

Ana Paula Moreira da Costa Folhadela Simões

Starting Material – Concept and Impact on Pharmaceutical Regulations

Tese do 3º Ciclo de Estudos Conducente ao Grau de Doutor
em Ciências Farmacêuticas, especialidade Tecnologia Farmacêutica

Trabalho realizado sob a orientação dos
Professores Doutores José Manuel Sousa Lobo e Ana Paula Martins

janeiro 2018

DE ACORDO COM A LEGISLAÇÃO EM VIGOR, NÃO É PERMITIDA A REPRODUÇÃO
DE QUALQUER PARTE DESTA TESE.

Agradecimentos

Gostaria de deixar expresso o meu sincero agradecimento a todos aqueles que estiveram comigo ao longo deste percurso.

Uma palavra de especial atenção, reconhecimento e profunda gratidão:

- ao meu orientador, Professor José Manuel Sousa Lobo, pelo caminho que me foi mostrando ao longo do tempo, fazendo-me ver, pensar e questionar. Acreditou! Acompanhou-me em cada momento de desânimo, e esteve presente nos pequenos momentos de conquista. Só assim foi possível chegar a este momento. Bem haja!

- à minha co-orientadora, Professora Ana Paula Martins, pelo apoio, por me fazer acreditar que o caminho pode ser sinuoso, mas é possível. Pelo espírito crítico, mas sempre construtivo, que demonstrou ao longo deste longo percurso, contribuindo para o enriquecimento da tese. Com a sua vasta e reconhecida experiência profissional e académica foi sobretudo uma inspiração.

- ao amigo Professor Pedro Granja pela inspiração, pelo apoio e exemplo de resiliência.

- aos meus colegas em BIAL que contribuíram para o resultado final e dos quais gostaria de destacar:

Sónia Dias, pelo seu apoio incondicional e espírito crítico, ao qual recorri várias vezes para tentar validar alguns dos conceitos regulamentares plasmados nesta tese; *Ingrid Oliveira* pelo aconselhamento na análise estatística e sua revisão; *Soraia Santos* pela esquematização das estruturas químicas e *Teresa Silveira* pelo apoio na pesquisa bibliográfica.

- uma palavra especial para a Dra Isabel Morgado, por me ter apoiado ao longo deste percurso, mas acima de tudo por ter sido, ao longo dos 20 anos do meu percurso profissional na área da regulação do medicamento, e por continuar a ser, um exemplo de mente e personalidade instigante de responsabilidade e de sucesso.

E por fim, à minha Família (com F grande!) e em particular ao meu filho Gonçalo e ao meu marido, Carlos. Quão pacientes foram...

Resumo

A definição e conceito de material de partida e a forma como as diferentes abordagens, científicas e regulamentares, podem ter impacto na atividade industrial e na qualidade dos medicamentos são aqui analisados.

Foi efetuado um levantamento exaustivo da legislação e “guidelines” aplicáveis ao conceito, definição e seleção de um material de partida.

Foi realizada uma análise retrospectiva dos relatórios disponíveis de avaliação de medicamentos que receberam autorização de introdução no mercado entre janeiro de 1999 e abril de 2015.

Os relatórios analisados foram emitidos por duas Autoridades Regulamentares - European Medicines Agency (EMA) e Food and Drug Administration of the United States of America (FDA). É apresentada uma análise estatística e tenta-se estabelecer uma relação entre os dados e a evolução da legislação. São analisados quatro estudos de caso (3 já submetidos e avaliados por uma Autoridade competente e 1 caso não submetido) e as vias de síntese descritas na literatura para 3 substâncias ativas. São apresentados e discutidos conceitos como a contribuição da estrutura química do material de partida para a estrutura da substância ativa final, propriedades físico-químicas e nível de conhecimento da via de síntese do material de partida.

Concluiu-se que, apesar da melhoria e esforço dos diferentes intervenientes para clarificar os aspetos relacionados com o material de partida ao longo do tempo, como refletido na “guideline” ICH Q11, entre outras, não foi conseguido um conceito claro de material de partida. Consequentemente, foi identificada a necessidade de se disponibilizar um “documento de reflexão” orientado mais especificamente para os problemas referentes à definição de material de partida e à justificação para a sua seleção. Por fim, este documento de reflexão poderá ser a base para abordar os critérios (alguns são propostos) a serem usados pelas Autoridades competentes para estabelecer os requisitos para a seleção do material de partida.

Palavras-chave: legislação farmacêutica; legislação do medicamento; material de partida.

Abstract

The definition and concept of starting material and how different approaches, scientific and regulatory, can impact industry activity and quality of medicines are discussed.

An extensive survey of the legislation and guidelines applicable to the concept, definition and selection of a starting material is conducted.

A retrospective analysis of the available assessment reports for medicinal products receiving a marketing authorisation between January 1999 and April 2015 is performed.

The reports considered are those issued by two Regulatory Authorities – European Medicines Agency (EMA) and Food and Drug Administration of the United States of America (FDA). A statistical analysis is presented and the relationship between the data and the evolution of legislation has tentatively been established. Four case studies (3 already submitted and assessed by a competent Authority and 1 case not submitted) and synthetic routes described in the literature for 3 active pharmaceutical ingredients are discussed. Concepts like the contribution of the chemical structure of the starting material to the final active pharmaceutical ingredient, physicochemical properties and the degree of knowledge of synthetic route of the starting material are presented and discussed.

It was concluded that, despite an improvement and effort from the different stakeholders to clarify the aspects related to the starting material along the time, as reflected by the ICH Q11 guideline among others, no clear concept of starting material was achieved.

Thus, the need to make available a concept paper addressing more specifically the problems concerning the definition of starting material and the justification of its selection was identified. Ultimately, the concept paper could be the basis for to address the criteria (some of them are proposed) to be used by the competent Authorities to establish the requirements for the selection of the starting material.

Key-words: pharmaceutical legislation; legislation of medicinal products; starting material.

Abbreviation list

AAA	Asymmetric allylic alkylation
Anvisa	Brazilian Health Surveillance Agency
API	Active pharmaceutical ingredient
APIMF	Active pharmaceutical ingredient master file
API SM	API Starting Material Working Group
AS	Active substance
ASMF	Active substance master file
BP	British Pharmacopeia
CEP	Certificate of suitability to the monographs of the European Pharmacopeia
CHMP (CPMP)	Committee of Human Medicinal Products
CMC	Chemical, manufacturing and controls
CSI	Chlorosulfonyl isocyanate
CTD	Common technical document
CVMP	Committee of Veterinary Medicinal Products
DEGME	Diethylene glycol monomethyl ether
DHP	3,4-dihydro-2H-pyran
DMAP	4-(Dimethylamino)pyridine
DMF	Drug master file
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DNA	Deoxyribonucleic acid
DS	Drug substance
DTTP	Thymidine 5'-triphosphate
DYKAT	Trost's Dynamic Kinetic Asymmetric Transformation
EC	European Commission
EDCI	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
EDMF	European drug master file
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA (EMA)	European Medicines Agency
EPAR	European public assessment report
EU	European Union
FDA	Food and Drug Administration of United States of America
FP	Finished product
GC	Gas chromatography
GMP	Good manufacturing practice
HC	Health Canada
HPLC	High performance liquid chromatography
HSA	Singapore Health Sciences Authority
IBCF	Isobutyl chloroformate
ICH	International Conference on Harmonisation
IGDRP	International Generic Drug Regulators Pilot
INN	International nonproprietary name
IPC	In process control
IQ	International Consortium for Innovation and Quality in Pharmaceutical Development
IR	Infra-red
JP	Japanese Pharmacopeia
LOD	Limit of detection
LOQ	Limit of quantification
MA	Marketing authorisation
MCC	South African Medicines Control Council
MFDS	South Korean Ministry of Food and Drug Safety

MI	Mutagenic impurity
MTBE	Methyl <i>tert</i> -butyl ether
NCE	New chemical entity
NMR	Nuclear magnetic resonance
OJ	Official Journal of the European Union
OMCL	Official Medicines Control Laboratory
Ph.Eur.	European Pharmacopeia
Ph.Int.	International Pharmacopeia
PMDA	Pharmaceuticals and Medical Devices Agency from Japan
PQT-WHO	Prequalification team of the World Health Organisation
QWP	Quality Working Group
SM	Starting material
Swissmedic	Swiss Agency for Therapeutic Products
TCA-NCO	Trichloroacetyl isocyanate
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TFDA	Taiwan Food and Drug Administration
TGA	Australian Therapeutic Goods Administration
THF	Tetrahydrofuran
TSE	Transmissible Spongiform Encephalopathy
USA	United States of America
USAN	United States adopted name
USP	United States Pharmacopeia
UV	Ultraviolet
WHO	World Health Organisation

Table of contents

1	Introduction	2
1.1	General remarks	2
1.2	Guidelines and legislation	5
1.3	Starting material	10
1.3.1	Definition of starting material	10
1.3.2	Selection of starting material and assessment	15
1.3.3	Relevance of starting material	24
1.3.4	Other aspects of starting materials	37
1.3.5	Remarks	45
2	Outcomes	47
2.1	Retrospective analysis of the assessment reports	47
2.1.1	Data collected	47
2.1.2	Statistical analysis	66
2.2	Cases described in the literature	73
2.2.1	Introduction	73
2.2.2	Eslicarbazepine acetate	76
2.2.3	Lacosamide	83
2.2.4	Retigabine	103
2.2.5	Zonisamide	109
2.3	Case studies	110
2.3.1	Introduction	110
2.3.2	Case Study I	118
2.3.3	Case Study II	125
2.3.4	Case Study III	129
2.3.5	Case study IV	133
3	Discussion	137
3.1	Introduction	137
3.2	Cases described in the literature	138
3.2.1	Introduction	138
3.2.2	Eslicarbazepine acetate	140
3.2.3	Lacosamide	147
3.2.4	Retigabine	159
3.3	Case studies	164
3.3.1	Introduction	164
3.3.2	Discussion of Case Study I	168
3.3.3	Discussion of Case Study II	171
3.3.4	Discussion of Case Study III	174

3.3.5	Discussion of Case Study IV	176
4	Conclusions	178
4.1	Guidelines, position papers and legislation available	181
4.2	Retrospective analysis of assessment reports	182
4.3	Cases described in the literature	184
4.4	Case studies	185
4.5	Recommendation for the definition of starting material	186
4.6	Recommendation for the criteria for selection of starting material	187
4.6.1	How to select a starting material?	188
4.6.2	What should be the Applicant's responsibility?	190
4.6.3	What documentation should be submitted to the Regulatory Authority regarding the starting material?	191
4.6.4	What should be the Regulatory Authority role?	192
4.7	Final remarks	193
5	References	195

List of Tables

Table 1:	List of Guidelines, Position papers and Legislation	6
Table 2:	Definition of starting material.....	10
Table 3:	Differences in the definition of starting material.....	14
Table 4:	Application of GMP requirements to API manufacturing ^a	16
Table 5:	Pharmacopeias and guidelines accepted ^a	20
Table 6:	Overview of API SM survey focus areas ^a	22
Table 7:	Comments on Draft guideline on the chemistry of active substances	28
Table 8:	CTD section and number of observed deficiencies ^a	31
Table 9:	Description of CTD section	32
Table 10:	Top 10 deficiencies and recommendations	33

Table 11: Listing of third countries	43
Table 12: List of marketing authorisations EMA & FDA.....	48
Table 13: Information for API and Starting materials	54
Table 14: Type of changes during cycle review.....	60
Table 15: Variables for the statistical analysis.....	66
Table 16: Classification of impurities.....	114
Table 17: Case studies and synthetic process	116
Table 18: Impact on the company activity.....	124
Table 19: Impact on the company activity.....	128
Table 20: Impact on the company activity.....	132
Table 21: Impact on the company activity.....	135
Table 22: List of Legislation and Guidelines	139
Table 23: List of Legislation and Guidelines	164
Table 24: Information to be included	166
Table 25: Similarities and differences between synthetic processes (case study I and case study II).....	173

List of figures and graphics

Figure 1: Schematic description (illustrative only) ^a	18
Graphic 1: Number and type of changes related to API starting material.....	71
Graphic 2: Type of changes.....	72
Graphic 3: Comparative results.....	75
Figure 2: Structure of eslicarbazepine acetate	76

Figure 3: Flow diagram of the synthetic route	77
Figure 4: Flow diagram of the synthetic process	81
Figure 5: Structure of lacosamide	83
Figure 6: Flow diagram of synthetic process	84
Figure 7: Schematic representation of the synthetic process	88
Figure 8: Key step of the synthesis of lacosamide	92
Figure 9: Flow diagram of synthetic process	93
Figure 10: Synthetic process of lacosamide	97
Figure 11: Flow diagram of synthetic process	101
Figure 12: Structure of retigabine	103
Figure 13: Flow diagram of synthetic process	104
Figure 14: Main steps of synthetic process	106
Figure 15: Structure of zonisamide	109
Figure 16: Structure of eslicarbazepine acetate	116
Figure 17: Oxcarbazepine	141
Figure 18: Eslicarbazepine acetate	141

1 Introduction

1 Introduction

1.1 General remarks

Relationship between the concept of starting material and the impact that different approaches, either scientific or regulatory could have in the Pharmaceutical Industry and the quality of the medicines is one of the aims of this thesis.

The global market constitutes a challenge to the different stakeholders, from Regulatory Authorities to the Pharmaceutical Industry, including the economic players in the different regions, with the possibility of supplying starting materials from multiple sources and in accordance with regulations that are not very much defined or harmonised.

The development of a new active pharmaceutical ingredient (API) is very expensive. The complexity of the manufacturing technology and the pressure to develop a process adequate for commercial use are key considerations for the design of the synthetic process.

The global market is generally keen to promote competition and reduce the price of medicines, but this is a burden for the authorities and the Pharmaceutical Industry. For one hand, the Pharmaceutical Industry is under pressure to deliver innovative therapies while the authorities are pressed to find mechanisms for faster approvals, bearing in mind the safety of medicines and the need to fill unmet needs for patients. The Authorities are also looking for cost-effective medicines, mainly due to increased pressure on healthcare budgets, without jeopardising the access of patients to novel medicines.

Production of chemical compounds is spread around the World with China and India assuming a relevant role on that field in the last years ([Shanley A, 2015](#)). These countries have been in the spotlight of fine chemistry, either by establishing companies fully capable to produce APIs at low cost or by celebrating partnerships with European and American companies to develop and produce new chemical entities ([Spadoni C, 2011](#)).

The very competitive global market is affecting the trade in raw materials. If the best binary “price-quality” is part of normal business, the Pharmaceutical Industry must ensure that the final product – “the medicine” - is of quality, safe and efficacious.

The current regulatory requisites applicable to the Pharmaceutical Industry in general, and particularly to the API, contribute, among others, to the dramatic increase of research and development costs of a medicine. Considering that one of the obligations of the

Pharmaceutical Industry is to supply the market avoiding shortages, in particular for essential medicines, the supply's strategy is quite important. Looking for a cost-effectiveness process capable to ensure the supply, and if needed, identify alternative suppliers during the development and during the entire product lifecycle is to be considered.

In a very recent past (70's – early 80's) the authorities approved medicines without a full knowledge of the origin/manufacturing site of the API and no information was provided for the origin/supplier of the starting material. Nowadays, extensive and detailed information, not only for the API, but also for the starting material must be provided in the marketing authorisation application.

The need for more detailed information is, most of the times, triggered by unexpected safety events. Not so long ago, the Transmissible Spongiform Encephalopathy (TSE), which was specifically related to the origin of the raw materials, demanded a quick action from the authorities and Pharmaceutical Industry. Assessment and confirmation of the origin of the multiple raw materials that are included in medicinal products, finding alternative sources for the raw materials affected, and reformulation of several raw materials – excipients, capsules, etc. – previously of animal origin, provoked a discussion around the safety of medicines and the capacity of Regulatory Authorities and Pharmaceutical Industry to predict this kind of problem.

A quite recent example is an alert issued by the World Health Organization (WHO) regarding to the active pharmaceutical ingredient dextromethorphan hydrobromide produced by an Indian company ([Information Exchange System Alert No. 126, 24 January 2013](#)). High levels of the isomer levomethorphan were found. The impact of that finding for the authorities and industry was tremendous. Dextromethorphan is an antitussant that centrally suppresses the cough reflex, with low toxicity, and that is very useful, from a clinical perspective, in the treatment of disruptive non-productive cough in infections and in palliative care (primary or metastatic lung cancer). Levomethorphan, the *l*-isomer of methorphan, is a potent narcotic analgesic controlled under schedule 1 of the single Convention on Narcotic Drugs 1961. Moreover, the hepatic metabolism of levomethorphan produces levorphanol, which is a pure opioid agonist. This situation resulted in overdoses and consequent deaths in some critical cases. The adverse reactions commenced immediately following distribution of the medicine produced with an API from that source. Automatically, several authorities around the world, namely from developing countries that do not have so strict regulatory mechanisms to control the

source of the API, asked the Marketing Authorization (MA) Holders to suspend the commercialization of all medicinal products containing that API, whatever the source.

So, the concepts and characterisation of starting material and API, and the relevance for the quality of a medicinal product, is of utmost importance.

The perspective of Regulatory Authorities and Pharmaceutical Industry is not always coincident in what concerns the definition of starting material, the justification for its selection and the level of detail to be included in the marketing authorisation application, even though the aim is the same: make safe and effective medicines available to the patients.

The selection of the adequate starting material(s) for the synthesis of an active pharmaceutical ingredient (API) that complies with the scientific and regulatory requisites is a quite recent discussion among the different stakeholders (Pharmaceutical industry, Quality Control Bodies and Regulatory Authorities). If in the past, the Authority looked to the quality of the API itself, namely by controlling the specifications, nowadays, it is trying to ensure the quality of the synthetic process by requesting the control of the starting materials, intermediates and ultimately, of the final ingredient, the API. The main concern of the Regulatory bodies resides in a trend observed in APIs for shorter synthetic routes, apparently leading to a lack of information on potential carryover of impurities and for outsourcing of synthesis of starting materials. These could lead to less and not so close control of the process and manufacturing practices.

During the lifecycle of a product, change of manufacturing site, improvement of synthetic process, change in suppliers of starting materials, update of the process triggered by new legislation and/or scientific progress can increase the burden of the whole regulatory process.

Key players such as, the European Pharmacopeia Working Groups under EDQM umbrella, relevant Authorities such as the European Medicines Agency (EMA) and Food and Drugs Administration of the United States of America (FDA), European Commission (EC), and International Associations representative of Traders and Pharmaceutical Industry, play an important role in this arena.

1.2 Guidelines and legislation

According to the definition provided in the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, a medicinal product is:

“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;

or

“(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

A medicinal product can only be available for the patients if it demonstrates, during the registration process, to be of quality, safe and efficacious.

Protection of Public Health is a major role for the Regulatory Authorities, and this triggers a need to ensure the quality and safety of medicinal products available, supported, among others, by:

- a) regulations adequate to the progression of the science;
- b) improvement of manufacturing processes and control strategies;
- c) adequate identification of sources;
- d) control of counterfeiting.

Indeed, in the past few years, Regulatory Authorities were dedicated to preparing, with the key stakeholders, several pieces of legislation and guidelines, including position papers, to support sustainable research and development of safe medicines. Guidelines, position papers and legislation considered relevant to the purpose of the discussion are depicted in [Table 1](#). The referenced documents are organised by date in ascending order.

Table 1: List of Guidelines, Position papers and Legislation

Reference	Description	Date for coming into effect
3AQ5a (Note for guidance)	Chemistry of Active Substances.	October 1987* <i>*(replaced by "EMA/454576/2016 - Guideline on the chemistry of active substances adopted by CHMP on 21 July 2016)</i>
CPMP/ICH/367/96 (ICH Topic Q6A)	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.	May 2000
CPMP/ICH/4106/00 (ICH Topic Q7)	Good Manufacturing Practice for Active Pharmaceutical Ingredients.	November 2000
Directive 2001/83 of the European Parliament and of the Council of 6 November 2011 (as amended)	Community Code Relating to Medicinal Products for Human Use.	6 November 2001* <i>*date of initial Directive</i>
CPMP/ICH/2737/99 (ICH Guideline Q3A (R2))	Impurities in New Drug Substances.	August 2002 <i>(October 2006 - revised attachment 2)</i>
CPMP/QWP/130/96 Rev1	Guideline on Chemistry of New Active Substances.	February 2004 <i>(replaced by "EMA/454576/2016 - Guideline on the chemistry of active substances adopted by CHMP on 21 July 2016)</i>
Regulation (EC) No.726/2004 of the European Parliament and of the Council of 31 March 2004	Laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency	31 March 2004* <i>*date of Regulation</i>

Reference	Description	Date for coming into effect
Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004	Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use.	31 March 2004
CPMP/QWP/1529/04	Guideline on Control of Impurities of Pharmacopeial Substances: Compliance with the European Pharmacopeia General Monograph "Substances for Pharmaceutical Use" and General Chapter "Control of Impurities in Substances for Pharmaceutical Use".	April 2004
Volume 2B - Notice to Applicants Medicinal products for human use – Presentation and format of the dossier – Common Technical Document (CTD) - (Module 3)	Module 3 – Quality - Chemical-pharmaceutical and biological information for chemical active substances and biological medicinal products.	July 2004
CHMP/QWP/297/97 Rev. 1 corr.	Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier.	1 February 2005
CHMP/ICH/167068/04 (ICH Guideline Q8 (R2))	On Pharmaceutical Development.	May 2006
EMA/CHMP/ICH/24235/2006 (ICH Guideline Q9)	On quality risk management.	January 2006
EMA/CHMP/ICH/214732/2007 (ICH Guideline Q10)	On pharmaceutical quality system.	June 2008
EMA/CHMP/CVMP/QWP/450653/2006	Recommendation on the Assessment of the quality of medicinal products containing existing/known active substances.	9 February 2009
PA/PH/OMCL (12) 51 3R	API Surveillance: Position Paper for OMCLs (OMCL Network of	September 2012

Reference	Description	Date for coming into effect
	the Council of Europe, General Document).	
CHMP/QWP/227/02 Rev. 3 corr.	Guideline on Active Substance Master File Procedure.	1 October 2012
EMA/CHMP/ICH/425213/2011 (ICH Q11)	On development and manufacture of drug substances (chemical entities and biotechnological/biological entities).	November 2012
EMA/CHMP/ICH/353369/2013 (ICH Q3D)	On elemental impurities.	December 2013 (Final adoption by CHMP). <i>(June 2016: date for coming into effect for new marketing authorization applications; December 2017: date for coming into effect for authorized medicinal products).</i>
Ares(2014)2674284	The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials.	September 2014
Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014	Supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for Human use.	25 May 2015
EMA/CHMP/ICH/83812/2013 (ICH Guideline M7)	On assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.	January 2016

Reference	Description	Date for coming into effect
European Pharmacopeia 9.0	General Text. 5.10. Control of Impurities in Substances for Pharmaceutical Use.	July 2016
EMA/454576/2016	Guideline on the chemistry of active substances*. *this guideline replaces "Note for guidance on chemistry of new active substances" (CPMP/QWP/130/96, Rev 1) and Note for guidance "Chemistry of active substances" (3AQ5a).	15 November 2016 (publication date) <i>(date for coming into effect: 6 months after publication).</i>
EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1	Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances*. *an initial version was adopted by the CHMP in September 2014 and was reviewed in September 2016; the CHMP adopted this version in December 2016 and published it at the EMA website on 3 July 2017.	December 2016 (date of adoption by CHMP).
EMA/CHMP/ICH/82260/2006 (ICH guideline Q3C (R6))	On impurities: guideline for residual solvents*. *replaces the (R5) of February 2009.	14 June 2017

1.3 Starting material

1.3.1 Definition of starting material

All the guidelines, position papers and legislation mentioned in the item “Guidelines, Position papers and Legislation” (Table 1), were searched for a definition of “starting material”. The result of such search is systematized below in Table 2. The reference of each guideline, position paper or legislation, including the date of coming into force, and the definition of starting material, if any, referred in such documents, are included in Table 2. As in Table 1, the references are organised chronologically and in ascending order. The year of coming into force of each document is also mentioned in the table to allow an analysis of the evolution of the definition of starting material.

