicines*" **[S3].**

Excipients suppliers/manufacturers have shown interest in having their products incorporated in the STEP database as such inclusion may support the justification required by the EMA. This is evidenced by promotional material in which companies have highlighted the inclusion of the STEP database as reference materials. Gattefossé, who manufacture lipid excipients for the development of dosage forms including paediatric medications, cite the STEP inclusion of Compritol® 888 ATO in their sales brochure **[S4]**, reflecting the importance attached to such inclusion for the use and sale of their excipients.

The STEP database is also acknowledged and supported by regulatory bodies. The EMA frequently refer to the database in their communications, while the Chinese Centre for Drug Evaluation have also cited the database in their recent guidelines **[S5].** The Therapeutic Product Directorate of Canadian regulator, Health Canada, recommended the STEP database as a significant resource during the presentation 'Excipients in Pediatric Medicines: A Health Canada Perspective' when highlighting differences between adult and child formulations as an extra layer of investigation when selecting excipients **[S6].**

5. Sources to corroborate the impact (indicative maximum of 10 references)

[S1] STEP database website. https://step-db.ucl.ac.uk/eupfi/appDirectLink.do?appFlag=login.
[S2] Testimonial from Senior Research Advisor, Eli Lilly
[S3] Testimonial from CEO, Proveca
[S4] 'Gattefossé products in pediatric dosage forms'. p3. Gattefossé corporate information brochure. Gattefossé, France. www.pharmaexcipients.com/wp-content/uploads/2020/03/Brochure_Gattefosse-Lipid-Excipients-in-Pediatric-Dosage-Form.pdf

[S5] Chinese Reform of the Regulatory Environment (Reference 118). Syneos Health. 2020. https://www.syneoshealth.com/sites/default/files/documents/China%20white%20paper%202020%20Q3.pdf

[S6] 'Excipients in Pediatric Medicines: A Health Canada perspective'. Presentation given 20 September 2019. Health Canada. http://www.cspscanada.org/wp-content/uploads/Lum-Susan-Excipients-in-Pediatrics.pdf