Table 2: Definition of starting material

Reference / Year of coming into force	Definition of starting material
3AQ5a (Note for guidance) (1987)	No definition included.
CPMP/ICH/367/96 (ICH Topic Q6A) (2000)	No definition included.
CPMP/ICH/4106/00 (ICH Topic Q7) (2000)	API Starting Material is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.
Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 (as amended) (2001)	No definition included.
CPMP/ICH/2737/99 (ICH Guideline Q3A (R2))	A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting

Reference / Year of coming into force	Definition of starting material
(2002)	materials are normally commercially available and of defined chemical and physical properties and structure.
CPMP/QWP/130/96 Rev1 (2004)	No definition included.
Regulation (EC) No.726/2004 of the European Parliament and of the Council of 31 March 2004 (2004)	No definition included.
Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 (2004)	No definition included.
CPMP/QWP/1529/04 (2004)	No definition included.
Volume 2B - Notice to Applicants Medicinal products for human use – Presentation and format of the dossier – Common Technical Document (CTD) - (Module 3) (2004)	No definition included.
CHMP/QWP/297/97 Rev. 1 corr. (2005)	No definition included.
CHMP/ICH/167068/04 (ICH Guideline Q8 (R2)) (2006)	No definition included.
EMA/CHMP/ICH/24235/2006 (ICH Guideline Q9) (2006)	No definition included.
EMA/CHMP/ICH/214732/2007 (ICH Guideline Q10) (2008)	No definition included.

Reference / Year of coming into force	Definition of starting material
EMA/CHMP/CVMP/QWP/450653/2006 (2009)	No definition included.
PA/PH/OMCL (12) 51 3R (2012)	No definition included.
CHMP/QWP/227/02 Rev. 3 corr. (2012)	No definition included.
EMA/CHMP/ICH/425213/2011 (ICH Q11) (2012)	A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials.
EMA/CHMP/ICH/353369/2013 (ICH guideline Q3D) (2013)	No definition included.
Ares(2014)2674284 (2014)	A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.
Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 (2015)	'Active substance starting material' means any substance from which an active substance is manufactured or extracted.
EMA/CHMP/ICH/83812/2013 (ICH Guideline M7) (2016)	No definition included.
European Pharmacopeia 9.0 (2016)	No definition included.
EMA/454576/2016 (2016)	Starting materials should be substances with defined chemical properties and structures.

Reference / Year of coming into force	Definition of starting material
EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1 (2016)	A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials.
EMA/CHMP/ICH/82260/2006 (ICH guideline Q3C (R6)) (2017)	No definition included.

From the analysis of [Table 2](#) above, and considering the documents mentioned, the first definition of starting material appears in the [CPMP/ICH/4106/00 \(ICH Topic Q7\)](#), of November 2000, “Good Manufacturing Practice for Active Pharmaceutical Ingredients”. According to this document, an *API Starting Material is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced inhouse. API Starting Materials normally have defined chemical properties and structure.*

In 2002, in [ICH Guideline Q3A \(R2\) \(CPMP/ICH/2737/99\)](#) Impurities in new Drug Substances, a definition of starting material is included:

“Starting Material: A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure”.

When comparing this definition with the one stated in ICH Topic Q7, slight differences, as stated below, are to be found: ([Table 3](#))

Table 3: Differences in the definition of starting material

In ICH Topic Q7 / (2000)	In ICH Guideline Q3A (R2) / (2002)
Raw material, intermediate, or an API.	Material used in the synthesis of a new drug substance.
Incorporated as a significant structural fragment into the structure of the API.	Incorporated as an element into the structure of an intermediate and/or of the new drug substance.
Can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.	Normally commercially available.
Normally have defined chemical properties and structure.	Are of defined chemical and physical properties and structure.

The next document containing a definition of starting material, issued 10 years later, is the ICH Q11 guideline on the development and manufacture of drug substances, of 2012. It is not properly a clear definition, but rather an approach to the concept and selection of starting material, using several criteria to identify/elect a starting material. It is mentioned that *“starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials”*. The same definition is included later in “EMA/454576/2016, Guideline on the chemistry of active substances”, of 2016.

Other definitions, that are not far way of none of the definitions stated above, can be found. In the “Ares(2014)2674284 - The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials, of 2014, a starting material is defined as to be:

“A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure”.

1.3.2 Selection of starting material and assessment

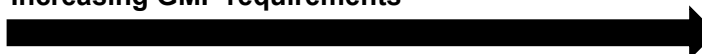
The synthetic processes are becoming more and more complex not only to comply with the needs of quality improvement and to satisfy the demands of Regulatory Authorities, but also to improve the yield. These aspects are also driven by cost reduction and by protection of the environment ([Jiménez-González C, et al., 2011](#)). It is not uncommon that improvements in synthetic processes are driven by the need to optimize yield, reducing the waste and consequently the impact on the environment. The use of enzymatic processes (biocatalysis) is more frequent now. Examples such as rosuvastatin and atorvastatin, pregabalin, sitagliptin, aliskiren or even amoxicillin are relevant for the discussion, as these substances are synthesized using enzymatic processes ([Wells A, 2012](#)). The biocatalyst process is known as a “green process” and is more productive. Indeed, some of the APIs mentioned above belong to pharmacotherapeutic groups greatly used around the world ([Jiménez-González C, et al., 2011](#)). For example, rosuvastatin, under the tradename Crestor®, sales are over 6 billion dollars per annum.

One of the major challenges during drug development is the selection, designation and justification of the appropriate starting material [[Faul MM, et al.,\(c\), 2014](#)]. The starting material is the point in the synthetic process in which the concept of Good Manufacturing Practices (GMP) starts to be applicable as illustrated in [Table 4 \(ICH Topic Q7, 2000\)](#). The application of GMP allows the Authority to conduct inspections and request more detailed information about the control steps applied. On the other hand, and sometimes driven by economical aspects, the production of starting materials is outsourced. That could lead to less and not so stringent control by the Authority and by the manufacturer of the API. The starting point for applying the GMP should be justified by the manufacturer and usually it is in that justification and acceptability that the grey area starts.

Table 4: Application of GMP requirements to API manufacturing^a

Type of manufacturing	Application of GMP requirements (illustrated in grey)				
Chemical manufacturing	Production of the API Starting Material	Introduction of the API starting Material into process	Production of Intermediate(s)	Isolation and Purification	Physical processing and packaging

Increasing GMP requirements



^a adapted from ICH Topic Q7

The Directive 2001/83, as amended by the Directive 2004/27/EC, on the Community Code Relating to Medicinal Products for Human Use, presents some concepts related to the API that can be supportive of the justification to be provided by the applicant for the selection of the starting material. The relevant concepts stated in the Directive are mentioned below:

“For the purposes of this Directive, manufacture of active substances used as starting materials shall include both total and partial manufacture or import of an active substance used as a starting material as defined in Part I, point 3.2.1.1 (b) Annex I, and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or relabeling, such as are carried out by a distributor of starting materials.” (...)

“The principles of good manufacturing practice for active substances used as starting materials referred to in point (f) of Article 46 shall be adopted in the form of detailed guidelines.

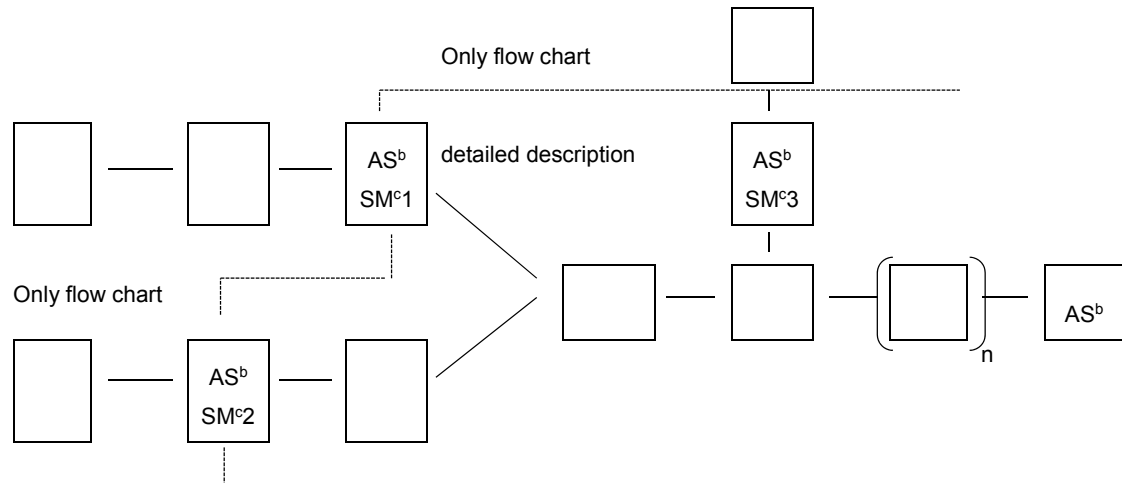
Also, according to article 46 (f) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, the manufacturing authorisation holders are obliged “to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials”. So, Part II of the GMP guide: Basic Requirements for Active Substances used as starting materials was adopted as the “detailed guidelines to comply with the article 46 (f) of Directive 2001/83/EC, as amended. The deadline for coming into operation was 1 September 2014.

In the [CPMP/QWP/130/96, Rev.1](#), Guideline on Chemistry of New Active Substances, of 2004, later replaced by [EMA/454576/2016](#) - Guideline on the chemistry of active substances adopted by CHMP on 21 July 2016, the criteria for the selection of an acceptable starting material are detailed. The guideline of 2004 and the new one of 2016, consider that an applicant of a marketing authorization or Drug Master File (DMF)/Active Substance Master File (ASMF) should propose and justify the selection of the starting material according to certain requisites such as:

- a) the SM should be incorporated in the structure of the active substance as a significant structural fragment;
- b) the name and address of the supplier should be provided;
- c) schematic synthetic process prior to the SM “may be useful”;
- d) the SM should be fully characterised for the intended use;
- e) complete specifications of the SM should be provided, including impurities profile;
- f) discussion of the impurities of the SM, including carryover through the synthetic process and their need to be controlled in the SM by appropriate acceptance criteria with suitable validated methods should be presented.

The guideline CPMP/QWP/130/96, Rev.1 also provided a schematic description of a synthetic route to illustrate a schematic description of a synthetic route, as an example of what is expected by the Regulatory Authorities ([Figure 1](#)).

Figure 1: Schematic description (illustrative only)^a



^a adapted from CPMP/QWP/130/96, Rev.1 and EMA/454576/2016

^b AS – active substance

^c SM – starting material

The guideline [CPMP/QWP/130/96, Rev.1](#) was in the meantime superseded by the Guideline on Chemistry of active substances ([EMA/454576/2016](#)) published on 21/11/2016 and effective from 21 May 2017. This document, as the previous one, describes the type of information required for the manufacture and control of active substances, existing or new chemical entities used in a medicinal product. Despite the new guideline contributing to adding more clarity to the definition and selection of the starting material, this clarification is still below the expectation. Also, the new guideline includes a schematic description of a synthetic route (Figure 1), that is the same as per previous guideline (CPMP/QWP/130/96, Rev.1).

None of the changes in the new guideline seem to be additional contributions to the clarity of the definition of starting material.

The lack of a clear definition of starting material in the guidelines, the existence of policy documents that are not publicly available and regional differences in the approach of different Authorities do not allow for the best selection of the starting material or an harmonised assessment by the Regulatory Authorities [[Faul MM, et al. \(c\), 2014](#); [Seevers R. et al., 2010](#); [CPMP/QWP/130/96 Rev. 1](#)]. [Matsuhama M, et al., 2016](#) published the results of a gap analysis survey of international practices for Active Substance Master Files (ASMFs)/Drug Master Files (DMFs) of Human use. The gap analysis was conducted as a project of the ASMF/DMF working group of International Generic Drug Regulators Pilot (IGDRP). The purpose of the survey was to identify similarities and differences

among ASMF/DMF procedures of 10 IGDRP members and two observers. Understanding the current situation of the assessment can help for a regulatory convergence in the assessment guide. The participants in the survey include Regulatory Authorities from all the regions of the globe. From the results, it can be highlighted that despite many similarities, there were also relevant differences such as:

- a) Assessment processes of ASMFs/DMFs;
- b) Technical requirements for APIs.

The topics outlined for the comparison of similarities and differences in the treatment of ASMFs/DMFs were the following:

- a) An outline of ASMF/DMF systems
- b) Submission requirements
- c) The assessment processes
- d) The technical requirements
- e) The generation of assessment reports
- f) Procedures for changing ASMF/DMF details
- g) Good Manufacturing Practice (GMP) inspection/certification of API manufacturers

Focusing on the technical requirements and the GMP inspection/certification of API manufacturers, the conclusions of the survey can be summarized as follows.

1. As technical requirements, it can be pointed out that the European Pharmacopeia (Ph.Eur.) is the most widely accepted pharmacopeia. The guidelines accepted by each Authority to control the quality of APIs were also identified. ICH guidelines are widely used in what concerns starting materials, impurities and stability testing while CHMP guidelines are also used regarding starting materials and impurities. There are several differences among the Regulatory Authorities for the stability requirements. All require stability testing of API. However, a few exceptions exist:

- a) the European Regulatory Authorities do not require stability testing if the API is tested immediately before usage and in case that it is corresponding to an API

that is considered “existing substance” and covered by a Ph.Eur. Monograph where degradation products are listed;

- b) the PMDA (Japanese Regulatory Authority) does not require submission of stability testing results for generic products, in general. The submission of stability testing results in case of generics is only required if the stability of the API cannot be deduced from the originator (e.g. different polymorphic form).

The details are summarized in Table 5.

Table 5: Pharmacopeias and guidelines accepted^a

Authority	Pharmacopeias					
	Ph.Eur.	USP	BP	JP	Ph.Int.	CEPs
Anvisa	•	•	•	•	•	
EDQM	•					
EU	•					
HC	•	•	•		•	•
HSA	•	•	•	•		•
MCC	•	•	•	•	•	•
MFDS	•	•	•	•		
PMDA	•	•		•		
PQT-WHO	•	•	•	•	•	•
Swissmedic	•					•
TFDA	•	•	•	•	•	•
TGA	•	•	•			•
	Guidelines					
	Starting material		Impurities		Stability Testing	
	ICH guideline	CHMP guideline	ICH guideline	CHMP guideline	ICH guideline	Other guideline
Anvisa	•		•			•
EDQM	•	•	•	•	•	
EU	•	•	•	•	•	
HC	•		•		•	
HSA	•		•		•	
MCC	•		•		•	
MFDS	•		•		•	
PMDA	•		•		•	
PQT-WHO	•		•	•	•	
Swissmedic	•	•	•	•	•	
TFDA	•	•	•	•	•	
TGA	•		•	•	•	

^aadapted from [Matsuhama M, et al., 2016](#).

2. The inspection of API manufacturers and GMP certification of API manufacturers is required by several Regulatory Authorities such as, TGA, Anvisa, the PMDA, the MFDS and the PQT-WHO, and more recently Health Canada. The moment in time to demonstrate the GMP evidence depends on the Regulatory Authority. For example, Anvisa requires such evidence at the time of the submission of the DMF while PMDA and TGA require the evidence at the time of the approval of the drug product. The GMP certification is not mandatory in EU, but the EU and Swissmedic require a GMP statement by a qualified person. The GMP certification is not also requested by the HAS, the MCC, the Swissmedic and the EDQM. In the EDQM, the API manufacturer has to declare compliance with the EU GMP Part II and inspections are carried out by the EDQM based on risk.

A relevant document, from a regulatory perspective, was, in the meantime, issued by the CHMP/Quality Working Group. This document ([EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1](#)), adopted by the CHMP in December 2016 and published by the EMA on 3 July 2017, pretends to be a position paper from the Quality Working Group of the CHMP at the EMA.

In a recent publication by [Faul MM, et al., \(b\), 2014](#), it is mentioned that the knowledge of current practices used within the industry are variable and depend on the interpretation of the regulatory guidelines by each company. To assess the current practices of the industry on this topic, a survey was set up in 2011 by a Working Group on API SMs. This Working Group was an initiative of “API and Analytical Leadership Groups” within the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), a not-for-profit American organization made up of representatives from pharmaceutical and biotechnology companies. This publication started with a first article reviewing the development of API starting material regulations over time, and discussed the industry perspective on these regulations. It addressed also the fact that Regulatory Authorities are applying differing interpretations to the designation of API Starting Materials and to the justifications needed to support the selection of the starting material.

The survey reflects case studies of 50 API Starting Materials that were used to prepare 24 late stage clinical or marketed drug substances, within the company members of the IQ. It included four areas considered key to understand the API SM designation practices:

- a) drug substance attributes;

- b) API starting material attributes;
- c) control strategy;
- d) regulatory practices and strategy.

The survey had the objective of gaining a better understanding of the approaches used by the industry to choose the chemical compound that can be considered “the” starting material. These four areas are detailed in the [Table 6](#).

The conclusion of the survey was that there is no single approach to justify API Starting Materials but rather key trends, i.e., no systematic risk-based decision has been taken to assess the justifications or to control the quality of the regulatory output for API Starting Material selection.

Table 6: Overview of API SM survey focus areas^a

DS attributes	API SM attributes	Control strategy	Regulatory strategy
• synthesis	• complexity	• process control	• regulatory status
• complexity	• manufacturing and validation	• manufacturing	• filing structure
• lot history	• sourcing	• propinquity	• information shared for justifications
• chiral impurities	• propinquity		• timing of final API SM strategy communication
• impurities	• impurities		• regulatory communications with USA, Canada, and EU
		<i>Analytical control</i>	
		<i>Impurities control</i>	
		• acceptance criteria	
		• analytical methods	
		• characterization	
		• fate and purge	
		• genotoxic and potential genotoxic impurities	

^aadapted from [Faul MM, et al.,\(b\), 2014](#)

In 2015, the same authors, [Faul MM, et al., \(a\), 2015](#) published a paper “Part 3: Designation and Justification of API Starting Materials: Proposed Framework for Alignment from an Industry Perspective”: The intention of this paper is to provide a guide for the justification of a proposed starting material to be included in a marketing authorisation application. The guide is based on the information collected in the two previous publications. It also considers the principles described in the guideline ICH Q11 and relevant experience of the members of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium). One of the Leadership Groups of the IQ Consortium, the API Leadership Group created the API Starting Material Working Group (API SM) with the objective to address three questions, in an attempt to understand how the companies composing the IQ Consortium make their decisions concerning the designation and justification of API Starting Material.

The three questions were:

- 1) How has the regulatory perspective on API SM designation developed over time?
- 2) What are peer companies doing now and how many steps from the API SM to the drug substance (DS) have been typically required to control carryover of impurities, with special consideration for mutagenic impurities (MIs)?
- 3) What should the industry do, if anything, to improve the current process?

The authors considered that the two first questions were addressed in the previous publications [[Faul MM, et al., \(c\), 2014](#); [Faul MM, et al., \(b\), 2014](#)].

For question 3), the authors are addressing it in the publication “Part 3: Designation and Justification of API Starting Materials: Proposed Framework for Alignment from an Industry Perspective” [[Faul MM, et al., \(a\), 2015](#)]. They concluded that, from the Industry’s perspective, the ICH Q11 was a considerable advance for the harmonisation of the requirements to designate and justify the selection of starting material. Nevertheless, there were inconsistent interpretations of ICH Q11 by the Regulatory Authorities of different regions. The authors are proposing a framework to harmonise, to the extent possible, the package of information to be presented to the Regulatory Authority to support the justification for the selected starting material. They also believe that, instead of relying on long synthetic routes, a science based approach should be preferred for the starting material designation, along with a robust quality management of the manufacturer of the starting material.

1.3.3 Relevance of starting material

As a general concept, it can be assumed that less detail and an apparent lack of clarity in the legislation could provide the industry with more flexibility at the time of putting together the data and compile the documentation to support the registration of a medicinal product. But, the same degree of flexibility is available to the Regulatory Authorities at the time of the assessment and that can contribute for a non-harmonised assessment (Seevers R, *et al.*, 2010). The lack of guidelines and legislation compelled the Regulatory Authorities inside the working groups to create policies, most of which are not in the public domain. Faul MM, *et al.*, (c), 2014 refers to a guide to assessors approved in 2012 by the EDQM Certifications Steering Committee which relates to API starting materials.

The Quality Working Group (QWP) of the EMA is involved in:

- the preparation, review and update of quality guidelines;
- the provision of scientific advice on general and product-specific matters relating to quality;
- the resolution of national divergences regarding the assessment of quality issues;
- the liaison with interested parties;
- the international co-operation on quality-related matters, including with the EDQM.

and is composed of European experts appointed according to their area of expertise and representing each Member State. These experts also demonstrate particular concerns regarding starting materials. In their meeting in December 2013 they included in the work plan for 2014 a discussion of the following aspects:

- New technologies and approaches to quality as described in ICH guidelines Q8 (pharmaceutical development), Q9 (quality risk management), Q10 (pharmaceutical quality systems) and Q11 (development and manufacture of drug substances);
- Human/Veterinary guidelines on the chemistry of new active substances (CPMP/QWP/130/96-Rev1 & EMEA/CVMP/541/03): revision;
- Human/Veterinary guideline on the chemistry of active substances (3AQ5a/ 1987): revision;
- Human/Veterinary guidance document on definition of starting materials.

During the December 2013 meeting of the CHMP, several guidelines and concept papers from the different working parties at the EMA were adopted. For this study, it is relevant to refer the following concept paper that was adopted for a 6 months public consultation ([EMA/CHMP/QWP/752676/2013](#)):

EMA/752676/2013	Revision of Guidelines on the Chemistry of New Active Substances & Guideline on the Chemistry of Active Substances
-----------------	--

The concept paper was made available in February 2014 and was under public consultation until August 2014. It addresses the need to update and revise the guidance on the chemistry of the active substance. One of the guidelines, Rev. 1 of *CHMP/QWP/130/96: Note for Guidance on the Chemistry of New Active Substances* was adopted in December 2013 and came into operation in February 2014. The other document, the note for guidance, *3AQ5a: Chemistry of the Active Substance*, quite old, was adopted 25 years ago, in October 1987. The aim of the concept paper was to combine information in a single document, considering the many changes in the regulatory requirements, changes to references to directives and guidelines, new guidelines, namely on limits for impurities that occurred since 1987. It was expected that the new document would clarify the requirements for all applications in respect of the active substances. It was not clear if the new guideline would include a discussion on the starting material. From the work plan of the QWP of December 2013 mentioned above, it was clear that, a need to develop guidance around the starting material was identified, but the CHMP, during the December 2013 meeting, adopted only the concept paper on the chemistry of the active substance. Looking at the minutes of the monthly CHMP meetings up to October 2017, there is no reference to any concept paper concerning starting material. Only two references related to the starting material were found:

- a) one concerning the adoption on the outcome from ad-hoc QWP CT on Aripiprazole API starting materials (Minutes of the CHMP meeting 20-23 October 2014); and
- b) one relating to the redefinition of the starting materials for Raxone, idebenone, an orphan drug. The CHMP discussed the new API manufacturer, that was submitted as a variation to the initial marketing authorisation, and noted there were issues which should be addressed and adopted a request for supplementary information.

According to the recommendation stated in the concept paper mentioned above *“this revision will clarify the requirements for all applications regarding active substances and will bring the guidance in line with recent development and the current EU legislation”*.

The new guideline, replacing the guideline CHMP/QWP/130/96, Rev. 1: *Note for Guidance on the Chemistry of New Active Substances*, was in the meantime published: EMA/454576/2016: *Guideline on Chemistry of active substances*, published on 21 November 2016 and effective from 21 May 2017. The new guideline, contrary to the expectations, is not a great advance clarifying the requirements for all the applications concerning the active substances. Also, it is not included a clear discussion on the starting material but only some details on the documentation and data to be included in the marketing authorisation application.

A reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances was adopted by the Quality Working Group (QWP) (EMA/448443/2014) in July 2014. A subsequent review was made available by September 2016 and adopted by the CHMP on December 2016. It was published on 3 July 2017 ([EMA/CHMP/CVMP/QWP/826771/2016](#)). This reflection paper can be quite relevant if it will be a step further in the discussion related to the definition and selection of a starting material. The QWG from the EMA made clear in the introduction of the document, that it is not intended to be a revision of ICH Q11 guideline but rather to be looked on as a reflection paper within the EU medicines regulatory network. The problematic around the selection of the adequate starting material from both perspectives – applicant and Authority – is recognised.

Nonconsensual approaches on the suitability of proposed starting materials have become more frequent in the last years. It was recognised that the current guidelines are addressing the concept of starting material in a non-objective way and that can contribute to different interpretations either by the applicant or by the Regulatory Authorities. Also, the tendency from the applicant is to propose short synthetic routes and to include a justification for the selection of a starting material, which is frequently deficient to allow a suitable assessment.

Other initiatives from key players have been promoted. In 2011, under the umbrella of EDQM a new API Working Group was established. The task of this group is to develop strategies and programs to be applied by the OMCL (Official Medicines Control Laboratory) Network that contributes to the efforts of the European Authorities to ensure

high API quality. One of the major outcomes of the work performed by this group has been the Geon Position Paper that addresses the general risks associated with APIs and includes strategies for the future surveillance of APIs. A new database on API testing was launched in February 2013 and allows the OMLC Network and national competent Authorities to share information on the testing of APIs.

Information regarding starting material, as noted above and as recognized in several publications, is relevant for the understanding of the characteristics of the active substance.

As basis for the discussion, some questions were initially posed:

- 1) Would the new guideline on chemistry of the active substance address the concept of starting material and the documentation needed to support the selection of a specific starting material by the marketing authorization applicant?
- 2) During the consultation period would any of the stakeholders identify the need for better guidance on starting material and which documentation is needed and what justification is to be provided as part of a MA application?
- 3) Would a concept paper concerning starting material be issued in 2014?

Currently, the responses to the above questions are the following:

- 1) The new guideline, *EMA/454576/2016: Guideline on Chemistry of active substances*, published on 21 November 2016 and effective from 21 May 2017, does not seem to add value, when compared to the previous guidelines, in what concerns the concept of starting material. It is assumed a definition of starting material as (...) *substances with defined chemical properties and structures*” that is too vague. There are cross-references to ICH Q11, as the requirements to be followed in relation to the selection of starting materials and its relevance to the active substances. A description of the information related to the starting material that should be included in a marketing authorisation applications is detailed.

- 2) Analyzing the comments from the different stakeholders to the concept paper one realises that the industry, independently of being companies investing in innovation or companies dedicated to production of generics, share the same concerns in which respect the justification of the selection of starting material and documentation to support that selection that needs to be included in the marketing authorisation application. Below, some of the related relevant comments (Table 7).

Table 7: Comments on Draft guideline on the chemistry of active substances

Comments from stakeholders	Comments from EMA
<i>Comment:</i> The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s), where applicable. All other involved sites (e.g. starting materials site, brokering site, testing site, stability site) should be omitted from the regulatory dossier, while appropriately managed through manufacturers' quality systems (including audit and audit programmes) and subject to regulators' supervision as part of GMP inspections of both API and Finished Product (FP).	Not agreed. Information on the manufacturers as described in the draft guideline is an essential part of the dossier.
<i>Comment:</i> 4.2.3 Control of Materials 3.2.S.2.3 We think it would be helpful to reduce the requirements on starting materials only to the requirements made in the ICH Q11, because this guideline comprehensively addresses the requirements for starting materials. Additional requirements can cause confusion and possibly redundancies.	Acknowledged but make no change. This guideline doesn't add requirements for starting materials in comparison to ICH Q11. At this stage, it appears difficult to ignore the EU reflection paper but it may be possible to evolve it in the light of future Q&A on Q11.
<i>Comment:</i> For new APIs, please provide more understanding of the basis for "adequate" specifications, what "information" is expected for identification, and how this may apply for the different raw materials i.e. starting materials compared to processing aids.	Acknowledged. Suggested rewording: "Adequate specifications for these materials should be provided and should include an identification test. The specifications should

Comments from stakeholders	Comments from EMA
	address the characteristics of the material and its suitability for the intended use.”
<i>Comment:</i> The guideline would benefit from a clear differentiation between starting material, reagents, solvents - definitions should be added. Definition between old (existing) and new DS related to starting material - if the old substance is fully under control with regards to impurities and long time on the market - please define the criteria if re-designation of starting material is needed in line with current guidelines.	Definitions of starting materials, reagents, etc are given in ICH guidelines (Q7, Q11 etc) Comment on need to re-define starting materials for existing APIs to be covered in the general comments.
<i>Comment:</i> Scope of ICH Q11 is NCEs. However, this paragraph does not distinguish between NCEs and existing APIs. <i>Proposed change:</i> Please add that requirements of section “Active Substance (AS) Starting Material(s)” do not apply to existing APIs.	Proposal not accepted. As stated in the first paragraph of this section, it applies to all active substances.
<i>Comment:</i> it is recommended that key point of the suitability of a proposed starting material is determinate by the control strategy (in term of impurities, carryover of the same etc...) instead of the based on the numbers of chemical steps/transformation. Hence it is suggested to amend the text, as per the below. <i>Comment: Proposed change</i> (if any): Typically, multiple chemical transformation steps should separate the starting material from the final active substance or an appropriate control strategy it is expected to be reported to justify shorter chemical transformation steps between the starting materials and the final active substance.	Proposal not accepted as not in line with ICH Q11 or EU reflection paper.
<i>Comment:</i> Commercially available substances, or relatively simple chemical structures entering the last step(s) of the synthesis should be able to be designated as starting materials based on	Proposal not accepted. Requirements for commercially available substances are described in ICH Q11, whether or not used in the final step.

Comments from stakeholders	Comments from EMA
risk assessments and appropriate control strategies. Proposed change: Add sentence in line 171: “Starting materials entering the last step(s) of the synthesis are normally acceptable in case of simple chemical structures or well-known commercial materials, based on risk assessments and appropriate control strategies.”	
<i>Comment:</i> The absolute statement that “Non-isolated compounds are not considered appropriate to be selected as starting materials” added to the section on active substance starting materials could be interpreted very broadly and the meaning of “non-isolated compounds” should be clarified. In certain circumstances liquid compounds, compounds in solution, or mixtures of compounds might be the most appropriate starting material for a synthesis and the use of these materials as starting materials should not be absolutely.	Proposal not accepted as it is not in line with ICH Q11 wording.
<i>Comment:</i> It should be clarified in the guideline (1) whether active substances which are starting materials for the current APIs, could be sourced from a non-COS certified supplier and (2) whether the quality standards for such APIs could be diluted from the EP monograph requirements, based on actual process requirements.	(1) CEP is not mandatory but the information on the manufacture is still required somehow. (2) If there is a monograph it should comply. This is an option; full details of non-Ph. Eur. grade manufacture can be provided without reference to ASMF.
<i>Comment:</i> It is well acknowledged that impurity tracking from the starting material down to the API is state of the art for new APIs. Nevertheless, this should not be the only approach for existing APIs.	Proposal acknowledged but not accepted. The same requirements apply to new and existing APIs.
<i>Comment:</i> For suitability of starting materials, it is mentioned to include an “impurity profile.” Does this refer to batch analyses data for	Reworded to clarify: “Complete specifications should be provided, including limits for impurities”.

Comments from stakeholders	Comments from EMA
proposed starting materials? If so, please provide the necessary clarification in this section.	

During the assessment of a dossier supporting the registration of a medicinal product, applicants are often surprised with the questions on the starting materials and APIs.

In a systematic review to determine the number and type of quality deficiencies in the API Master Files, conducted by [Diego IO, et al., 2014.](#), a pattern was found. The authors were members from Prequalification Team – Medicines, World Health Organization, Geneva Switzerland and Regulations of Medicines and other Health Technologies Unit, WHO, Geneva Switzerland.

The study included an analysis of deficiency letters sent to the applicants and covered the period from 1 January 2007 to 31 December 2012. It included all the new API Master Files for non-sterile APIs that had been assessed for the first time. The scope of the study was quite broad and involved data collected from 159 deficiency letters. The Common Technical Document (CTD) subsections used to classify the API deficiencies and the number of deficiencies by section are illustrated in Table 8.

Table 8: CTD section and number of observed deficiencies^a

CTD ^b section	3.2.S.1	3.2.S.2	3.2.S.3	3.2.S.4	3.2.S.5	3.2.S.6	3.2.S.7
Number of APIMF ^c deficiencies (median and range)	1 (0-4)	17 (2-66)	5 (0-12)	4 (0-17)	1 (0-6)	0 (0-5)	3 (0-11)
APIMF deficiencies (mean and standard deviation)	0.9 (0.9)	18.1 (8.6)	4.8 (2.6)	5.1 (3.6)	1.2 (1.2)	0.7 (0.9)	3.5 (2.0)
Number of deficiencies to total Number of deficiencies by CTD subsection (%)	2.5%	52.9%	14.1%	14.8%	3.4%	2.0%	10.3%

^a in [Diego IO, et al., 2014.](#)

^b Common Technical Document

^c Active Pharmaceutical Ingredient Master File

To help interpreting the table above (Table 9) is detailing the CTD sections as per the Volume 2B of Notice to Applicants.

Table 9: Description of CTD section

3.2.S.1: General information.
3.2.S.2: Manufacturer; manufacturing process and control.
3.2.S.3: Elucidation of structure; Other characteristics.; Impurities.
3.2.S.4: Specification; justification; analytical proc. and validation; batch analyses.
3.2.S.5: Reference standards.
3.2.S.6: Container closure system.
3.2.S.7: Stability testing.

The most frequent critical deficiencies were found to be related to the manufacturing process and the key materials used, in particular the API starting material, and how that impacted on API impurity content. This conclusion is consistent with the findings in similar studies as reported by the FDA, the EDQM and the EMA. The similarities and differences are discussed by [Diego IO, et al., 2014](#). and of relevance to the discussion, it should be highlighted the fact that deficiencies identified for *Section 3.2.S.2.2.: Description of Manufacturing Process and Process Controls*, namely insufficient detail in the synthetic process (chemical structures of starting materials and intermediates, etc), represented 6.9% of the total number of deficiencies.

The analysis of the information provided with respect to the quality of the API starting material noted the following four main deficiencies:

- 1) lack of detail on or unsatisfactory quality of the starting material;
- 2) missing information regarding the starting material manufacturer;

- 3) high complexity of the starting material resulting in a request to redefine the starting material;
- 4) specifications for the starting material considered unsatisfactory.

It was found that these aspects represented 20.2% of the total number of deficiencies.

One can conclude that the applicants of the API Master File and manufacturers need technical advice and more detailed guidelines.

In 2016, the EDQM released a document (PA/PH/CEP(16)58) about the Top Ten deficiencies found for the new applications for certificates of suitability (CEP) between 2015 and 2016. This document is important from a regulatory perspective. Even if it is not directly related to the information for the API to be included in a marketing authorization application, it can work as a guideline and help the industry to understand some of the expectations of the Regulatory Authorities.

The Table 10 summarises the top ten deficiencies and the expectations and recommendations on how to address the specific deficiencies, as stated in the document.

Table 10: Top 10 deficiencies and recommendations

Deficiencies	Recommendations
Absence or deficient discussion on the risk of having potential mutagenic impurities in the final substance.	Expected a complete discussion on mutagenic impurities; Expected that potential mutagenic impurities from the synthesis of the substance or its starting materials be listed and classified in the dossier as per ICH M7. Depending on the classification with respect to the mutagenic and carcinogenic potential of the impurities (classes 1 to 5, as per ICH M7), the information to be provided should follow the ICH M7 approach.

Deficiencies	Recommendations
Absence or insufficient discussion on fate and carryover of related substances of starting materials (included) to the final substance.	The impurity profile of the designated starting material(s) (SM) should be well characterised. Expected a detailed discussion for the carryover of impurities from the SM to the final API and to their fate. It is particularly important the related substances since usually these are substances that can react according to the chemistry process foreseen by the process, leading to impurities in intermediates and in the final substance.
Lack of details and/or poor description of the manufacturing process of the substance from the introduction of starting materials.	The process needs to be well described since this is the main source of information that allows assessors to take position on potential formation of impurities and on the potential ability of the process to remove impurities.
Non-acceptable starting materials, necessity to redefine them earlier in the process.	Starting materials are the starting point for GMP application and should be representative of the overall synthetic process. SM should be identified and selected according to the requirements set by ICH Q11 and any additional related available guideline. The criteria to the adequacy of the proposed SM should be explained in detail. The SM may need to be redefined back in the process with major consequences – usually the SM initially proposed become intermediates, subject to EU GMP and probability of manufacturer of that materials to be inspected.

Deficiencies	Recommendations
Non-adequate or poorly justified specifications in place to control the quality of starting materials.	The quality of the starting materials should be sufficiently characterised and kept under control by specifications adequately justified. The expectation is that specifications in place to control the quality of starting materials reflect their manufacturing processes. The justification of the specification should include evaluation of the risks and the ability of subsequent steps to purge impurities. It should be assured in the dossier that there are no risks of having uncontrolled impurities in the final substance potentially above acceptable limits.
Non-adequate or missing specifications (and analytical methods) for reagents and solvents (recovered and recycled included) used to manufacture the substance from the introduction of starting materials.	Expected that specifications, including analytical methods in place are described in the dossier for all chemicals and reagents used to manufacture the substance from the introduction of starting materials.
Non-adequate or missing discussion on carryover of reagents and elemental impurities to the final substance.	A discussion on fate and carryover to the final substance of reagents and elemental impurities is expected to be provided, as applicable.
Non-adequate or poorly justified specifications in place to control the quality of isolated intermediate.	Expected that the impurity profile of isolated intermediates is sufficiently characterised and kept under control by adequate specifications. This information is particularly relevant for, as part of the control strategy of the substance, for intermediates that are isolated late in the process, for intermediates that show low purity, or when an impurity is tested in an intermediate instead of the final substance.
Absence or insufficient discussion on fate and carryover of impurities from synthetic intermediates (included) to the final substance.	Isolated intermediates are most of the times contaminated by related substances that can react the same way as the intermediate to

Deficiencies	Recommendations
	give intermediate-like and eventually final substance-like impurities. It is expected to be included in the dossier a discussion based on evidence (e.g. analytical data, literature, information from process development, etc) on fate and carryover of impurities presented in intermediates. The risks of having uncontrolled impurities in the final substance potentially above acceptable limits should be addressed.
Non-adequate or missing information on the synthesis of starting materials and their manufacturers.	A brief description of the preparation of the starting materials (flow diagram of the process including solvents and reagents used), along with name and address of their manufacturers (not their suppliers) is expected to be included in the dossier. The purpose of this information is to evaluate the suitability of the proposed starting material and its specification. In case of more than one source of the same starting material is used, quality equivalence should be demonstrated by means of batch data collected on the final substance manufactured using all the possible sources of the same starting material.

From the above it can be concluded that the Authorities look for very detailed information on the starting materials that can increase the level of confidence in the adequate quality of the API.

1.3.4 Other aspects of starting materials

1.3.4.1 Impurities

If the definition of “Starting material” is a challenge for both Regulatory Authorities and the Pharmaceutical Industry, the potential impurities that could affect the safety of a medicinal product are also relevant to control the quality of the final product.

Both the impurity profile and the safety of the medicinal product based on its pharmacological activity, contribute to the safety assessment.

The impurities are one of the main quality attributes of an active pharmaceutical ingredient that attract particular attention from the Regulatory Authorities. The establishment of an appropriated impurity profile for the API is expected by the Authorities. The knowledge of the process-related impurities is a progressive work that is part of the development of the synthesis, but an understanding of potential impurity profile of the API is recommended at early stages. Nowadays during the process of submission to get authorization to conduct clinical studies, the Regulatory Authorities already request detailed information on the API. It is crucial to get early information for the impurities and in this regard the selection of the starting material based on the capability of the synthetic process to tolerate the impurity profile of the starting material and the need to conduct toxicological studies to qualify certain impurities is of utmost relevance ([Gavin PF, et al., 2006](#)).

Recently a guideline that came into force by January 2016 (*ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*), revealed the concerns of the Authorities across the world. This guideline defines levels of mutagenic impurities that are expected to pose carcinogenic risk, and highlights considerations of safety and quality risk management. Based on the intended use in humans, recommendations for assessment and control of mutagenic impurities that appear (or are reasonably expected to appear) in the API are provided.

In [Argentine MD, et al., 2007](#), strategies for the investigation and control of process-related impurities in new drug substances are presented. The identification and quantification of impurities in drug substances, as well as the understanding of their origin (i.e. from synthetic process of starting material or as by-products of the synthetic process), and implementation of appropriate analytical controls are noted as important to define the quality of the API.

Indeed, impurity control is an important and relevant goal in the development of a medicinal product.

1.3.4.2 Regulatory changes after approval

From a regulatory point of view and for an already approved product, changes in the supplier of the starting material and/or in the specifications of the starting material are considered very minor changes provided they do not impact in the specifications of the final API. This contributes to the “uncomfortable position” of the Regulatory Authorities when reviewing short synthetic routes. Independently of the type of the process (enzymatic or traditional) the Authorities are not keen to accept short synthetic process i.e. those with only a few steps separating the starting material from the final API. Of course, the difficulty of this position is, as for the definition of the starting material, how many steps are considered too few. Multiple factors can contribute to the appropriate design of a synthetic process in addition to the aspects clearly set out in guidelines and legislation:

- 1) Is a substance that is commercially available or has a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) or a monograph in the USA Pharmacopeia (USP) or Ph.Eur. appropriate to be designated as starting material?
- 2) Is the selection of a starting material complying with the above or that has been assessed by an Authority through an Active Substance Master File corresponding to a medicine approved enough for a synthetic process of two or three steps to be considered?

Theoretically, the response to these questions can be **“YES”** but this is not what happens in the real-life scenario of the MA application process.

There is an opportunity for the Pharmaceutical Industry and Regulatory Authorities to set up a think-task process and develop easy to use decision trees, common language and concepts. The standardization of the scientific and technical packages supporting an application to a specific Regulatory Authority is in the interest of all the key players. Avoiding surprises during the assessment is key for the industry. Standard approaches

will contribute for sure to less painful and quicker approvals, leading to better medicines reaching the patients sooner.

1.3.4.3 Economic aspects

The global market is one of the greatest challenges faced by both, Regulatory Authorities and Pharmaceutical Industry. On one hand, the pharmaceutical companies are looking to develop cost-effective processes, easy to transfer and industrialise and for which it can be ensured that a specific API of intended quality is consistently produced. On the other hand, the Authorities are looking for sufficient information to demonstrate that a specific synthetic process and its associated control strategy will consistently provide API of satisfactory quality. ([EMA/CHMP/CVMP/QWP/826771/2016](#)).

An additional concern for the Regulatory Authorities is the tendency for APIs and starting materials from multiple sources ([Gavin PF, et al., 2006](#)). Also, 71% of the API Starting Materials known as commodity chemicals (group of chemicals that are made on a very large scale to satisfy global markets) are outsourced from emerging markets [[Faul MM, et al., \(b\), 2014](#)].

Developing a new API can be very expensive. The regulatory needs to set up a commercial synthetic process and consequent post-approval variations such as:

- (a) change of manufacturing site,
- (b) improvement of the process to adapt to the scientific progress,
- (c) update of the process due to regulatory aspects triggered by new legislation,
- (d) improvement of costs of production of APIs, or
- (e) other external factors, may represent most of the time a huge economic effort for the Pharmaceutical Industry, namely to the small-medium size companies.

The current regulatory requisites applicable to the Pharmaceutical Industry contributes, among other factors, to the dramatically increase of R&D costs. The Pharmaceutical Industry is under pressure to deliver innovative therapies. With the threat of generics, pressure of the governments to attribute less value to the innovation, increasing of

complexity and extension of development stages, it seems to be noted a tendency of big pharma to outsource some of the development work and not only the manufacture of the API or finished product ([Challener CA, 2015](#)). One of the key aspects is related to the synthesis of API – development of synthetic process along with the development of the medicine. It is more and more critical to find, as early as possible in the development, the ideal synthetic process – controlled and cost-effective. One of the critical aspects in the development of a synthetic process is the selection of an adequate starting material. Redefinition of the starting material during development and, namely during the assessment of a marketing authorisation application can contribute to a setback in the development with delay in access of the medicine to the patients and lost-profit to the companies.

Most big pharma used to keep in house the development and production of API, building large scale units. The main reasons are:

- (a) protection of industrial property,
- (b) control of the process from the very begin till the production of commercial API,
- (c) flexibility of the process.

The pressure for a quicker development and the need for more potent compounds transformed existing production sites to obsolete ones and outsourcing became a reality. The production sites were shaped for large scales and the conversion to more efficacious units due to the increase of potency of the compounds seem not to be feasible at reasonable costs. To balance costs and quality, India and China are two of the countries with a significant increase in the number of companies celebrating partnerships with European and North American pharma to develop and produce APIs. The labour costs are much lower than in Europe or North America and the quality standards are increasing. From a [MarketLine report](#) published in April 2014, and related to Pharmaceuticals in India, the major suppliers to the pharmaceutical market are manufacturers of active pharmaceutical ingredients. These are investing strongly in the market of finest chemistry and are offering contract research and manufacturing services (CRAMS) to the Pharmaceutical Industry.

In the past, access to APIs was based on criteria of price and availability. Nowadays, GMPs compliance, growing of control measures by the Authorities and safety concerns triggered changes in the API distribution rules. Need for auditing and for inspection policies, implementation of quality system management, together with a need to better know and control the API supply chain, quickly changed the setup of the business. Quality is now a flag, but the time to make a medicine available at the lowest price possible creates new challenges.

If in a recent past the originator companies tend to retain their inventions and have their own facilities to develop and synthesise the API, they are being more open to find new ways to bring new therapies to the market. If in the past, India and China only attract the lower value areas, such as discovery chemistry and off-patent manufacturing, the trend now is for pharmaceutical companies to find partners in these countries that can take part in key API development areas (development of APIs to be used in clinical studies of phase II and phase III, improvement of synthetic process and its industrialisation). The possibility to establish trusting business relationships, the increase in quality and the labour costs that can be 3 to 5 times less of yearly-full time equivalent (FTE) rate to hire a chemistry, when compared to other countries, added to the need of Pharmaceutical Industry to reduce the fixed costs and the need to reconvert production sites to adapt to the production of more potent compounds, have been a major incentive to outsource chemistry work to Asia ([Spadoni C, 2011](#)).

Some of the biggest players in the field of fine chemistry business, such as Lonza, closed few years ago sites in USA, United Kingdom and Canada and expand in Asia. Other followed this trend. It seems now that speciality API manufacturing is moving back to the USA and Europe. Maybe, that is a consequence of protective rules in Europe and tax incentives in USA ([Shanley A, 2016](#)).

In Europe, the Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, is establishing new rules regarding the prevention of the entry into the legal supply chain of falsified medicinal products. Harmonised principles and guidelines for inspections of manufacturers and wholesalers of medicinal products as well as of active substances (API) are established. The application of good manufacturing

(GMP) and good distribution practices (GDP) according to the EU requisites or equivalent are requested regardless the origin of the API – European Union or third countries. For the third countries, it should be ensured that the manufacture of API as well the inspections of facilities follow equivalent legislative provisions to the European Union, at least providing for a level of protection of public health equivalent to that provided for by the European Union law. To comply with that dispositions several articles of the Directive 2001/83/EC were amended or new one introduced. According to the article 46b(2) (new article), several conditions are established for the importation of API as such:

- (a) the manufacture has been according to the standards of GMP at least equivalent to those laid down by the European Union,
- (b) the API is accompanied by a written confirmation issued by the competent Authority of the exporting third country. The written confirmation must state that:
 - (1) the standards of GMP applicable to the manufacturing site are at least equivalent to those laid down in the EU;
 - (2) the manufacturing site is subject to regular, strict and transparent controls and to effective enforcement of GMP;
 - (3) information to the EU is supplied by the exporting country without delay in case of findings relating to non-compliance for the manufacturing site.

As of 2 January 2013, all imported active substances must follow the requisites established by the Directive 2011/62/EU and are subject to the rules on the written confirmation. The exceptions from the requirement of a written confirmation are the list of countries published by the European Commission which, following their request, have been assessed and are considered as having equivalent rules for GMP to those in the EU. The list is published in the *Official Journal of the European Union* (OJ) and available at http://ec.europa.eu/health/human-use/quality/index_en.htm.

The equivalence assessment takes several months from the request from the non-EU country and the Commission is publishing an update to the list once an equivalent assessment has been finalised. A list of third countries that have so far requested to be included in the list of equivalent third countries in accordance with article 111b(1) of Directive 2001/83/EC, as amended, as well as the status of the request is presented in [Table 11](#).

Table 11: Listing of third countries

Country	Date of request	Status, date of publication in the OJ of the EU
Switzerland	4 April 2012	Adopted, Commission implementing Decision (OJ L325, 23.11.2012).
Israel	9 May 2012 3 September 2014	Contacts ongoing. Adopted, Commission implementing Decision (OJ L171/23, 2.07.2015).
Australia	18 September 2012	Adopted. Commission implementing Decision (OJ L113, 25.04.2013).
Singapore	17 September 2012	No listing for the moment (the relevant Singapore legislation provides for a non-mandatory GMP certification scheme). Contacts ongoing. In the meantime, Singapore issues written confirmation.
Brazil	4 October 2012	Adopted. Commission implementing Decision (OJ L171/23, 2.07.2015).
Japan	6 December 2012	Adopted. Commission implementing Decision (OJ L152/52, 05.06.2013).
United States of America	17 January 2013	Adopted. Commission implementing Decision (OJ 169/71, 21.06.2013).
New Zealand	26 June 2013	Assessment on hold, pending clarification of the scope of existing MRA.

South Korea	22 January 2015	Equivalent assessment ongoing.
-------------	-----------------	--------------------------------

Source: http://ec.europa.eu/health/human-use/quality/index_en.htm (accessed on line, 26 Jun 2017); OJ: Official Journal; MRA: Mutual Recognition Agreement

In conclusion, the protective measures in Europe and USA can impact in the near future in the resurrection of the chemical industry in these regions. How costly will be this strategy for the Pharmaceutical Industry in addition to the increase of quality control measures and tightness of regulations is still a question. For sure, the final costs of an API will increase and ways to produce quality and safe medicines optimising quality control and synthetic processes will be found. If the work performed during the APIs development or drug life-cycle were considered as part of the costs impacting the price of the medicines, the companies could be incentivised to develop new medicines and apply for improvements, increasing the availability of new medicines and reducing the risks of shortage (Panzitta M, *et al.*, 2017).

1.3.5 Remarks

The global market and the identified need, from a regulatory and industry perspective, to have clear and transparent guidance regarding the API and API starting materials is a challenging situation.

The definition of starting material and its influence in the quality of the active pharmaceutical ingredients used in the manufacture of medicinal products is in the spotlight of the regulatory bodies. Rules implemented by the European Commission restricting the import of APIs, concept papers and policy documents published by the Regulatory Authorities have focused on the control of medicinal products, including APIs and API SMs, and have underlined questions to be addressed:

- How should the characterization of the starting material be balanced between its definition and its control?
- How far do the characteristics required by the Regulatory Authorities for a starting material impact the quality of a medicinal product?

According to the current legislation and guidelines the concept of Good Manufacturing Practices (GMPs) only applies for the steps of the synthetic process from the starting material to the active pharmaceutical ingredient.

Considering that, the concern of the Regulatory Authority in ensuring a standard quality of the starting material:

- Is the GMP concept application to the production of the starting material the way to be chosen?
- However, is that relevant considering that the API is well controlled, validated and tested from a quality, safety and efficacy perspective?

But, how far should the control of the starting material go to really impact the quality of the finished product?

2 Outcomes

2 Outcomes

2.1 Retrospective analysis of the assessment reports

2.1.1 Data collected

A list of medicinal products with positive opinion issued between 01 January 1999 and 12 April 2015 (*this date was the date of the extraction of the list and this is the reason why a specific day of April is mentioned*) was extracted from the European Medicines Agency (EMA). The list includes 145 medicines.

A list of medicinal products approved by U.S. Food & Drug Administration (FDA) for the same period was extracted from FDA website.

A filter to the lists was applied with the following exclusion criteria:

- 1) Biological substances, including biosimilar compounds;
- 2) Generics;
- 3) Medicines using active substances of semi-synthesis processes;
- 4) All the marketing authorisations prior to January 1999;
- 5) All the marketing authorization approved by informed consent⁽¹⁾;
- 6) Topic formulations and diagnosis products.

After application of the exclusion criteria and considering only the medicines for which a marketing authorisation was granted by both Regulatory Authorities (EMA and FDA), a compiled list was created ([Table 12](#)). There are 5 medicinal products for which no detailed information will be provided since:

- a) the medicinal product is only approved by one of the Authorities (EMA or FDA) in the time frame defined for the search (January 1999 to 12 April 2015) and above mentioned;
or
- b) the date of issuance of marketing authorization is out of search date for one of the Authorities (EMA or FDA).

⁽¹⁾ Marketing authorisation based in the pharmaceutical, pre-clinical and clinical documentation contained in the file of a medicinal product previously approved possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form

Table 12: List of marketing authorisations EMA & FDA

Name of Medicinal Product	Active Substance	Common name	ATC code	Therapeutic Indication	Date of Marketing Authorisation (EMA)	Date of Marketing Authorisation (FDA)
Abilify	aripiprazole	aripiprazole	N05AX12	schizophrenia; maniac episodes in Bipolar	Jun-04	Dec-04
Ameluz ^a	5-aminolevulinic acid hydrochloride	5-aminolevulinic acid hydrochloride	L01XD04	actinic keratosis	Dec-11	-
Aubagio	teriflunomide	teriflunomide	L04AA31	multiple sclerosis (MS).	Aug-13	Sep-12
Azilect	rasagiline	rasagiline	N04BD02	Parkinson's disease (PD)	Feb-05	May-06
Corlentor (Corlanor USA)	ivabradine hydrochloride	ivabradine	C01EB17	coronary-artery disease; chronic heart failure	Oct-05	Apr-15
Daklinza ^b	daclatasvir dihydrochloride	daclatasvir	-	hepatitis C	Aug-14	Jul-15
Efient	prasugrel	prasugrel	B01AC22	thrombotic events	Feb-09	Jul-09
Eklira Genuair (Turcosa Pressair)	acclidinium bromide, micronised	acclidinium bromide	R03BB	COPD	Jul-12	Jul-12

Name of Medicinal Product	Active Substance	Common name	ATC code	Therapeutic Indication	Date of Marketing Authorisation (EMA)	Date of Marketing Authorisation (FDA)
Giotrif (Gilotrif - USA)	afatinib	afatinib	L01XE13	Cancer	Sep-13	Jul-13
Invokana	canagliflozin	canagliflozin	A10BX11	diabetes mellitus	Nov-13	Mar-13
Latuda	lurasidone	lurasidone	N05AE05	schizophrenia	Mar-14	Oct-10
Mirvaso ^(b)	brimonidine tartrate	brimonidine	D11AX21	facial erythema of rosacea	Feb-14	1996
Moventig (Movantik- USA)	naloxegol oxalate	naloxegol	A06AH03	opioid-induced constipation	Dec-14	Sep-14
Neupro	rotigotine	rotigotine	N04BC09	Parkinson's disease (PD)	Feb-06	May-07
Nexium Control	esomeprazole	esomeprazole	A02BC05	reflux symptoms	Aug-13	Feb-01
Noxafil	posaconazole	posaconazole	J02AC04	fungal infections	Oct-05	Sep-06

Name of Medicinal Product	Active Substance	Common name	ATC code	Therapeutic Indication	Date of Marketing Authorisation (EMA)	Date of Marketing Authorisation (FDA)
Onglyza	saxagliptin	saxagliptin	A10BH03	diabetes mellitus	Oct-09	Jul-09
Otezla	apremilast	apremilast	L04AA32	Psoriatic arthritis	Jan-15	Mar14
Prezista	darunavir	darunavir	J05AE10	HIV-1	Feb-07	Jun-06
Ranexa (previously Latixa)	ranolazine	ranolazine	C01EB18	angina pectoris	Jul-08	Jan-06
Resolor ^a	prucalopride succinate	prucalopride	A06AX05	chronic constipation	Oct-09	-
Sivextro	tedizolid phosphate	tedizolid phosphate	J01	skin infections	Mar-15	Jun-14
Stivarga	regorafenib	regorafenib	L01XE21	Cancer	Aug-13	Sep-12
Tecfidera	dimethyl fumarate	dimethyl fumarate	N07XX09	multiple sclerosis (MS)	Jan-14	Mar-13

Name of Medicinal Product	Active Substance	Common name	ATC code	Therapeutic Indication	Date of Marketing Authorisation (EMA)	Date of Marketing Authorisation (FDA)
Temodal (Temodar - USA)	temozolomide	temozolomide	L01AX03	Cancer	Jan-99	Aug-99
Trobalt (Potiga - USA)	Retigabine (esogabine)	retigabine	N03AX21	Epilepsy	Mar-11	Jun-11
Vargatef (Ofev - USA)	Nintedanib	nintedanib	L01XE	cancer	Nov-14	Oct-14
Victrelis	Boceprevir	boceprevir	J05AE	hepatitis-C	Jul-11	May-11
Vimpat	Lacosamide	lacosamide	N03AX18	Epilepsy	Aug-08	Oct-08
Vipidia (Nesina - USA)	Alogliptin	alogliptin benzoate	A10BH04	diabetes mellitus	Sep-13	Jan-13
Xarelto	rivaroxaban	rivaroxaban	B01AF01	embolism	Sep-08	Jul-11
Xelevia (Januvia - USA)	Sitagliptin	sitagliptin	A10BH01	diabetes mellitus	Mar-07	Oct-06

Name of Medicinal Product	Active Substance	Common name	ATC code	Therapeutic Indication	Date of Marketing Authorisation (EMA)	Date of Marketing Authorisation (FDA)
Xtandi	enzalutamide	enzalutamide	Not yet assigned	Cancer	Jun-13	Aug-12
Zebinix (Aptiom USA)	eslicarbazepine acetate	eslicarbazepine acetate	N03AF04	epilepsy	Apr-09	Nov-13
Zonegran	zonisamide	zonisamide	N03AX15	epilepsy	Mar-05	Mar-00
Zontivity	vorapaxar sulfate	vorapaxar	B01	Cancer	Jan-15	May-14
Zydelig	Idelalisib	idelalisib	L01XX47	atherothrombotic events	Sep-14	Jul-14
Zypadhera ^(b)	olanzapine pamoate	olanzapine	N05AH03	Cancer	Nov-08	1996

Notes:

^aNot approved at FDA; ^bOut of search date range for FDA approval; SM: starting material; N: No; Y: Yes

For the medicinal products identified in the list above ([Table 12](#)) information about the starting materials and synthetic process of the API was collected using the following queries:

- a) is the starting material identified, and if Yes, what is it?
- b) is any information stated about the commercial availability of the starting material?
- c) is the information about the API covered by a DMF (ASMF/EDMF)?
- d) how many steps are described for the synthetic process of the API?
- e) were any post approval variations, (and if any and if Yes, which type of changes), related to the synthetic process of API and/or to the starting material submitted/approved by the Regulatory Authority?

To compile the information, the following documents related to the approval of the medicinal products were consulted:

- European Public Assessment Reports (EPARs) and correspondent updates published at the EMA webpage;
- List of procedural steps taken after authorization, that correspond to the activities post-approval and available at the EMA webpage;
- “Chemistry review” section from the public available documents concerning the approval of NDA or sNDA at the FDA webpage (Drugs@FDA: FDA Approved Drug Products).

The cut-off date to compile the information was 31 July 2017.

The [Table 13](#) details, by product, the information collected for the queries above, from **a)** to **d)**. The list is ordered by alphabetic order of the tradename.

Table 13: Information for API and Starting materials

Name of Medicinal Product	Active Substance	Name of SM	Information from EMA			Information from FDA	
			Commercial availability of SM	ASMF/EDMF/DMF	No. Steps of synthetic process	Information from FDA	DMF mentioned in Chemistry review document
Abilify	aripiprazole	7-hydroxy-3,4-dihydro-2(H)-quinolinone	no information	EDMF	2-steps	no information	DMF
Aubagio	teriflunomide	4-(Trifluoromethyl) aniline, cyanoacetic acid and acetic anhydride	no information	No	3-main steps starting. Teriflunomide is then crystallized and jet-milled	no information	DMF
Azilect	rasagiline	1-aminoindan	no information	no information	3-steps	no information	DMF
Corlantor (Corlanor USA)	ivabradine hydrochloride	azepan and butamine hydrochloride	no information	no information	1-step	6-step	DMF
Efient	prasugrel	simple molecules	No	no information	3-steps	no information	DMF
Eklira Genuair (Turdosa Pressair)	acridinium bromide, micronised	well characterized	No	ASMF	n-steps followed by purification and recrystallisation	no information	DMF
Giotrif (Gilotrif - USA)	afatinib	well defined	No	no information	6-main steps including formation of the dimaleate salt and its crystallisation	no information	DMF

Name of Medicinal Product	Active Substance	Name of SM	Information from EMA			Information from FDA	
			Commercial availability of SM	ASMF/EDMF/DMF	No. Steps of synthetic process	Information from FDA	DMF mentioned in Chemistry review document
Invokana	canagliflozin	well defined	No	no information	4-main steps and 2 purification steps	No info; starting materials discussed as major issue	No DMF
Latuda	lurasidone	3-well defined	No	ASMF	9-steps	no information	DMF
Moventig (Movantik-USA)	naloxegol oxalate	naloxone hydrochloride dihydrate (CEP) + 2 other well-defined starting materials	no information	no information	4-steps	no information	No
Neupro	Rotigotine	3 starting materials	no information	no information	5-steps	no information	DMF
Nexium Control	esomeprazole	well defined	Yes	no information	4-main steps and crystallisation	no information	DMF
Noxafil	posaconazole	well defined	yes	no information	4-main steps and crystallisation	no information	DMF
Onglyza	saxagliptin	information given for the synthesis of starting materials	no information	no information	5-steps	no information	DMF

Name of Medicinal Product	Active Substance	Name of SM	Information from EMA			Information from FDA	
			Commercial availability of SM	ASMF/EDMF/DMF	No. Steps of synthetic process	Information from FDA	DMF mentioned in Chemistry review document
Otezla	apremilast	well defined (the designation of starting materials was revised during the assessment procedure)	Yes/well defined	no information	4-main steps or 3 main steps	no information	DMF
Prezista	darunavir	2 starting materials	no information	ASMF	3-step and crystallisation	no information	DMF
Ranexa (previously Latixa)	ranolazine	2,6-dimethylaniline (2,6-DMA), chloroacetyl chloride (CAC), piperazine dihydrochloride, and guaiacol glycidyl ether (GDE)	no information	ASMF	3-steps and purification, drying and milling	no information	DMF
Sivextro	tedizolid phosphate	well-defined	Yes	no information	4-main steps	no information	DMF
Stivarga	regorafenib	well-defined	no information	no information	3-main steps	no information	DMF
Tecfidera	dimethyl fumarate	well-defined	Yes	no information	2-main steps	no information	No DMF
Temodal (Temodar - USA)	temozolomide	4-amino-5-imidazole carboxamide hydrochloride	no information	no information	3-steps	no information	DMF

Name of Medicinal Product	Active Substance	Name of SM	Information from EMA			Information from FDA	
			Commercial availability of SM	ASMF/EDMF/DMF	No. Steps of synthetic process	Information from FDA	DMF mentioned in Chemistry review document
Trobalt (Potiga - USA)	Retigabine (esogabine)	well-characterised	no information	no information	n-steps (with a recrystallisation and milling)	no information	DMF
Vargatef (Ofev - USA)	Nintedanib	well-defined	no information	no information	6-steps (crystallisation)	no information	No DMF
Victralis	Boceprevir	3-key starting materials	no information	no information	3-steps	no information	No DMF
Vimpat	Lacosamide	D-serine	no information	no information	5-steps and recrystallisation	no information	No DMF
Vipidia (Nesina - USA)	Alogliptin	well-defined (from vendors that demonstrated ability supply materials consistently meet established acceptance criteria. Appropriate specifications adopted for starting materials, taking into account their route of synthesis & impact on active substance quality)	yes	no information	3-steps and milling	no information	DMF
Xarelto	rivaroxaban	4-(4-nitrophenyl)-3-morpholinone	no information	no information	5-steps	no information	DMF

Name of Medicinal Product	Active Substance	Name of SM	Information from EMA			Information from FDA	
			Commercial availability of SM	ASMF/ EDMF/ DMF	No. Steps of synthetic process	Information from FDA	DMF mentioned in Chemistry review document
Xelevia (Januvia - USA)	Sitagliptin	morpholinone	no information	no information	2-steps and crystallisation	no information	DMF
Xtandi	enzalutamide	3 well-defined	Yes	no information	4-main steps	no information	No DMF
Zebinix (Aptiom USA)	eslicarbazepine acetate	no information	no information	no	5-steps and crystallisation	no information	DMF
Zonegran	zonisamide	no information	no information	Yes	no information	no information	DMF
Zontivity	vorapaxar sulfate	3 well-defined	Yes	no information	7-steps	no information	No DMF
Zydelig	Idelalisib	well-defined	Yes	no information	5-steps-crystallisation	no information	No DMF

The changes related to the synthetic process of API and starting material(s), resulting from query **e**) (*were any post approval variations, (and if any and if Yes, which type of changes), related to the synthetic process of API and/or to the starting material submitted/approved by the Regulatory Authority?*), see pages 60 to 65, are depicted in [Table 14](#) and include:

- changes in the synthetic process of API;
- changes of manufacturer of API or starting material (excluding changes to sites of control or batch release);
- changes in the starting material(s).

Table 14: Type of changes during cycle review

Name of Medicinal Product	Active Substance	Description of change: date of approval
Abilify	aripiprazole	• Additional manufacturing site of the active substance. Change(s) to the manufacturing process for the active substance. 20JAN2005
Aubagio	teriflunomide	NA
Azilect	rasagiline	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 11JUN2014 • Minor change in the manufacturing process of the active substance:22OCT2008; • Minor change in the manufacturing process of the active substance: 02MAY2006
Corlentor (Corlanor USA)	ivabradine hydrochloride	NA
Efient	prasugrel	NA
Eklira Genuair (Turcosa Pressair)	aclidinium bromide, micronised	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation:01DEC2014 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 01DEC2014; • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 01DEC2014 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS:17DEC2013
Giotrif (Gilotrif - USA)	afatinib	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 16JUN2017 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 12DEC2014 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS:25SEP2014

Name of Medicinal Product	Active Substance	Description of change: date of approval
Invokana	canagliflozin	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 9JUN2017 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer:11JAN2017 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved:4NOV2016 • Changes in the manufacturing process of the AS - Other variation: 31 AUG2016 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 28JUL2016; • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 28JUL2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 28JUL2016 • Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal 28JUL2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 14AUG2015 • Changes in the manufacturing process of the AS - Other variation: 1JUL2015 • Changes in the manufacturing process of the AS - Other variation: 19DEC2013 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS:19DEC2013
Latuda	lurasidone	NA
Moventig (Movantik-USA)	naloxegol oxalate	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 17DEC2015 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 15JAN2016
Neupro	Rotigotine	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions: 10NOV2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation - To include an alternative manufacturer of the starting material for the active substance:18DEC2014
Nexium Control	esomeprazole	NA

Name of Medicinal Product	Active Substance	Description of change: date of approval
Noxafil	posaconazole	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 12JAN2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 12JAN2016 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 12JAN2016 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 30MAY2013 • Minor change in the manufacturing process of the active substance: 4JUN2007
Onglyza	saxagliptin	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 7JUL2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 7JUL2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer - To add an alternate manufacturer of the active substance Saxagliptin and intermediates: 19SEP2013
Otezla	apremilast	NA
Prezista	darunavir	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 24JUN2015 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 20MAR2015 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 04FEB2014 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 18MAR2011 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 31MAR2010 • To introduce a minor change in the manufacturing process: 24SEP2009 • Quality changes (This variation application was submitted in order to optimise the manufacturing process of intermediates and of the drug substance. As a result of this optimisation, some consequential changes have been submitted. Also an alternative secondary packaging material is proposed for the container of the drug substance. None of the changes affect the benefit-risk balance of this product): 30MAY2008
Ranexa (previously Latixa)	ranolazine	• Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF: 08OCT2014 • Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF: 10FEB2014 • Addition of a new manufacturer with two manufacturing site for the production of the drug substance. That is supported by an ASMF: 15NOV2012 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF: 15NOV2012

Name of Medicinal Product	Active Substance	Description of change: date of approval
		To introduce an additional manufacturing site for the production of the active substance. The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions:18NOV2010
Sivextro	tedizolid phosphate	- Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS:22JUL2016 - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS:13MAY2016
Stivarga	regorafenib	NA
Tecfidera	dimethyl fumarate	- Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 22MAR2016 - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 22APR2015
Temodal (Temodar - USA)	temozolomide	NA
Trobalt (Potiga - USA)	Retigabine (esogabine)	- Changes in the manufacturing process of the AS - Other variation: 13DEC2012 - Addition of a new synthetic route for the active substance. The approved process remains authorised: 17NOV2011 - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions:17NOV2011 - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation:17NOV2011 - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation:17NOV2011
Vargatef (Ofev - USA)	Nintedanib	Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation: 11MAY2017
Victrelis	Boceprevir	- Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 28OCT2013 - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 26MAR2013

Name of Medicinal Product	Active Substance	Description of change: date of approval
Vimpat	Lacosamide	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions: 01DEC2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 8JUN2015 • Addition of an alternative manufacturer for the active substance lacosamide: 23JUN2011 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions: 23JUN2011 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 23JUN2011; • Change to the manufacturing process for the active substance, i.e, addition of an alternative manufacturing site. Change(s) to the manufacturing process for the active substance:22OCT2009
Vipidia (Nesina - USA)	Alogliptin	NA
Xarelto	rivaroxaban	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation: 26MAY2015
Xelevia (Januvia - USA)	Sitagliptin	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer: 30NOV2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation:23APR2015 • To introduce 2 new manufacturing sites for the production of sitagliptin active substance and a synthetic intermediate: 21NOV2013 • Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product: 21NOV2013; • To add a new site responsible for the manufacture and control of the active substance and to reduce the loading of one starting material: 21JUN2012 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation:21JUN2012 • Addition of a manufacturing site: 22SEP2011 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation:22SEP2011 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 23JUN2011 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS:23JUN2011

Name of Medicinal Product	Active Substance	Description of change: date of approval
Xtandi	enzalutamide	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 7JUL2016 • Change in manufacture of the AS - Other variation: 12OUT2015 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 23JUL2015 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 24JUN2015 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 18DEC2013
Zebinix (Aptiom USA)	eslicarbazepine acetate	• Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions: 15DEC2016 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 29JAN2014 • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 02JUL2013 • To add an alternative manufacturer of the active substance (eslicarbazepine acetate): 15DEC2011 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions: 15DEC2011 • Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer: 05JUN2009
Zonegran	zonisamide	• To add a new active substance manufacturer supported by an ASMF (Active Substance Master File) for the manufacture of hard capsules: 26JUN2014 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF: 26JUN2014
Zontivity	vorapaxar sulfate	NA
Zydelig	Idelalisib	• Changes in the manufacturing process of the AS - Other variation: 12MAY2017; • Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS: 03OCT2016 • Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation: 22DEC2014

NA - Not applicable

2.1.2 Statistical analysis

A statistical analysis of the retrospective data collected was conducted with the aim to establish a relationship of the data with the evolution of the legislation. Considering that the main purpose of the analysis is to assess if it exists a relationship between different variables, the Chi-Square test was chosen.

The Chi-Square test is applied when there are two categorical variables from a single population. It is used to decide whether there is a significant relationship between the two variables.

The null hypothesis says that knowing the level of Variable X does not help to predict the level of Variable Y, meaning that the variables are independent. The alternative hypothesis is that knowing the level of Variable X, can support to predict the level of Variable Y, meaning that the variables are dependent.

H0: Variable X and Variable Y are independent.

Ha: Variable X and Variable Y are dependent.

For this analysis, the significance level is 0.05. Using sample data, a chi-square test for independence was conducted.

The variables, based in the information collected and detailed in the [Table 13](#), were grouped as below (Table 15).

Table 15: Variables for the statistical analysis

Product	Name of SM stated Yes(1) / No(2)	Commercially available Yes(1) / No(2)	DMF Yes(1)/ No(2)	Nº steps	Date of approval
Temodal	1	2	2	3	1999
Abilify	1	2	1	2	2004
Azilect	1	2	2	3	2005
Corlantor	1	2	2	1	2005
Noxafil	2	1	2	5	2005
Zonegran	2	2	1	1	2005
Neupro	2	2	2	5	2006
Prezista	2	2	1	4	2007
Xelevia	1	2	2	2	2007
Ranexa	1	2	1	4	2008
Vimpat	1	2	2	6	2008

Product	Name of SM stated Yes(1) / No(2)	Commercially available Yes(1) / No(2)	DMF Yes(1)/ No(2)	N° steps	Date of approval
Xarelto	1	2	2	5	2008
Efient	2	2	2	3	2009
Onglyza	2	2	2	5	2009
Zebinix	2	2	2	6	2009
Trobalt	2	2	2	1	2011
Victreliis	2	2	2	3	2011
Eklira Genuair	2	2	1	1	2012
Aubagio	1	2	2	3	2013
Giotrif	2	2	2	6	2013
Invokana	2	2	2	6	2013
Nexium Control	2	1	2	5	2013
Stivarga	2	2	2	3	2013
Vipidia	2	1	2	3	2013
Xtandi	2	1	2	4	2013
Latuda	2	2	1	8	2014
Moventig	1	2	2	4	2014
Tecfidera	2	1	2	2	2014
Vargatef	2	2	2	7	2014
Zydelig	2	1	2	6	2014
Otzela	2	1	2	4	2015
Sivextro	2	1	2	4	2015
Zontivity	2	1	2	7	2015

The Chi-square test ran using the following groups:

a) Variable A - Interval of time

Group A: less than 2000 and by 2005 (<2000 – 2005)

Group B: more than or equal to 2006 less than 2012 (≥ 2006 - <2012)

Group C: more than or equal to 2012 until 2015 (≥ 2012 - 2015)

b) Variable B - If the starting material is identified

Group 1: Yes

Group 2: No

c) Variable C - If information about the commercial availability of the starting material is stated

Group 1: Yes

Group 2: No

d) Variable D - If the information about the API is covered by a DMF (ASMF/EDMF)

Group 1: Yes

Group 2: No

e) Variable E - Number of steps for the synthetic process of the API

Group 1: Less than 4 steps

Group 2: Equal or more than 4 steps

The selection of **Variable A**– *Interval of time*, that was common to all the analysis, was based in the time points for which the relevant changes in the guidelines and legislation, related to the starting material and API occurred. The time points and guidelines/legislation into force in each time point were the following:

- *Period of <2000 to 2005*: Note for guidance 3AQ5a – Chemistry of Active Substances of October 1987; Guideline CPMP/QWP/130/96 rev 1 – Guideline on Chemistry of New Active Substances, of February 2004; Directive 2001/83 – Community Code Relating to Medicinal Products for Human Use, of 6 November 2001;
- *Period of ≥ 2006 to <2012*: Guideline CHMP/QWP/297/97 Rev. 1 corr. - Guideline on Summary of Requirements for Active Substances in the Quality Part of the

Dossier came into effect in February 2005 and is reputed as applicable to the period of.

- *Period of ≥ 2012 to 2015:* ICH Q 11 guideline (EMA/CHMP/ICH/425213/2011 – On Development and manufacture of drug substances, came into force in November 2012 is the relevant guideline applicable to the period.

The selection of the **variables B, C, D** and **E** was based in the data as grouped and collected from the information analysed.

For the analysis of the relationship between **variable A – Interval of time** and **variable B - If the starting material is identified**, the metadata is as follows:

	Variable B	Identification of SM (Yes)	Identification of SM (No)
Variable A	<2000 - 2005	4	2
	≥ 2006 - <2012	4	7
	≥ 2012 - 2015	2	14

The p-value calculated was 0.0418 and $\chi^2 = 6.35$; therefore, the null hypothesis is rejected. The relationship between variables was established.

The metadata used to determine if there is a relationship between **variable A – Interval of time** and **variable C - If information about the commercial availability of the starting material is stated**, is illustrated below:

	Variable C	Commercial availability stated (Yes)	Commercial availability stated (No)
Variable A	<2000 - 2005	1	5
	≥ 2006 - <2012	0	11
	≥ 2012 - 2015	8	8

The null hypothesis is rejected because $p=0.0134$ ($\chi^2 = 8.63$) and it is concluded that there is a relationship between variables.

For the analysis of **variable A** – *Interval of time* and **variable D** – *If the information about the API is covered by a ASMF/EDMF/DMF* the metadata is included in the table below:

	Variable D	Information covered by DMF (Yes)	Information covered by DMF (No)
Variable A	<2000 - 2005	2	4
	≥2006 - <2012	2	9
	≥2012 - 2015	2	14

The null hypothesis cannot be rejected so the **variable A** and **variable D** are independent ($p=0.5291$ and $\chi^2=1.27$).

Considering the metadata below to assess if a relationship can be established for the variables **A** – *Interval of time* and **E** – *Number of steps for the synthetic process of the API*, the value of $p=0.0434$ and $\chi^2=6.27$, which mean a relationship between variables.

	Variable E	No. of steps (<4)	No. steps (≥ 4)
Variable A	<2000 - 2005	5	1
	≥2006 - <2012	3	7 ^(a)
	≥2012 - 2015	4	11 ^(b)

(a) Trobalt was considered an outlier since it is not common to have only 1 step described for the synthetic process in 2011, date of approval of the MA

(b) Eklira was considered an outlier since it is not common to have only 1 step described for the synthetic process in 2012, date of approval of the MA

So, in conclusion, it was possible to establish a relationship between the date of approval of the marketing authorisation and the different variables analysed, except for the **variable D** – *if the information for the API is covered by a DMF (or ASMF/ESMF)*.

From [Table 14](#) that describes the type of changes related to the starting material and the API during the lifecycle and considering only the information collected from the list of “Procedural steps taken and scientific information after the authorisation”, available at the EMA webpage for each of the medicinal products, it can be conclude the following:

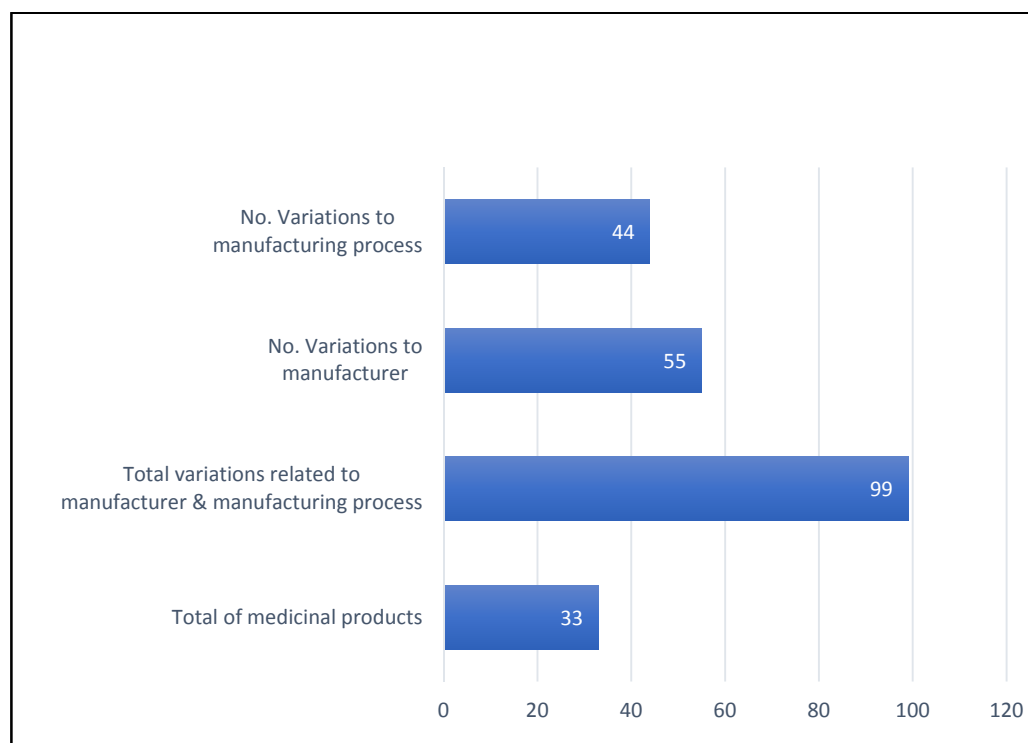
- For a universe of 33 medicinal products, approved between January 2009 and 12 April 2015, and considering the cut-off date for the table, 31 July 2017, a total of 99

variations concerning change in the manufacturer or to the process of manufacturing were approved.

- From the 99 variations, 55 are related to a new manufacturer or a change in the manufacturer and 44 are related to the manufacturing process of the API.

The Graphic 1 is illustrating the above data.

Graphic 1: Number and type of changes related to API starting material



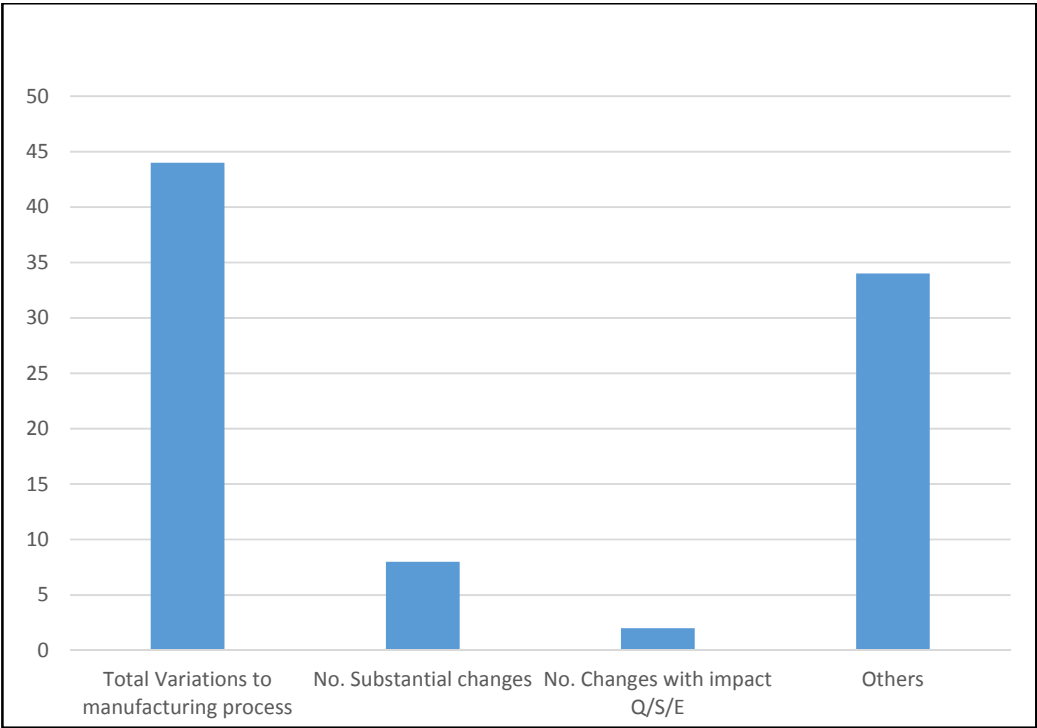
It can be concluded that a considerable number of variations related to the supply chain is submitted and approved along the life cycle of a medicinal product.

When considering the 44 variations to the manufacturing process:

- 8 of the 44 variations were considered substantial changes to the manufacturing process.
- From that 8 substantial changes to the manufacturing process of the active substance, 2 were classified as potentially having an impact on the quality, safety or efficacy of the medicinal product and the remaining 6 have substantially different route of synthesis or manufacturing conditions.

A graphic representation (Graphic 2) to illustrate the data is presented below:

Graphic 2: Type of changes



It can be concluded that the number of variations substantially affecting the synthetic process is quite low (18%) when compared to other type of variations to the manufacturing process (77%).

2.2 Cases described in the literature

2.2.1 Introduction

A retrospective analysis of the available assessment reports for medicinal products receiving a marketing authorisation between January 1999 and April 2015 was conducted. Detailed information is included in chapter [2.1. Retrospective analysis of the assessment reports](#). From the list of products identified, four active substances were selected to be analysed in this chapter. The criterion for the selection was the therapeutic indication – epilepsy – since the case study presented in [2.3. Case studies](#) concerns an antiepileptic drug, eslicarbazepine acetate. The four active substances are:

- Eslicarbazepine acetate
- Lacosamide
- Retigabine
- Zonisamide

The objective of this chapter is to describe synthetic routes found in the literature for the four active substances. The search was conducted in the reference databases PubMed, Scopus and Web of Science, using the following terms and queries:

- synthesis AND eslicarbazepine acetate;
- synthesis AND lacosamide;
- synthesis AND retigabine;
- synthesis AND zonisamide.

All searches were customised data range between January 1999 and December 2015. The results are described below, by search term ([2.2.1.1](#); [2.2.1.2](#); [2.2.1.3](#); [2.2.1.4](#)) and the comparative results are described in [2.2.1.5](#) and depicted in [Graphic 3](#).

2.2.1.1 Search term: *synthesis AND eslicarbazepine acetate*

54 articles were identified in PubMed, 11 in Scopus and 6 in Web of Science. After eliminating the duplicates, the result was 66 publications. The abstract of each publication

was consulted and 2 articles describing the synthetic process of eslicarbazepine acetate were identified as relevant.

2.2.1.2 Search term: synthesis AND lacosamide

98 articles were identified in PubMed, 31 in Scopus and 24 in Web of Science. After eliminating the duplicates, the result was 122 publications. The abstract of each publication was consulted and 5 articles describing the synthetic process of lacosamide were identified as relevant.

2.2.1.3 Search term: synthesis AND retigabine

183 articles were identified in PubMed, 37 in Scopus and 18 in Web of Science. After eliminating the duplicates, the result was 219 publications. The abstract of each publication was consulted and 2 articles describing the synthetic process of lacosamide were identified as relevant.

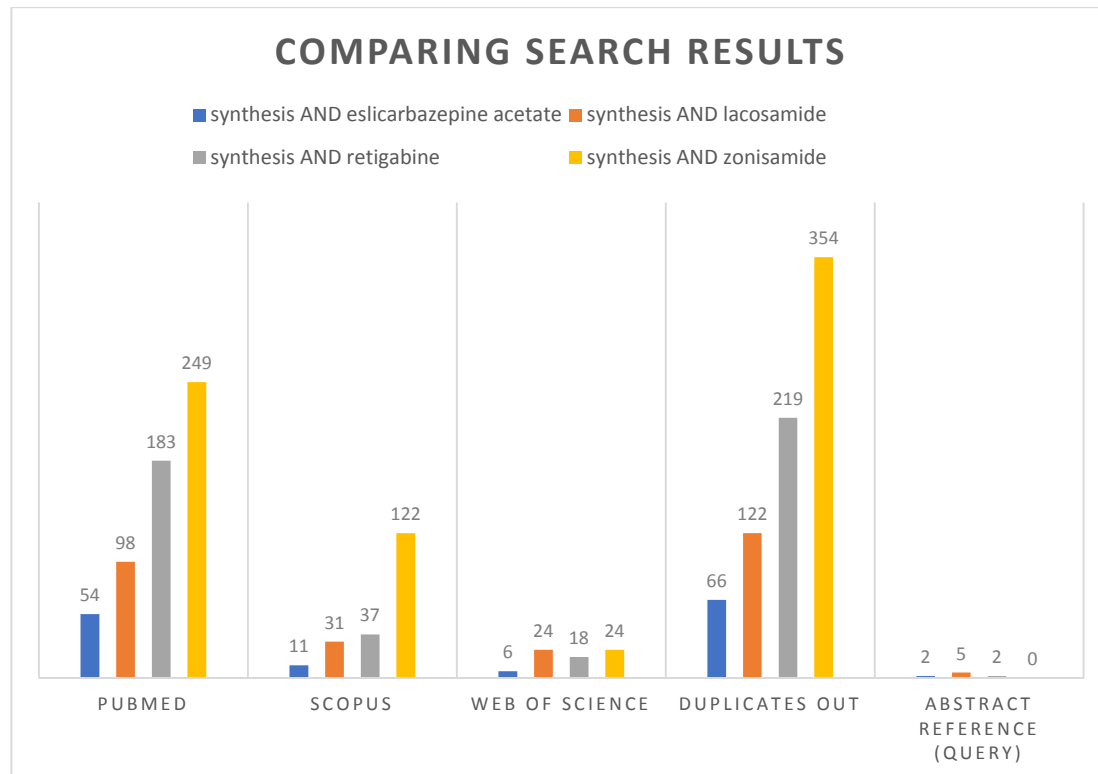
2.2.1.4 Search term: synthesis AND zonisamide

249 articles were identified in PubMed, 122 in Scopus and 24 in Web of Science. After eliminating the duplicates, the result was 354 publications. The abstract of each publication was consulted and 0 articles describing the synthetic process of lacosamide were identified as relevant.

2.2.1.5 Comparison and systematisation of search results

The [Graphic 3](#) summarises and compares the filtering and sorting search.

Graphic 3: Comparative results



The filtered and sorted results were systematised by active substance and the information of each publication was organised into the following categories:

1. Information on starting material
2. Considerations and information about synthetic process and control strategy
3. Description of main steps of synthetic process

The regulatory status and name and chemical structure of each active substance are also mentioned.

A regulatory analysis of whether each of the synthetic process described is approvable by the competent Regulatory Authority is carried out hereinafter and the discussion is included in [3.2. Discussion - Cases described in the literature](#).

2.2.2 Eslicarbazepine acetate

Eslicarbazepine acetate was first approved as medicinal product in April 2009 by the EMA in Europe and approved in USA by the FDA in November 2013.

Eslicarbazepine acetate is chemically designated as (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine- 5-carboxamide and has the following structure:

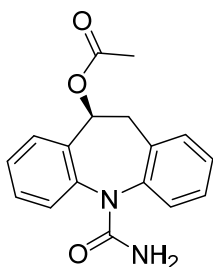


Figure 2: Structure of eslicarbazepine acetate

From the search conducted, two publications describing synthetic processes for eslicarbazepine acetate were identified:

(1) Liu K-CK, Sakya MS, O'Donnell JC, Flick CA, Li Jin. **Synthetic approaches to the 2009 new drugs**. Bioorg Med Chem 2011; 19: 1136-1154.

(2) Ravinder B, Reddy RS, Sridhar M, Mohan M M, Srinivas K, Reddy PA, *et al.* **An efficient synthesis for eslicarbazepine acetate, oxcarbazepine and carbamazepine**. Tetrahedron Lett 2013; 54: 2841-2844.

The information collected by publication is stated below.

2.2.2.1 Liu K-CK, Sakya MS, O'Donnell JC, Flick CA, Li Jin. Synthetic approaches to the 2009 new drugs. Bioorg Med Chem 2011; 19: 1136-1154.

2.2.2.1.1 Information of starting material

The starting material used is oxcarbazepine. As it was written before, it is a well-established medicine registered worldwide in the treatment of epilepsy.

2.2.2.1.2 Considerations and information about synthetic process and control strategy

Two synthetic schemes are presented and consist of:

Process 1: an asymmetric reduction of ketone (oxcarbazepine) followed by esterification or,

Process 2: asymmetric hydrogenation of vinyl acetate to give directly eslicarbazepine acetate.

Both approaches include two chemical steps

There is no reference to the control strategy.

2.2.2.1.3 Description of the main steps of the synthetic process

The flow diagram for the overall synthetic route (either Process 1 and Process 2) is depicted below (Figure 3):

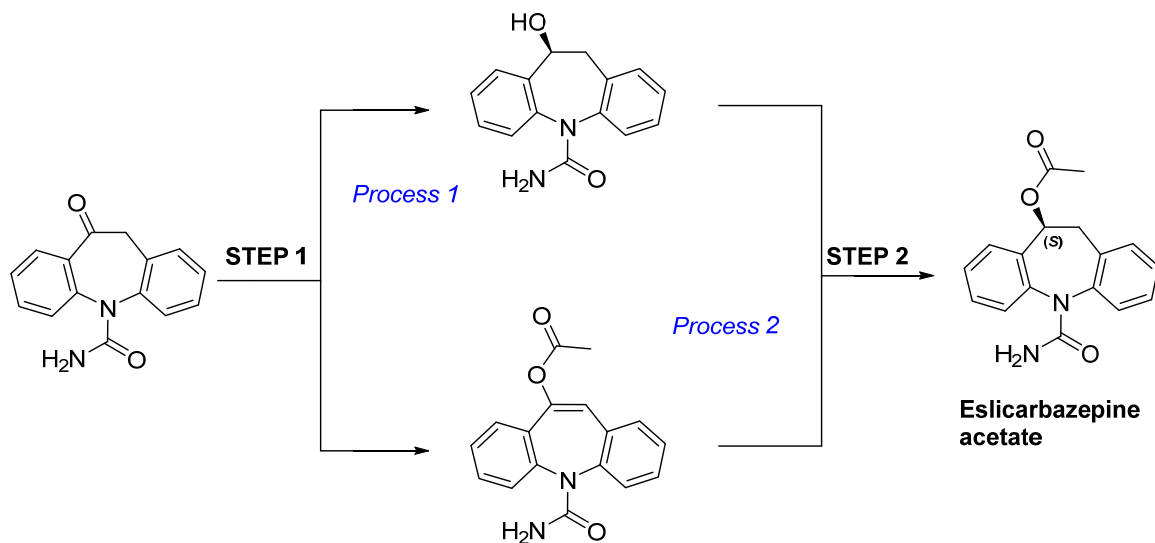


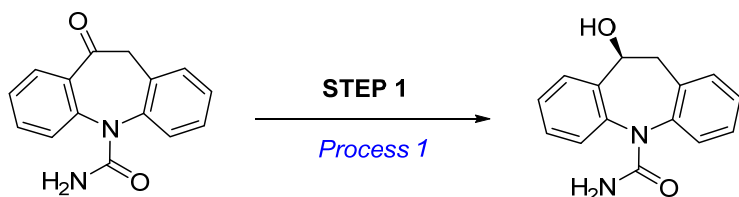
Figure 3: Flow diagram of the synthetic route

For **Process 1**, the two synthetic steps are described below:

Step 1 – Reduction (chemical step)

The asymmetric reduction of oxcarbazepine was achieved using as catalyst, $\text{Ru}(\text{Cl}_2)(\text{p-cymene})_2$, (S,S)-TsDAEN with formic acid (stoichiometric reductant) in a mixed solvent system at reflux followed by cooling to 80°C . Addition of MTBE (methyl *tert*-butyl ether), followed by a slow cooling to room temperature afforded the crystals of alcohol, which were collected by filtration and dried to obtain a 95% isolated yield in 97,8% ee.

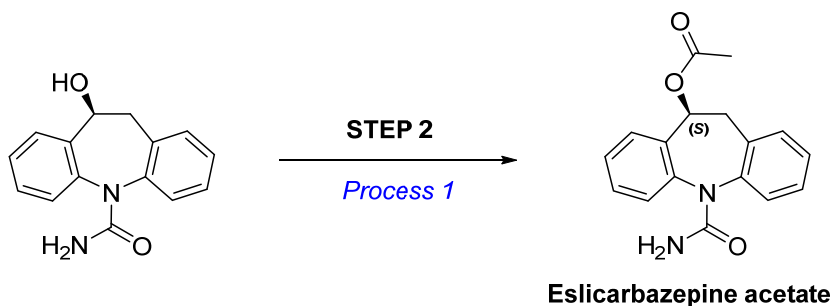
Reaction for step 1



Step 2 – Acetate protection (chemical step)

The alcohol was converted to eslicarbazepine acetate by reacting with acetic anhydride in the presence of DMAP and pyridine in refluxing dichloromethane. After aqueous work-up, the crude product was crystallised from isopropanol to give the desired product, eslicarbazepine acetate in 90% yield with 99,96% purity with undetectable amount of *R* isomer.

Reaction for step 2

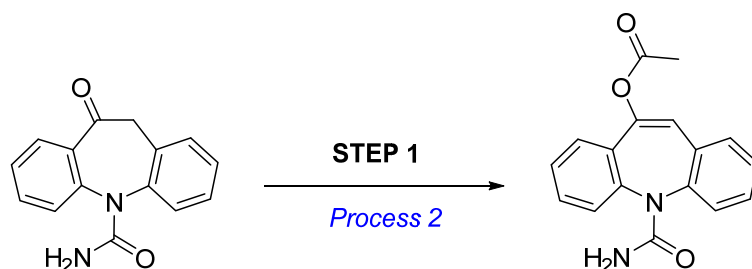


For the second approach described by the authors (**Process 2**), the 2 steps of the synthetic process are detailed below:

Step 1 – Enol acetate formation (chemical step)

The acetate was formed in this step in 88% yield.

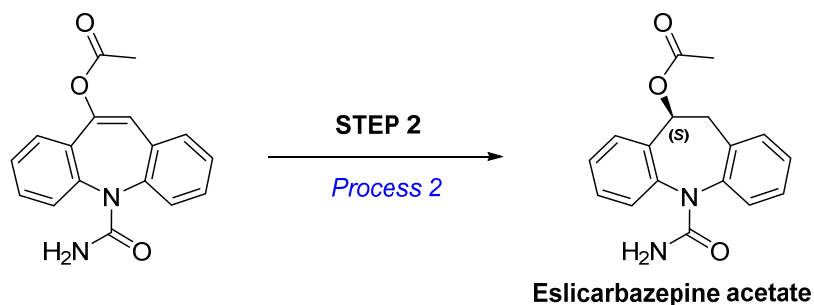
Reaction for step 1



Step 2 – Enol acetate reduction (chemical step)

The acetate is reduced via catalytic hydrogenation in the presence of preformed catalyst to give eslicarbazepine acetate in approximately 94% ee. No yield was given for the formation of the product using this route.

Reaction for step 2



The process 2 is a variation of process 1 and in that way does not deserve much discussion.

2.2.2.2 Ravinder B, Reddy RS, Sridhar M, Mohan MM, Srinivas K, Reddy PA, et al. **An efficient synthesis for eslicarbazepine acetate, oxcarbazepine and carbamazepine.** *Tetrahedron Lett* 2013; 54: 2841-2844.

2.2.2.2.1 Information of starting material

As per the information included in the publication there are several potential synthetic routes involving different compounds used as starting material:

- Oxcarbazepine
- Licarbazepine
- 10-methoxy-5*H*-dibenzo[*b,f*]azepine

Oxcarbazepine is a well-established medicine used worldwide in the treatment of epilepsy, psychosomatic diseases and some neural disorders. Licarbazepine is not a compound registered as a medicinal product. 10-methoxy-5*H*-dibenzo[*b,f*]azepine is a chemical compound commercially available.

2.2.2.2.2 Considerations and information about synthetic process and control strategy

The authors refer several methods described in the literature that use resolution of (S)- licarbazepine. The authors developed an enantioselective approach and R-2-Me-CBS was the catalyst employed in the reduction step. The synthetic process described consist in 4 chemical steps. The starting material used is 10-methoxy-5*H*-dibenzo[*b,f*]azepine. The yield of the reaction was 77%.

There is no reference to a control strategy.

2.2.2.2.3 Description of the main steps of the synthetic process

The schematic process is represented in [Figure 4](#).

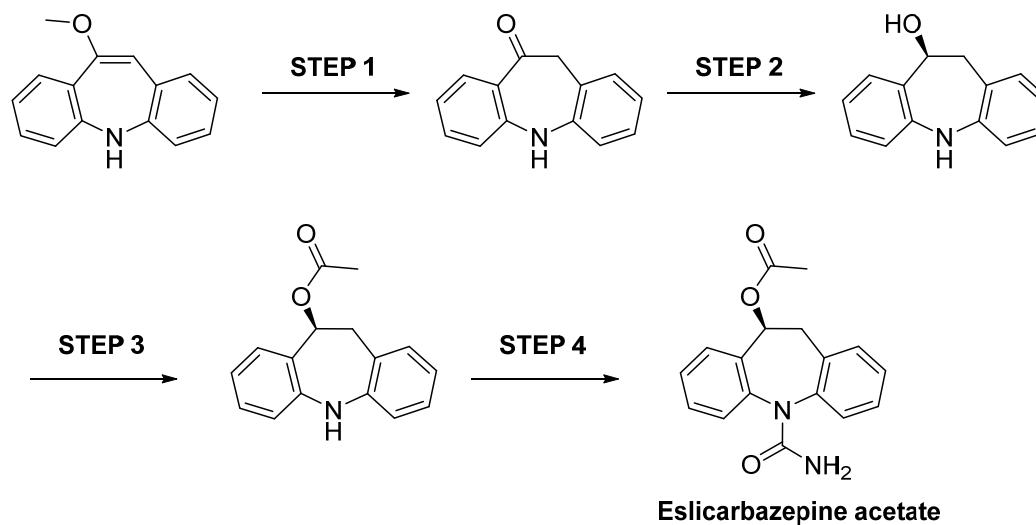


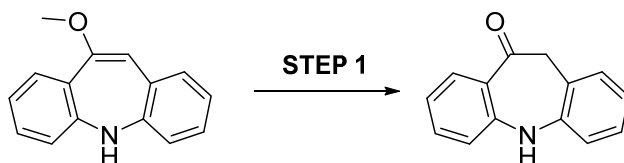
Figure 4: Flow diagram of the synthetic process

The 4 steps of the process are described below in detail.

Step 1 - De-methylation (chemical step)

The starting material, 10-methoxy-5H-dibenzo[*b,f*]azepine, involving a de-protection strategy, in the presence of 50% HCl in isopropyl alcohol, afforded the 5,11-dihydro-10H-dibenzo[*b,f*]azepin-10-one in more than 85% yield.

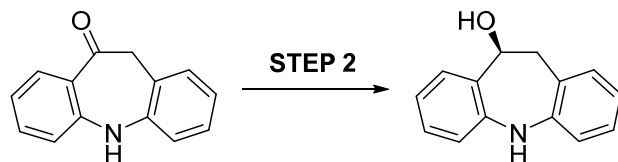
Reaction for step 1



Step 2 – Reduction (chemical step)

By employing the catalyst R-2-Me-CBS, an asymmetric reduction of ketone functionality in the 5,11-dihydro-10H-dibenzo[*b,f*]azepin-10-one results in the corresponding alcohol.

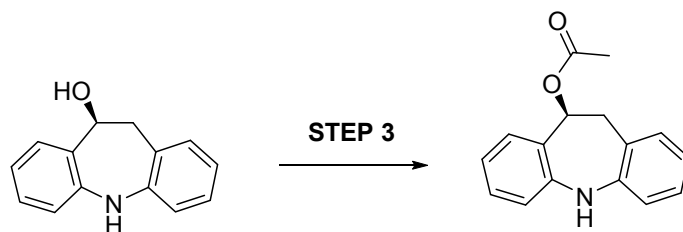
Reaction for step 2



Step 3 – Acetylation (chemical step)

The alcohol from the previous step was subjected to acylation affording the intermediate (S)-10,11-dihydro-5H-dibenzo[b,f]azepin-10-yl acetate in 80% yield.

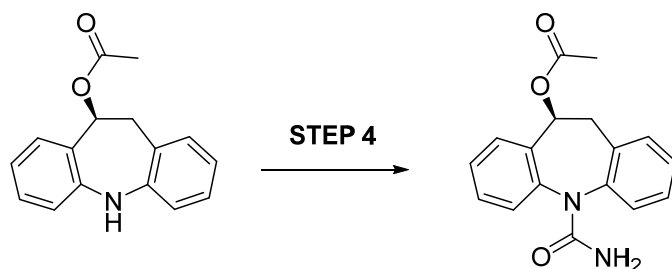
Reaction for step 3



Step 4 – Urea formation (chemical step)

The compound resulting from step 3 was treated with chlorosulfonyl isocyanate (ClSO_2NCO) to obtain eslicarbazepine acetate. The yield was of 77%.

Reaction for step 4



2.2.3 Lacosamide

Lacosamide is used in the treatment of epilepsy and was first approved as a medicinal product in Europe by the EMA, and in USA by the FDA, respectively in August and September of 2008.

Lacosamide is chemically designated as (2*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide and can be represented by the following structure (Figure 5):

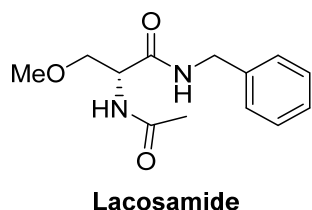


Figure 5: Structure of lacosamide

From the literature search, 5 publications were identified describing synthetic approaches for lacosamide:

- (1) Morieux P, Stables PJ, Kohn H. **Synthesis and anticonvulsant activities of *N*-benzyl (2*R*)-2-acetamido-3-oxysubstituted propionamide derivatives**. Bioorg Med Chem 2008; 16: 8968-8975.
- (2) Wadavrao BS, Narikimalli A, Narsaiah VA. **A non-infringing Route for Enantioselective Synthesis of Antiepileptic Agent Lacosamide**. Synthesis 2013; 45: 3383-3386.
- (3) Stecko S. **Total Synthesis of Lacosamide**. J Org Chem 2014; 79: 6342-6346.
- (4) Garg Y, Pandey KS. **An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (*R*)-Lacosamide**. J Org Chem 2015; 80: 4201-4203.
- (5) Aratikatla KE, Bhattacharya KA. **Chiral pool approach for the synthesis of functionalized amino acids: synthesis of antiepileptic drug (*R*)-lacosamide**, Tetrahedron Lett 2015; 56: 5802-5803.

The information taken from each publication is stated below.

2.2.3.1 Morieux P, Stables PJ, Kohn H. *Synthesis and anticonvulsant activities of N-benzyl (2R)-2-acetamido-3-oxysubstituted propionamide derivatives*. *Bioorg Med Chem* 2008; 16: 8968-8975.

2.2.3.1.1 Information of starting material

The authors referred to an earlier process reported in 1996 using an expeditious three-step synthesis starting from *D*-serine. The synthetic process described in 2008 used as starting material *D*-serine methyl ester.

2.2.3.1.2 Considerations and information about synthetic process and control strategy

The synthetic process reported is a five-step stereospecific synthesis. There is no reference to the control strategy.

2.2.3.1.3 Description of the main steps of the synthetic process

The synthetic process is described below (Figure 6):

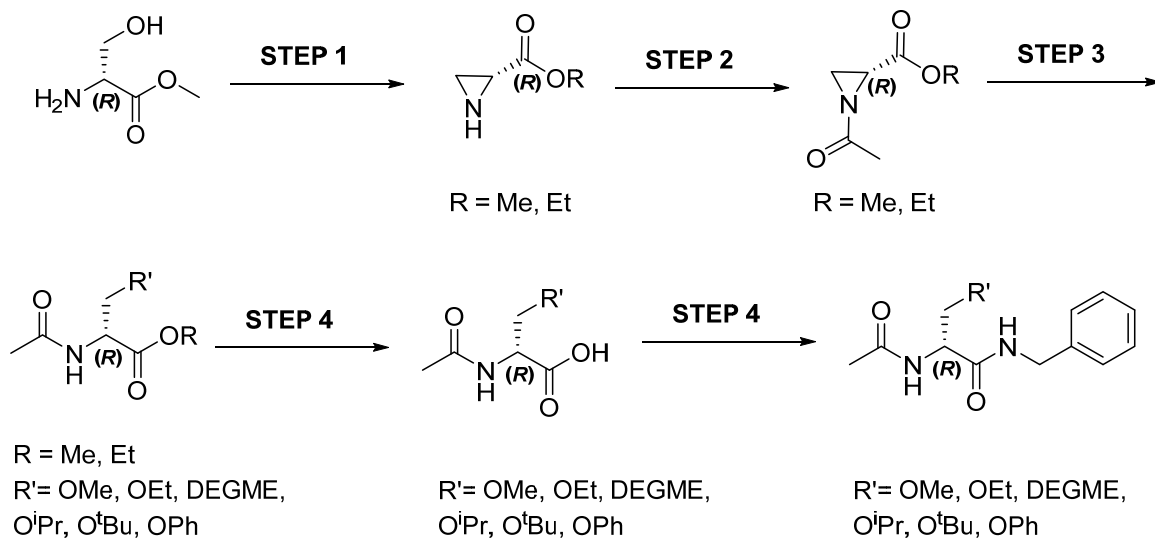


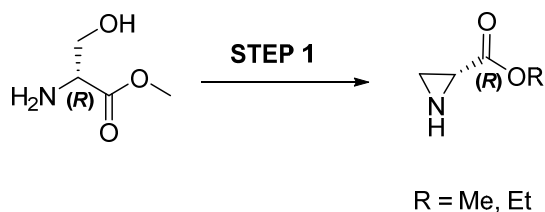
Figure 6: Flow diagram of synthetic process

The description of each step is detailed below.

Step 1 – Aziridine formation (chemical step)

The starting material *D*-serine methyl ester is treated with DTTP to give methyl (2*R*)-aziridine-2-carboxylate. As a by-product, the corresponding ethyl ester is formed.

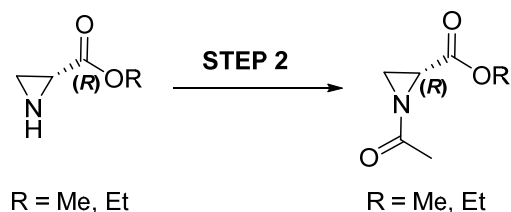
Reaction for step 1



Step 2 – Acetate protection (chemical step)

The carboxylate and the ethyl ester are converted to methyl and ethyl (2*R*)-*N*-(acetyl)aziridine-2-carboxylates, with acetic anhydride, Et₃N, and a catalytic amount of DMAP.

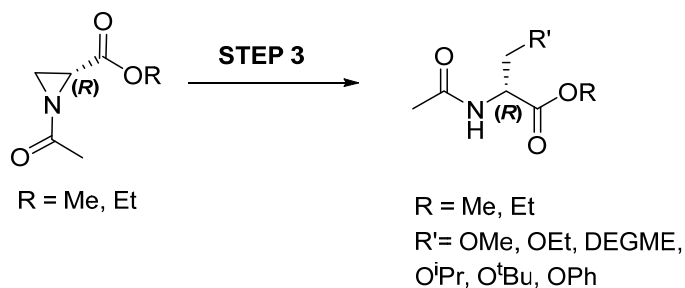
Reaction for step 2



Step 3 – Aziridine ring opening (chemical step)

The methyl and ethyl carboxylates are treated with MeOH, the primary alcohols, EtOH and diethylene glycol monomethyl ether (DEGME), the secondary alcohol, *i*PrOH, the tertiary alcohol, *tert*-BuOH, and phenol with one equivalent of BF₃•Et₂O giving the corresponding aziridine ring-opening products in 50-60% isolated yield.

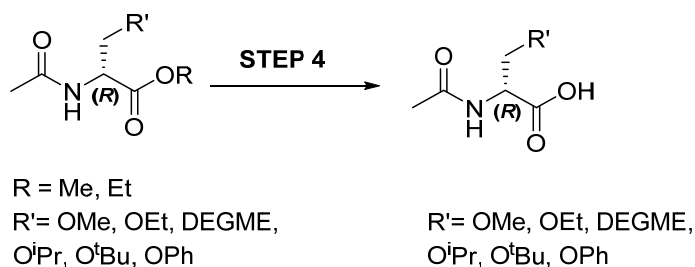
Reaction for step 3



Step 4 – Ester hydrolysis (chemical step)

The conversion of the esters from the previous step to the *N*-benzyl amides (free acids) is obtained by hydrolysis with stoichiometric amounts of LiOH.

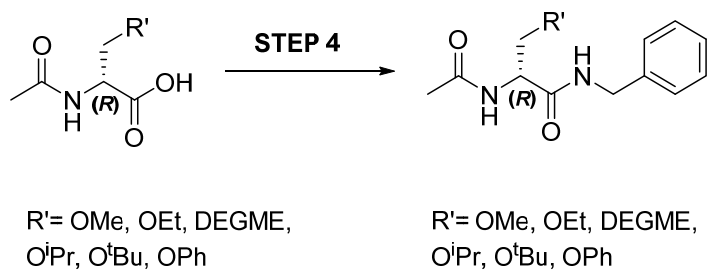
Reaction for step 4



Step 5 – Amide formation (chemical step)

The free acids are coupled with benzylamine and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), to give lacosamide.

Reaction for step 5



2.2.3.2 Wadavrao BS, Narikimalli A, Narsaiah VA. *A non-infringing Route for Enantioselective Synthesis of Antiepileptic Agent Lacosamide*. *Synthesis* 2013; 45: 3383-3386.

2.2.3.2.1 Information of starting material

The starting material used is a non-amino acid, acrylic acid, a compound commercially available.

2.2.3.2.2 Considerations and information about synthetic process and control strategy

The synthesis of lacosamide is completed in 8 steps using Sharpless asymmetric dihydroxylation as a key step. The overall yield was 29%. According to the authors, all the reactions were very clean and presented good yields.

There is no reference to any control strategy.

2.2.3.2.3 Description of the main steps of the synthetic process

The scheme for the synthetic process is presented in [Figure 7](#).

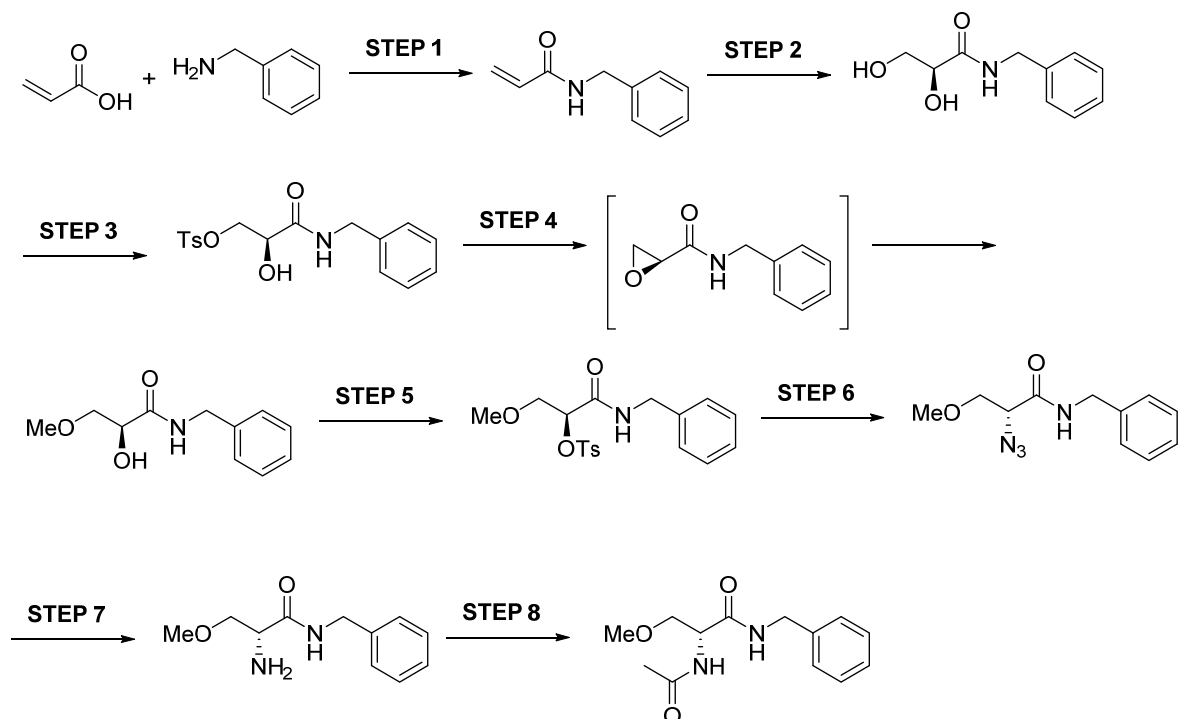


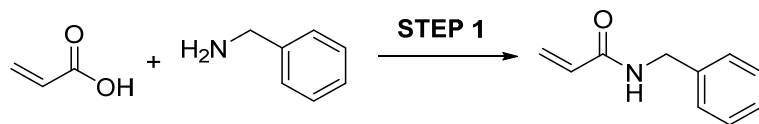
Figure 7: Schematic representation of the synthetic process

The description and schematic representation of each step is included.

Step 1 – Amide coupling (chemical step)

The acrylic acid reacts with benzylamine in the presence of 1-hydroxybenzotriazole in *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDCI) at 0°C to room temperature to obtain, *N*-benzylacrylamide in 70% yield.

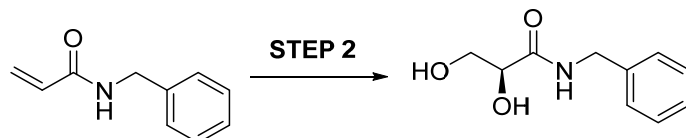
Reaction for step 1



Step 2 – Sharpless asymmetric dihydroxylation (chemical step)

The amide compound formed in Step 1 was subjected to Sharpless asymmetric dihydroxylation with AD-mix-β and methanesulfonamide using a mixture of *tert*-butyl alcohol-water (1:1) as solvent at 0°C to produce (*S*)-*N*-benzyl-2,3-dihydroxypropanamide in 93% yield.

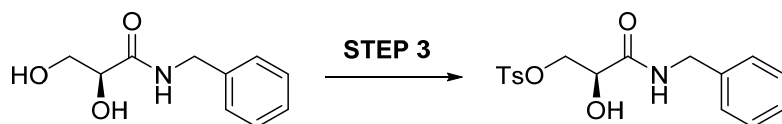
Reaction for step 2



Step 3 – Tosylation (chemical step)

The dihydroxy compound obtained in the previous step is treated with tosylchloride and dibutyltin oxide in the presence of triethylamine at 0°C to obtain the primary hydroxy group tosylated product, (S)-3-(benzylamino)-2-hydroxy-3-oxopropyl 4-toluenesulfonate, in 95% yield.

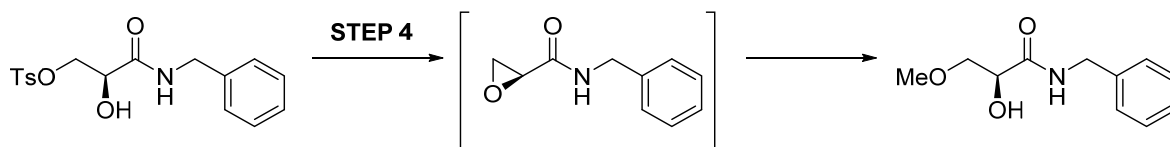
Reaction for step 3



Step 4 – Nucleophilic Substitution (chemical step)

The tosyl compound was treated with potassium carbonate in methanol at 0°C resulting in the *in situ* formation of an epoxide that was opened by methanol to give (S)-N-benzyl-2-hydroxy-3-methoxypropanamide in 90% yield.

Reaction for step 4

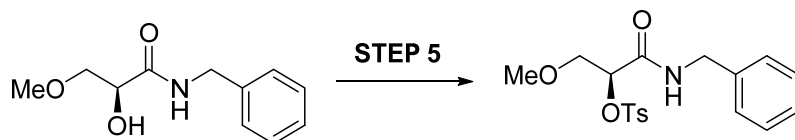


Step 5 – Tosylation (chemical step)

The compound resulting from step 4 was treated with tosyl chloride in the presence of 4-(dimethylamino) pyridine at 0°C to obtain the secondary alcohol protected product, (S)-1-

benzylamino)-3-methoxy-1-oxopropan-2-yl 4 toluenesulfonate. The authors referred to the yield as “excellent”.

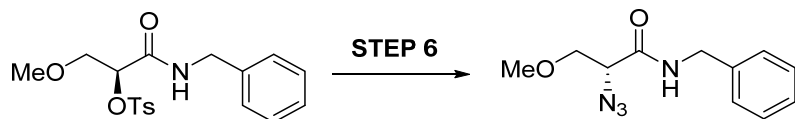
Reaction for step 5



Step 6 – Azide formation (chemical step)

The tosylated compound was treated with sodium azide in *N,N*-dimethylformamide at 70°C to give (*R*)-2-azido-*N*-benzyl-3-methoxypropanamide in a 87% yield.

Reaction for step 6



Step 7 – Azide reduction (chemical step)

The reduction of the azide compound obtained in the previous step with triphenylphosphine in a tetrahydrofuran-water (9:1) mixture at 50°C is conducted and (*R*)-2-amino-*N*-benzyl-3-methoxypropanamide is obtained. According to the authors the yield is very good.

Reaction for step 7



Step 8 – Amine protection (chemical step)

The amine compound obtained was treated with acetic anhydride in dichloromethane at 0°C for one hour, to give lacosamide in 90% yield.

Reaction for step 8



2.2.3.3 Stecko S. *Total Synthesis of Lacosamide*. *J Org Chem* 2014; 79: 6342-6346.

2.2.3.3.1 Information of starting material

There is a reference to earlier synthetic strategies using non-natural *D*-serine as starting material. The synthetic processes were considered too expensive because of the costs of silver compounds and the need of recovery and regeneration of silver by-products. Alternative strategies used *D,L*-serine as starting material. The authors explored the use of an enantiopure starting material obtained from ethyl L-lactate.

2.2.3.3.2 Considerations and information about synthetic process and control strategy

The synthetic process is described in eight-steps. The overall yield for the targeting molecule (lacosamide) was of 22%.

There is no reference to a control strategy.

The key step (Figure 8) is the stereospecific rearrangement of allyl cyanate-to-isocyanate, which proceeds with chirality transfer.

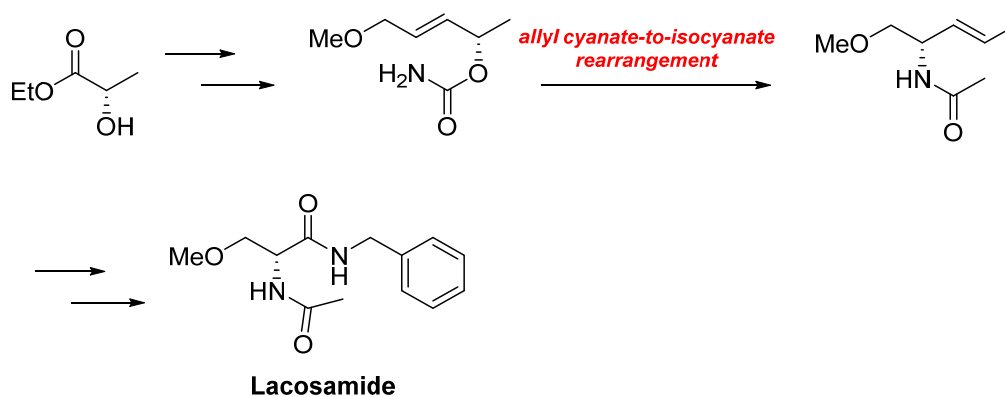


Figure 8: Key step of the synthesis of lacosamide

2.2.3.3.3 Description of the main steps of the synthetic process

Different methods either for the entire synthetic process or to alternative routes in each step are mentioned. Since the aim of this chapter is to describe synthetic routes for the

evaluation of the regulatory feasibility, one of the routes was chosen to be described here, but not following any specific criterion. The selection was random.

The selected synthetic process is depicted in Figure 9.

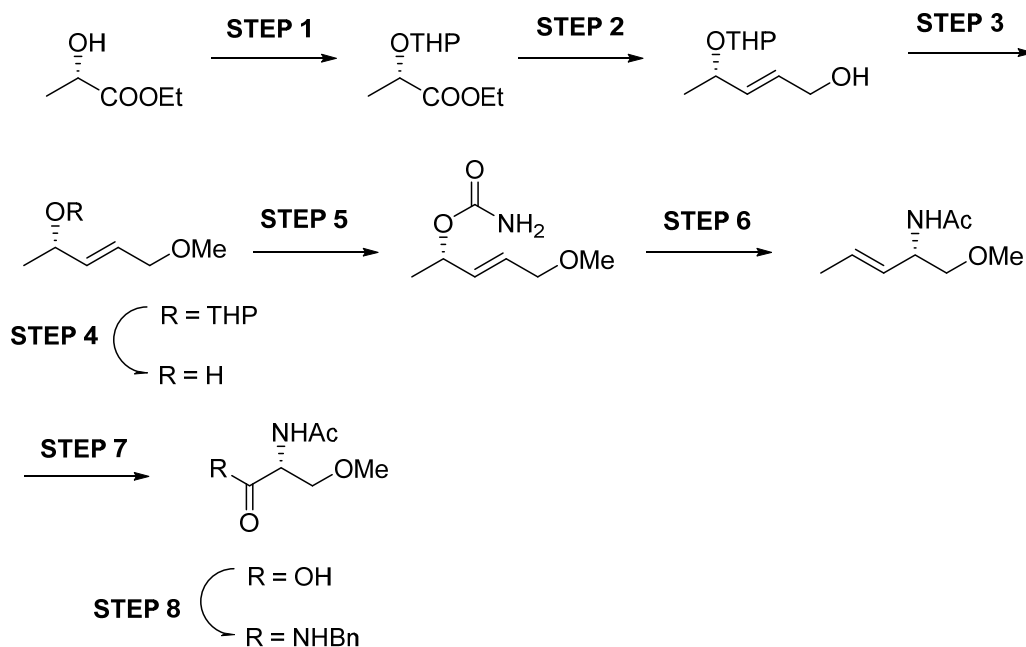


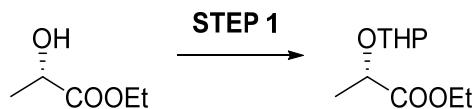
Figure 9: Flow diagram of synthetic process

The description of each step is presented below.

Step 1 – Esterification (chemical step)

In the presence of pyridinium tosylate (catalyst), ethyl *L*-lactate reacts with 3,4-dihydro-2*H*-pyrane (DHP) and the O-THP protected lactate (ester) is obtained.

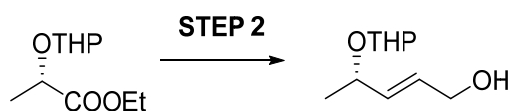
Reaction for step 1



Step 2 - Reduction, HWE alkene formation followed by ester reduction (chemical step)

Step 2, this includes 3-steps. The ester is treated with DIBAL-H, giving the aldehyde, which reacts with Horner-Wadsworth-Emmons reagent generated from triethyl phosphonoacetate and NaH. After extractive work-up, the α,β -unsaturated ester (crude), after extractive work-up, is reduced to provide the allyl alcohol.

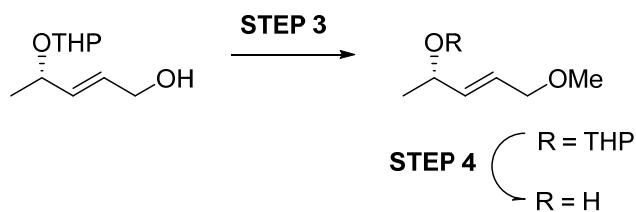
Reaction for step 2



Step 3/4 – Methylation and alcohol deprotection (chemical step)

The allyl alcohol suffers a methylation, followed by deprotection of the hydroxyl group, to produce another allyl alcohol compound. This reaction includes 2-steps. The allyl alcohol resulting from step 2 is treated with NaH and methyl iodide (MeI) in THF at room temperature to give a methyl ether (crude). The methyl ether is dissolved in MeOH and treated with AcCl (5 mol %), giving an allyl alcohol.

Reaction for step 3/4

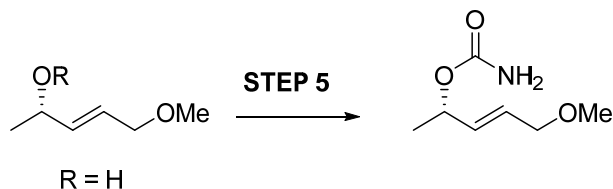


Step 5 – THP removal (chemical step)

The carbamate, which is the compound resulting from this step, was prepared by reaction of the allyl alcohol (compound from step 3) with trichloroacetyl isocyanate (TCA-NCO), followed by hydrolysis (82% overall yield). The author mentioned that the TCA-NCO can

be replaced by a cheaper reagent, chlorosulfonyl isocyanate (CSI). In the case of the use of CSI, the yield of the reaction is 78% yield.

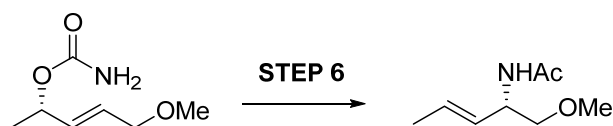
Reaction for step 5



Step 6 – Carbamate rearrangement (chemical step)

The carbamate suffers a dehydration with TFAA in the presence of Et₃N and provided an allyl cyanate, which spontaneously undergoes [3,3] sigmatropic rearrangement to afford an allyl isocyanate. This compound was not isolated but directly treated with an excess of MeMgBr to afford *N*-acetylated allyl amine. The yield is 74%.

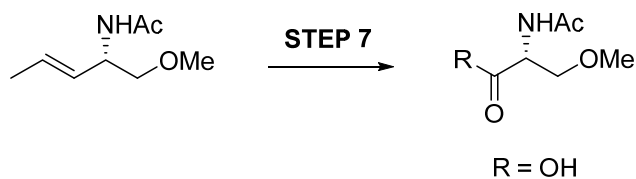
Reaction for step 6



Step 7 – Oxidation (chemical step)

The allyl amide resulting from previous step is submitted to oxidative cleavage of the double bond to give a serine derivative.

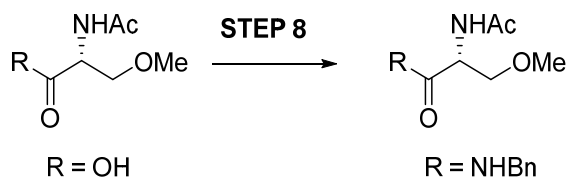
Reaction for step 7



Step 8 – Amidation (chemical step)

After filtration and drying, the serine derivative is submitted to the amidation step by treatment with isobutyl chloroformate (IBCF) in the presence of *N*-methyl morpholine in THF, followed by treatment with BnNH₂, to give lacosamide. The yield of this step is 79%. The product is isolated by filtration and crystallization from ethyl acetate.

Reaction for step 8



2.2.3.4 Garg Y, Pandey KS. An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (R)-Lacosamide. *J Org Chem* 2015; 80: 4201-4203.

2.2.3.4.1 Information of starting material

The starting material used is the racemic butadiene monoepoxide, commercially available. and easily synthesised from silver-catalysed oxidation of 1,3-butadiene

2.2.3.4.2 Considerations and information about synthetic process and control strategy

The synthesis described uses the palladium catalysed Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) as key step. It is a five-step process and is described as a simple, flexible and highly efficient synthetic approach. The synthetic process is high enantioselective with high yielding reaction steps, protection free synthesis, catalyst regenerability and cost-effective strategy. The overall yield is of 52%.

2.2.3.4.3 Description of the main steps of the synthetic process

The synthetic process is described below (Figure 10):

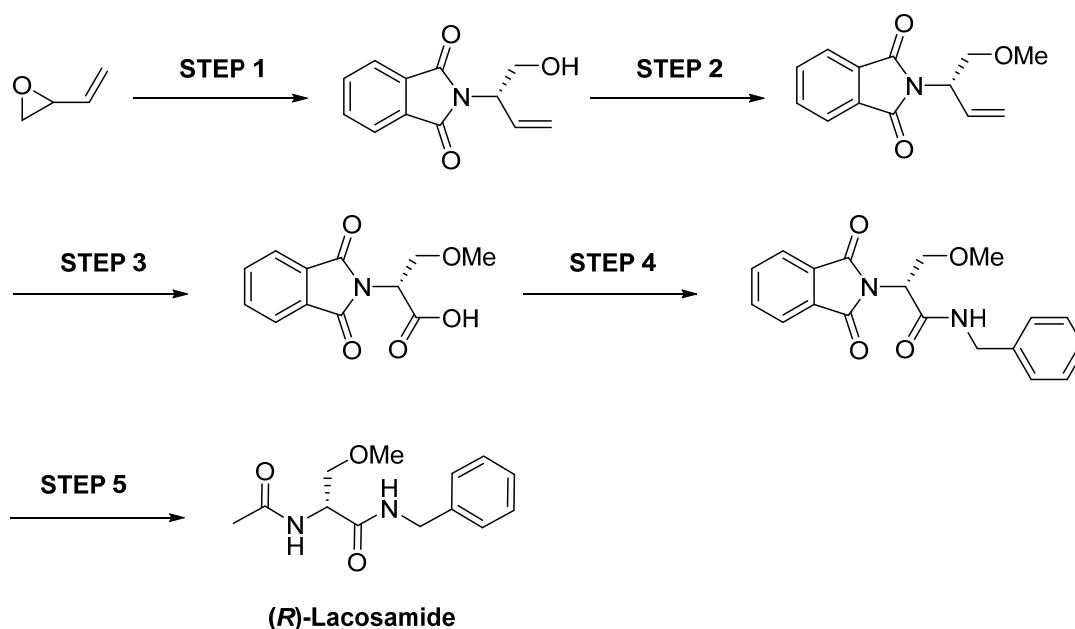


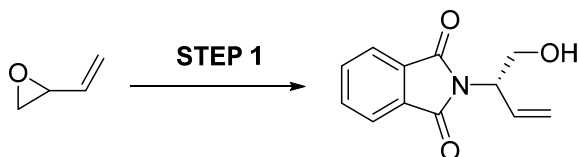
Figure 10: Synthetic process of lacosamide

The details for each step are described below.

Step 1 – Asymmetric allylic alkylation (chemical step)

Deracemisation of butadiene monoepoxide with palladium catalysed Trost's DYKAT in the presence of (R,R)-DACH and $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$, phthalimide and Na_2CO_3 afforded asymmetric allylic alkylation (AAA) product phthaloyl alcohol as a single enantiomer in 98% yield.

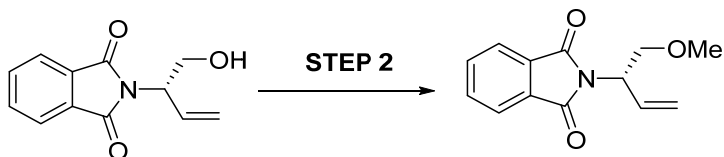
Reaction for step 1



Step 2 – Methylation (chemical step)

The enantiomerically pure alcohol is subjected to O-methylation with MeI (methyl iodide) in the presence of NaH to give a methyl ether in 86% yield.

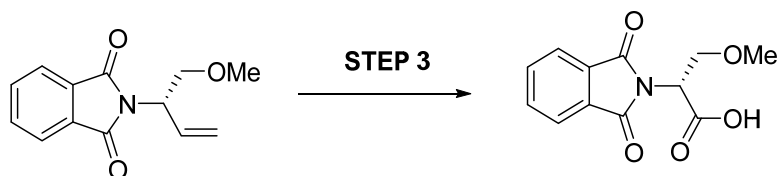
Reaction for step 2



Step 3 – Oxidation (chemical step)

The compound resulting from the previous step suffers an oxidative cleavage in the presence of OsO_4 and sodium periodate, followed by oxidation with oxone giving the phthaloyl acid.

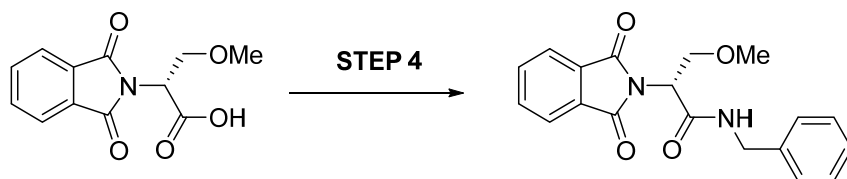
Reaction for step 3



Step 4 – Amide coupling (chemical step)

The treatment of the acid with benzylamine in the presence of isobutyl chloroformate and *N*-methyl morpholine in THF gives the phthaloyl amide in 88% yield.

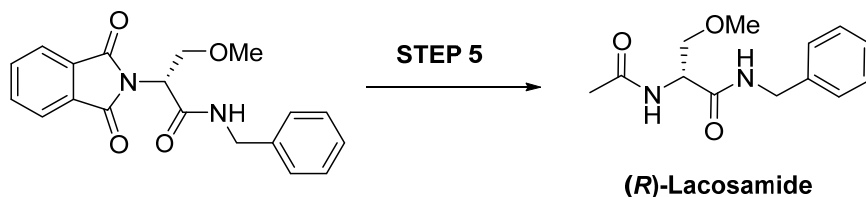
Reaction for step 4



Step 5 - Phthalamide cleavage (amine deprotection) (chemical step)

The phthalimide group of the amide suffers a cleavage with hydrazine monohydrate in the presence of isopropyl alcohol followed by *N*-acetylation using acetyl chloride under basic conditions. The target compound (*R*)-lacosamide is obtained with a 91% yield.

Reaction for step 5



2.2.3.5 Aratikatla KE, Bhattacharya KA. *Chiral pool approach for the synthesis of functionalized amino acids: synthesis of antiepileptic drug (R)-lacosamide*, *Tetrahedron Lett* 2015; 56: 5802-5803.

2.2.3.5.1 Information of starting material

The synthetic process described is, according to the authors, a short and straightforward synthesis of *R*-lacosamide. The synthesis started from readily available *N*-Boc-*N*,*O*-isopropylidene-*L*-serinol. The key starting material can easily be synthesised from natural *L*-serine in four steps.

2.2.3.5.2 Considerations and information about synthetic process and control strategy

The key starting material can easily be synthesised from natural *L*-serine in four steps. Any of the intermediates doesn't require purification. After protection/deprotection and functional group manipulation, it is possible to obtain lacosamide from the alcohol, *N*-Boc-*N*,*O*-isopropylidene-*L*-serinol. The synthetic process is described in five-steps with an overall yield of 54%. The reaction steps are short and present a high yielding. In this way, it is commercially viable as there is no need for kinetic resolution or for the use of chiral ligands.

There is not any reference to a control strategy.

2.2.3.5.3 Description of the main steps of the synthetic process

The synthetic process is depicted in the flow diagram below ([Figure 11](#)):

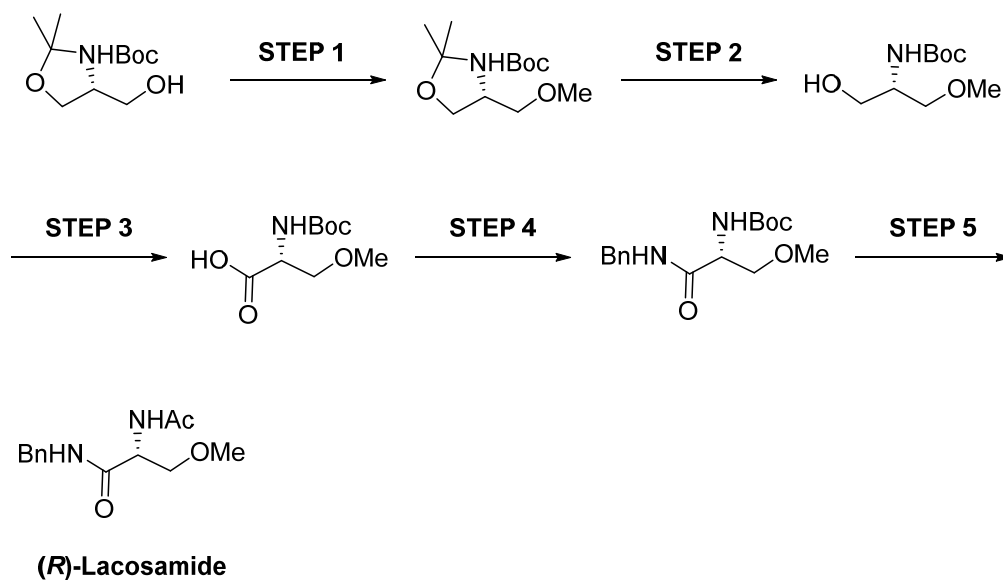


Figure 11: Flow diagram of synthetic process

The five steps are described and schematised below.

Step 1 – Methylation (chemical step)

After methylation of the starting material with methyl iodide in THF and in the presence of sodium hydride, the ether is obtained in an 88% of yield.

Reaction for step 1



Step 2 – Deprotection (chemical step)

The deprotection of acetonide group of the ether with *p*-toluene sulphonic acid in methanol forms an alcohol.

Reaction for step 2



Step 3 – Oxidation (chemical step)

The oxidation of the primary alcoholic group with TEMPO results in the formation of an acid with a yield of 99%.

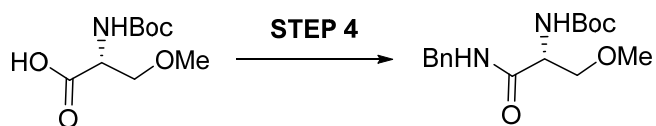
Reaction for step 3



Step 4 – Amide coupling (chemical step)

The acid is coupled with benzyl amine using *N*-methyl morpholine and isobutyl chloroformate in THF to give the amide in 90% of yield.

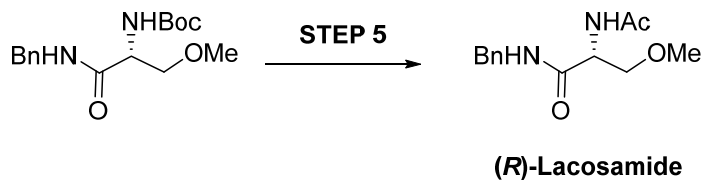
Reaction for step 4



Step 5 – Boc deprotection/Acetate protection (chemical step)

The deprotection of Boc group followed by acetylation of the amine resulting from step 4, results in the target product, lacosamide, with a yield of 80%.

Reaction for step 5



2.2.4 Retigabine

Retigabine (INN) or Ezogabine (USAN) is an anticonvulsant used as treatment of partial epilepsies and was developed by Valeant Pharmaceuticals and GlaxoSmithKline. It was first approved by Food and Drug Administration of the United States of America (FDA) on June 10, 2010 and by the European Medicines Agency (EMA) on March 28, 2011.

Retigabine is chemically designated as ethyl *N*-[2-amino-4-[(4-fluorophenyl) methylamino] phenyl] carbamate. The chemical structure is represented in Figure 12 depicted below.

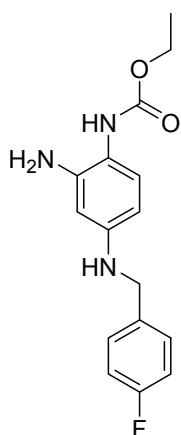


Figure 12: Structure of retigabine

Two publications describing synthetic processes for retigabine were identified from the literature search conducted:

(1) Blackburn-Munro G, Dalby-Brown W, Mirza NR, Mikkelsen JD, Blackburn-Munro RE. **Retigabine: Chemical Synthesis to Clinical Application.** CNS Drug Rev 2005; 11 (1): 1-20.

(2) Ding XH, Liu K-CK, Sakya MS, Flick CA, O'Donnell JC. **Synthetic approaches to the 2011 new drugs.** Bioorg Med Chem 2013; 21: 2795-2825.

The information included in each publication is detailed in the overleaf pages.

2.2.4.1 Blackburn-Munro G, Dalby-Brown W, Mirza NR, Mikkelsen JD, Blackburn-Munro RE. *Retigabine: Chemical Synthesis to Clinical Application*. *CNS Drug Rev* 2005; 11 (1): 1-20.

2.2.4.1.1 Information of starting material

Retigabine was prepared from the reaction of two compounds (starting materials): 2-Nitro-1,4-phenylenediamine and 4-fluorobenzaldehyde.

2.2.4.1.2 Considerations and information about synthetic process and control strategy

The synthetic process is a 3-step process. The yield of the last step is 62%

There is no reference to a control strategy.

2.2.4.1.3 Description of the main steps of the synthetic process

The main steps of the synthetic process are represented below (Figure 13):

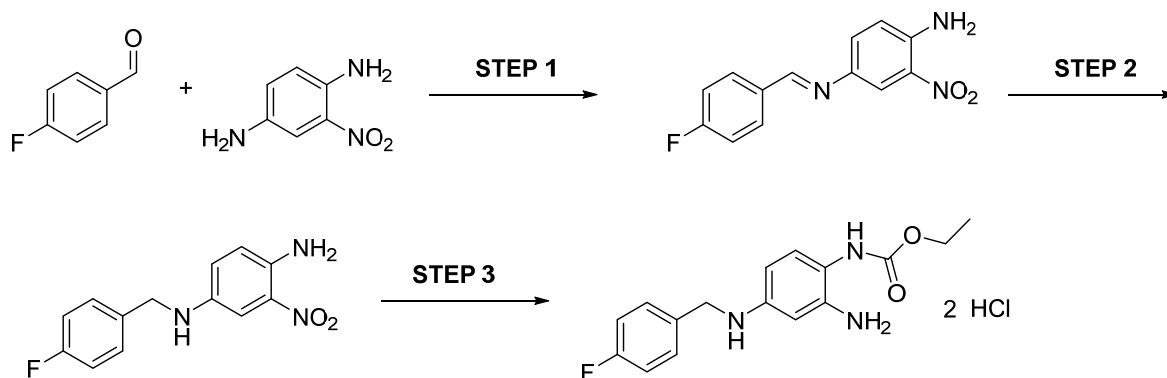


Figure 13: Flow diagram of synthetic process

Step 1 – Imine formation (chemical step)

2-Nitro-1,4-phenylenediamine reacts with 4-fluorobenzaldehyde under Dean Stark conditions to give imine. The yield of this step is 69%.

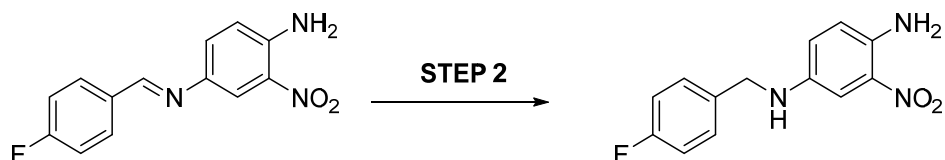
Reaction for step 1



Step 2 – Imine reduction (chemical step)

After extraction, the imine is reduced using a metal hydride to give a nitro compound. The yield is 70%.

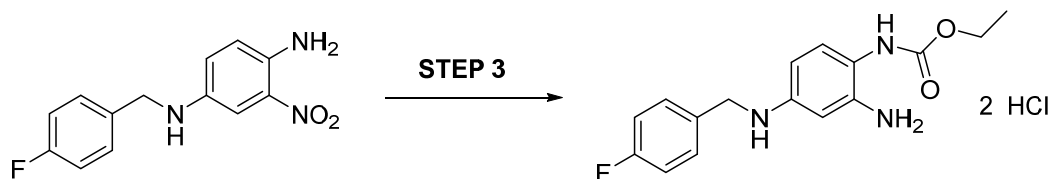
Reaction for step 2



Step 3 – Nitro reduction/Carbamate formation (chemical step)

The nitro compound is reduced to the aryldiamine using palladium on carbon and is then “one pot” derivatised directly to the ethyl carbamate. The ethyl carbamate is then precipitated by the addition of alcoholic hydrogen chloride. The yield is 62%.

Reaction for step 3

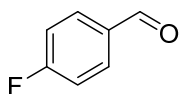


2.2.4.2 Ding XH, Liu K-CK, Sakya MS, Flick CA, O'Donnell JC. *Synthetic approaches to the 2011 new drugs*. *Bioorg Med Chem* 2013; 21: 2795-2825.

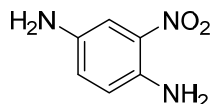
The publication refers two synthetic processes but only one will be considered for the analysis, as since it is the one that has more information about the different steps.

2.2.4.2.1 Information of starting material

The starting materials described are 4-fluorobenzaldehyde and 4-amino-2-nitroaniline, both commercially available.



4-fluorobenzaldehyde
CAS [459-57-4]



4-amino-2-nitroaniline
CAS [5307-14-2]

2.2.4.2.2 Considerations and information about synthetic process and control strategy

The synthetic process is a 3-step process. The target compound is obtained in a yield of 70-90%.

There is no reference to any control strategy.

2.2.4.2.3 Description of the main steps of the synthetic process

The main steps are represented in Figure 14.

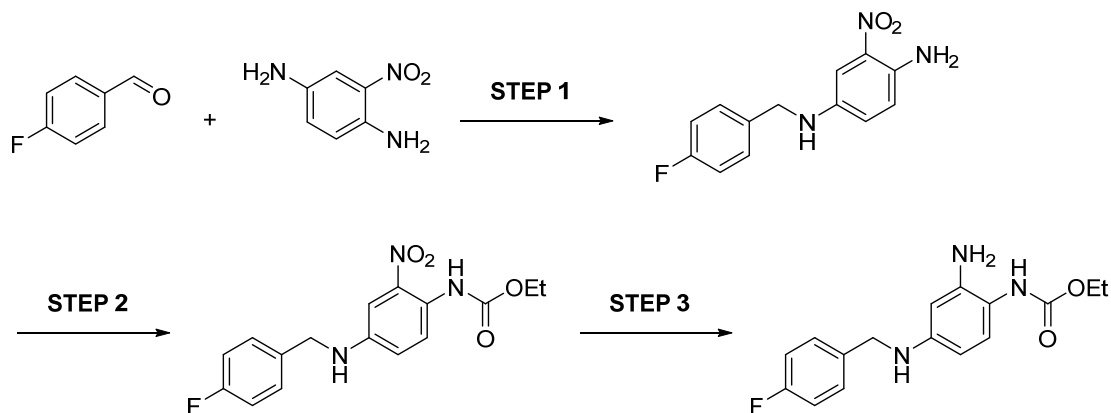


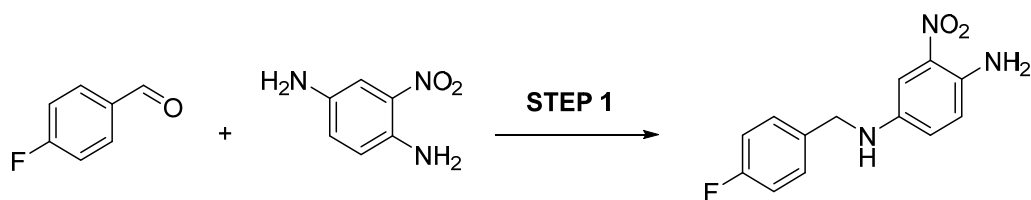
Figure 14: Main steps of synthetic process

The detail of each step of the synthetic process is presented hereinafter.

Step 1 – Imine formation / Imine reduction (chemical step)

The 4-fluorobenzaldehyde is condensed with 4-amino-2-nitroaniline and the resulting imine is reduced with sodium borohydride to give aniline. The yield of this step is 79-85%.

Reaction for step 1



Step 2 – Carbamate formation (chemical step)

Aniline is acylated with diethylcarbonate to give nitrobenzene in 80-88% yield.

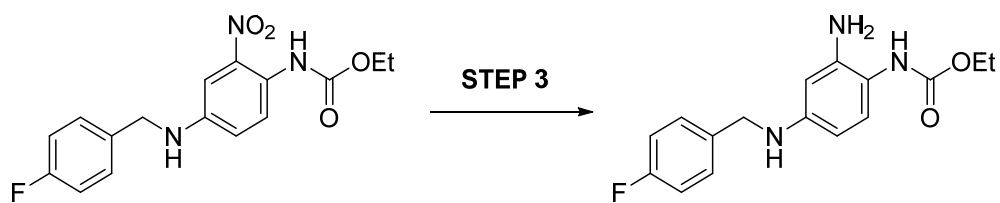
Reaction for step 2



Step 3 – Hydrogenation (chemical step)

The nitro group is reduced via catalytic hydrogenation to obtain the target compound, retigabine. The yield is between 70 to 90%.

Reaction for step 3



In summary, five papers were considered for the analysis. The starting material mentioned was different for all the synthetic processes described. Three of the processes consider 5-steps while the other two consider 8-steps.

2.2.5 Zonisamide

The development of zonisamide was initiated in Japan by Dainippon Pharmaceutical Company Limited. It is marketed since 1989 in Japan and since 2000 in the USA, by FDA. Zonisamide is approved in Europe, by the EMA, as medicinal product since March 2005.

Zonisamide is chemically designated as 1,2-benzoxazol-3-yl-methanesulfonamide. The chemical structure is depicted below (Figure 15).

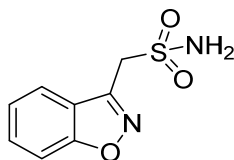


Figure 15: Structure of zonisamide

In case of zonisamide no relevant literature references were found, so it will not be conducted any regulatory analysis for this active substance.

2.3 Case studies

2.3.1 Introduction

Four cases presenting practical examples of synthetic processes of an active drug substance are considered for the discussion on starting material and active pharmaceutical ingredient.

For clarity, some definitions, and technical and scientific concepts are included as an introduction to the case studies presented.

Definitions:

Medicinal product:

- Any substance which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (*in Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, as amended*).

Well-established use:

- Per definition, and according to the Directive 2001/83 of the European Parliament and of the Council of 6 November 2001, as amended, an active substance for which is recognised well-established medicinal use is a substance commercialised within the Community for at least ten years, with recognised efficacy and an acceptable level of safety.

New active pharmaceutical ingredient / new active drug substance / new drug substance / new active substance:

- The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be complex, simple ester, or salt of a previously approved drug substance.^{(2),(5)}

Starting material:

- A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structured;⁽²⁾
- A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.⁽⁶⁾

Impurity:

- Any component of the new drug substance that is not the chemical entity defined as the new drug substance;^{(2),(5)}
- Any component present in the intermediate or API that is not the desired entity;⁽⁶⁾
- Any component of the drug substance that is not the drug substance.⁽³⁾

Identified impurity:

- An impurity for which a structural characterisation has been achieved.^{(2),(5)}

⁽²⁾ Definitions from ICHQ3A(R2) (replaced by guideline EMA/454576/2016)

⁽³⁾ Definitions from ICHM7

⁽⁵⁾ Definitions from ICHQ6A

⁽⁶⁾ Definitions from ICHQ7

Unidentified impurity:

- An impurity for which a structural characterisation has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time);⁽²⁾
- An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).⁽⁵⁾

Specified impurity:

- An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified;⁽²⁾
- An identified or unidentified impurity that is selected for inclusion in the new drug substance and is individually listed and limited in order to assure the quality of the new drug substance.⁽⁵⁾

Unspecified impurity:

- An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug substance specification.⁽²⁾

Potential impurity:

- An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance.⁽²⁾

Impurity profile:

- A description of the identified and unidentified impurities present in a new drug substance;⁽²⁾
- A description of the identified and unidentified impurities present in an API.⁽⁶⁾

⁽²⁾ Definitions from ICHQ3A(R2) (replaced by guideline EMA/454576/2016)

⁽⁵⁾ Definitions from ICHQ6A

⁽⁶⁾ Definitions from ICHQ7

Reagent: A substance other than a starting material, intermediate or solvent that is used in the manufacture of a new drug substance.^{(2),(5)}

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance^{(2),(5)}; An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API⁽⁶⁾.

Degradation products: An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system⁽⁴⁾

Degradation product: A molecule resulting from a chemical change in the drug substance brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system⁽³⁾.

Intermediate: A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance⁽²⁾; A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated⁽⁶⁾.

Heavy metals: Refer to (1) transition elements; (2) rare earth elements, which can be subdivided into the lanthanides and the actinides, including La and Ac themselves; (3) a heterogeneous group including the metal Bi, the elements that form amphoteric oxides (Al, Ga, In, Tl, Sn, Pb, Sb and Po), and the metalloids Ge, As and Te⁽⁷⁾.

DNA-reactive: The potential to induce direct DNA damage through chemical reaction with DNA⁽³⁾

⁽²⁾ Definitions from ICHQ3A(R2) (replaced by guideline EMA/454576/2016)

⁽³⁾ Definitions from ICHM7

⁽⁴⁾ Definitions from ICHQ3B

⁽⁵⁾ Definitions from ICHQ6A

⁽⁶⁾ Definitions from ICHQ7

⁽⁷⁾ Klaus-J. Appenroth, Definition of “Heavy Metals” and Their Role in Biological Systems, October 2009

Concepts

Impurities

The impurity profile of an active substance is one of the main quality attributes of an active pharmaceutical ingredient (API) that can impact the safety profile of a medicine. The establishment of an appropriate impurity profile of the API is expected by the Regulatory Authorities. While ICH Q3A(R2): Impurities in New Drug Substances provides guidance for qualification and control for most of the impurities, the recent guideline, that came into effect in January 2016, ICH Guideline M7 provides a practical framework for identification, categorisation, qualification and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. It is a complement to guideline ICH Q3A(R2) outlining recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to stand in final API, taking into consideration the intended conditions of human use.

The classification of impurities is described in Table 16.

Table 16: Classification of impurities

Categories	Origin	Identification	Types
Organic	Process-and drug related	Identified or unidentified	Starting materials
			By-Products
			Intermediates
			Degradation products
			Reagents, ligands and catalysts
Inorganic impurities	Process related	Known and identified	Reagents, ligand and catalysts
			Heavy metals or other residual metals
			Inorganic salts
			Other materials (e.g., filter aids, charcoal)

Categories	Origin	Identification	Types
Residual solvents	Process related	Known toxicity	Inorganic liquids
			Organic liquids

Note: the information included is according to the ICH Q3A(R2)

The specifications for a new active pharmaceutical ingredient should include, where applicable, the impurities listed as:

- a) Organic Impurities, that are specified as:
 - i. Each specified identified impurity
 - ii. Each specified unidentified impurity
 - iii. Any unspecified impurity with an acceptance criterion of not more than the identification threshold (e.g. a limit above which an impurity should be identified)
 - iv. Total impurities
- b) Residual solvents
- c) Inorganic impurities

To support the discussion of the regulatory aspects for the selection of a starting material for the synthetic process of an active pharmaceutical ingredient, its characterisation and impact on the quality of medicinal products four case studies are considered. Due to intellectual property matters some detailed aspects of the four cases are omitted. Nevertheless, the non-disclosure of that detailed information is considered not relevant for the aim of the analysis of the regulatory aspects.

[Case Study I](#) describes a 6-step process, five of them being considered chemical steps and one a physical step. The starting material is an active substance of well-established use and having a Ph.Eur. monograph. [Case Study II](#) is a 3-step synthetic process using two chemical steps and one physical step. The starting material is an active substance of well-established use, and worldwide marketed as a generic medicine for several years now. In [case study III](#), the starting material is a chemical substance commercially available but not marketed as a medicine. The synthetic process described in case study III is a five-step process that includes three chemical steps, one purification step and one

physical step. [Case Study IV](#) is a 3-step synthetic process using two chemical steps and one physical step. The starting material is an active substance of well-established use, with a recent Ph.Eur. monograph and worldwide marketed as a generic medicine.

The first three cases were already assessed by different Regulatory bodies, including FDA and/or EMA. Case Study IV has not for the time being made part of any application to a Regulatory Authority.

To be able to fit the discussion of the cases presented with the regulatory requirements over time, the Table 17 illustrates the date of submission to the European Medicines Agency and the number of steps of the synthetic process in each case.

Table 17: Case studies and synthetic process

Case studies	Number of steps	Type of step	Year of submission
Case Study I	6-steps	5-chemical steps	2008
		1-physical step	
Case Study II	3-steps	2 chemical steps	2011
		1-physical step	
Case Study III	5-steps	3-chemical step	2011
		1-purification step	
		1-physical step	
Case Study IV	3-steps	2 chemical steps	NA
		1-physical step	

All the cases are referring to the new active drug substance, an antiepileptic drug, eslicarbazepine acetate. The active substance (API), eslicarbazepine acetate is chemically designated as (S)-10-Acetoxy-10,11-dihydro-5Hdibenz[b,f]azepine- 5-carboxamide and has the following structure (Figure 16):

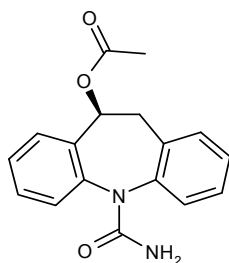


Figure16: Structure of eslicarbazepine acetate

Eslicarbazepine acetate was first approved as medicinal product in April 2009 in Europe.

Hereinafter, eslicarbazepine acetate is designated as “active substance” or “API”.

The description of each case study is in the overleaf pages and includes:

- Regulatory status
- Starting material
- Considerations – synthetic process and control strategy
- Description of main steps of the synthetic process
- Specifications and impurities
- Impact on the company activity

2.3.2 Case Study I

2.3.2.1 *Regulatory status*

An initial application by centralised procedure was submitted to the European Medicines Agency (EMA) in 2008 for a medicine having eslicarbazepine acetate as active substance (API). The synthetic process described is approved.

2.3.2.2 *Starting material*

The starting material is a well-established active pharmaceutical ingredient, commercially available and duly characterised. The name and address of the supplier is known. No flow chart describing the synthetic process of the starting material was provided.

Appropriate specifications for starting material were also established, analytical methods described and non-compendia analytical methods suitably validated, for the described process.

2.3.2.3 *Considerations – synthetic process and control strategy*

The synthesis of the API as described in the initial application consists of five chemical steps followed by a micronisation step (physical step). The process had been adequately described in the documentation submitted to the Authority, critical steps and in-process controls had been defined to ensure quality of the final compound. The in-process controls were established based on the experience gained in laboratory development work and manufacturing and are suitable to control the reaction progress. The end-products of each of the synthesis steps 1 to 4 are defined as intermediates, and appropriate specifications have been also established. The analytical methods used to control the key intermediates were provided and the non-compendia methods were suitably validated.

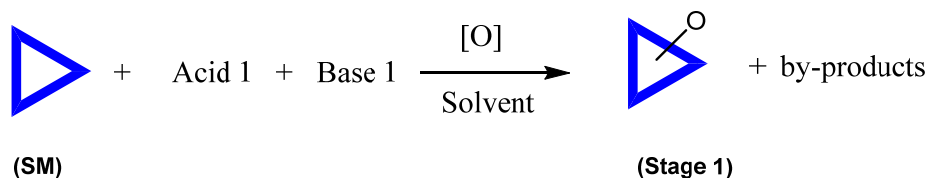
2.3.2.4 *Description of main steps of the synthetic process*

The main steps of the synthetic process are described and pictured below:

Step 1 – Epoxidation (chemical step)

The starting material is converted to an epoxide. After crystallisation and washing, the epoxide is used in the next stage and is defined as an intermediate in the synthetic process.

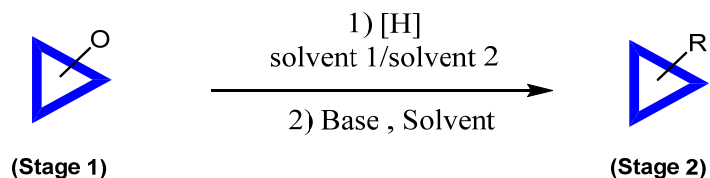
Reaction for step 1



Step 2 – Hydrogenation (chemical step)

The epoxide is reduced under hydrogenation conditions to the racemic alcohol. In Process controls (IPCs) are performed to reconfirm complete conversion of the epoxide to the racemic alcohol. The racemic alcohol is used in the next step and defined as a key intermediate.

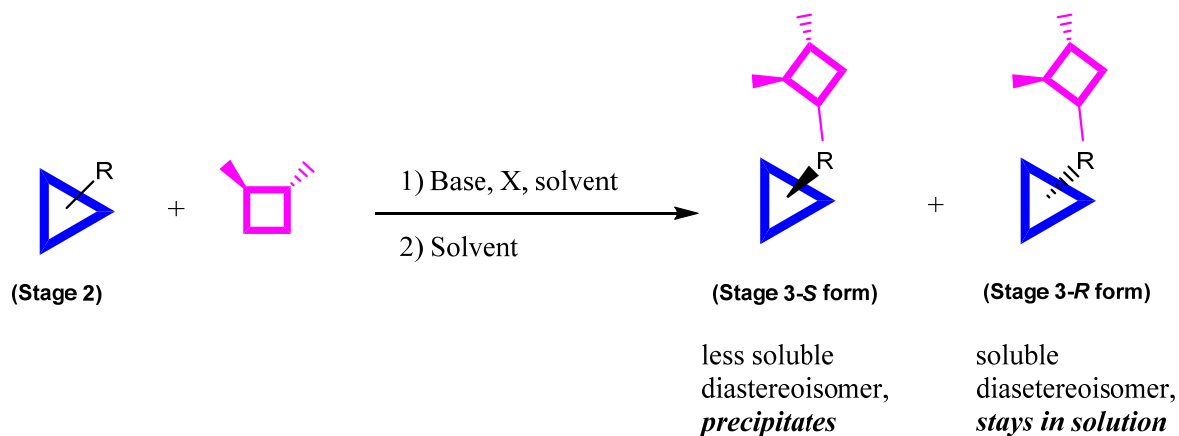
Reaction for step 2



Step 3 – Diastereomeric esterification (chemical step)

In the third step, the racemic alcohol is reacted to obtain a mixture of diastereomeric esters. Whilst the unwanted (R)-diastereomer remains in solution, the (S)-diastereomer is precipitated and used in the next stage. The (S)-diastereomer is defined as an intermediate.

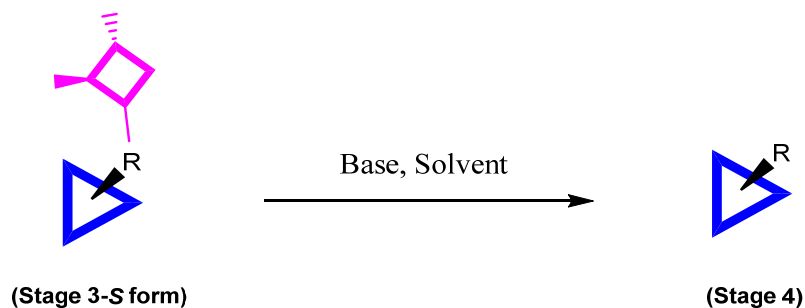
Reaction for step 3



Step 4 – Saponification (chemical step)

In step four, the precipitated (S)-diastereomer is hydrolysed to release the optically enriched (S)-alcohol. An IPC is performed to ensure adequate conversion of the (S)-diastereomer to the (S)-alcohol. The (S)-alcohol is defined as a key intermediate.

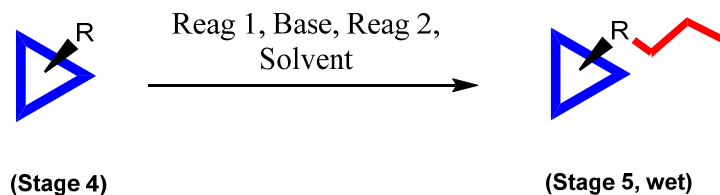
Reaction for step 4



Step 5 – Acetylation (chemical step)

In step five, the (S)-alcohol is acetylated. An IPC is performed to confirm adequate conversion of the (S)-alcohol to the ester (eslicarbazepine acetate).

Reaction for step 5



Step 6 – Milling (physical step)

At this step, the active substance is micronised according to the specifications defined for the particle size and particles size distribution.

2.3.2.5 Specifications and Impurities

Eslicarbazepine acetate drug substance has been sufficiently characterised by numerous analytical techniques, its structure has been adequately elucidated. The potential impurities, by products of the synthesis and degradation products, have been discussed in detail. The limits proposed for specified related substances are the qualification thresholds.

The drug substance specification includes:

- tests for appearance,
- particle size distribution (laser diffraction),
- identification (IR and HPLC),
- assay (HPLC),
- purity, including enantiomeric purity (HPLC),
- water content (Karl-Fisher),
- melting point,
- residue on ignition,
- heavy metals,
- residual solvents (GC),
- microbial purity,
- and sulphated ash, as per ICH Q6A Guideline.

Residual solvents and heavy metals are routinely controlled according to the applicable Guidelines (ICH Q3A and Q3C).

All non-compendial analytical methods have been validated according to the ICH Q2 Guideline. The HPLC methods for assay and purity have been validated for:

- specificity (selectivity),
- linearity,
- accuracy,
- precision (system precision, analysis repeatability, intermediate precision),
- recovery,
- limit of detection (LOD),
- limit of quantification (LOQ),
- stability of solutions,
- and robustness.

Forced degradation studies with eslicarbazepine acetate were performed under several stress conditions e.g. by treatment with heat, under acidic and alkaline conditions as well as under oxidizing conditions to justify the specificity of the method for purity.

The GC method for residual solvents has been validated regarding:

- specificity (selectivity),
- linearity,
- accuracy,
- precision (system precision, analysis repeatability, intermediate precision),
- limit of detection (LOD),
- limit of quantification (LOQ),
- stability of solutions,
- and robustness.

Suitable validation data for the water determination (Karl-Fischer) and the particle size test method have also been provided.

Batch analysis data on 6 batches of eslicarbazepine acetate has been provided. All results were within specifications and showed batch-to-batch consistency.

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in relation to their origin and potential carryover into the final drug substance. Assessment of the potential impurities was based on the chemical structures and purity of the starting materials and intermediates, as well as the chemical reactions involved in the production process.

Standards of the potential impurities were purchased or synthesised for test purposes and characterised in terms of chemical structure by:

- ^1H and ^{13}C NMR spectroscopy,
- IR and UV spectroscopy and
- elemental analysis.

Validated analytical methods have been developed for the assay and purity determination of eslicarbazepine acetate drug substance to allow for determination of each potential impurity. Potential impurities which theoretically could arise have not been detected in batch samples of drug substance and therefore are not included in the specifications for eslicarbazepine acetate drug substance.

Testing of several batches of eslicarbazepine acetate drug substance for heavy metal levels gave results that were consistently below the limit of detection. So, justification exists for the non-inclusion of these metals in the drug substance specifications.

Routine testing of several batches of eslicarbazepine acetate drug substance for other process-related solvents have shown that these solvents are consistently below the limit of detection. Accordingly, justification exists for the non-inclusion of these solvents in the drug substance specifications.

The impurity level of eslicarbazepine acetate was established considering chemical and non-clinical work.

The quality profile of eslicarbazepine acetate has been correctly established.

2.3.2.6 Impact on the company activity

In summary;

- the use of the starting material was duly justified, corresponding to an active substance authorised in Europe as of well-established use medicine;
- the synthesis of eslicarbazepine acetate consists of five chemical steps;

- the applicant defined appropriate specifications for the starting material, intermediates and drug substance, and the analytical methods were suitably validated;
- discussion on the potential impurities was presented;

During the assessment procedure, the Authority requested more details about the starting material origin and synthetic pathway. The available Certificate from European Pharmacopeia (CEP) for the starting material was provided to EMA during the assessment.

The requests from the Authority resulted in a more complex dossier with impact on the activity of the company. The detail and complexity of a dossier can increase the number of post-approval variations to be submitted, increase in costs, delays in the approval, limitation to one single starting material manufacturer and increase the probability of shortage. The impact on the activity of the company is summarised in table 18.

Table 18: Impact on the company activity

Impact
- increased number of potential post-approval variations to be submitted; - higher costs (potential increase of SM cost; fees to Authorities); - impact on timelines for API use; - restricted to one starting material manufacturer (business continuity plan); - increased odds for a shortage.

2.3.3 Case Study II

2.3.3.1 *Regulatory status*

In 2011, two years after the initial approval, a new manufacturer for eslicarbazepine acetate using a substantially different route of synthesis was submitted to the assessment of the EMA. According to the regulations, this is considered a major variation and should include as documentation of support a quality overall summary (expert's assessment) and detailed information in Module 3 – Chemical and Pharmaceutical Documentation.

2.3.3.2 *Starting material*

The starting material proposed consists in a well-established compound marketed worldwide as a well-established use medicine. No Certificate of European Pharmacopeia (CEP) or monograph of European Pharmacopeia was available at that time. The synthetic process proposed for eslicarbazepine acetate using the well-known active substance, involves two chemical steps. It proceeds through the final intermediate eslicarbazepine - to eslicarbazepine acetate. Additionally, it was possible to establish specifications for the starting material aligned with a set of specifications characteristic of an API and demonstrate the GMP grade for the synthesis of such starting material. Analytical results for the starting material were presented for 39 batches demonstrating the consistency of the starting material quality.

2.3.3.3 *Considerations – synthetic process and control strategy*

The new synthetic process consists of 2 chemical steps, a stereoselective asymmetric transfer hydrogenation of the starting material followed by the acetylation of eslicarbazepine to obtain eslicarbazepine acetate and a physical step (micronisation). The two steps of manufacture process of eslicarbazepine acetate include in-process controls, as appropriate, to ensure the suitability of the process materials throughout the synthesis. The analytical methods used to control the key intermediates were provided and the non-compendia methods were suitably validated.

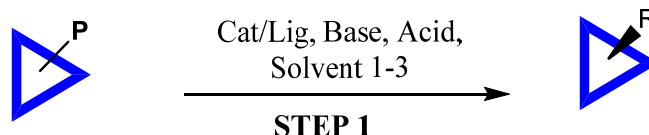
2.3.3.4 *Description of main steps of the synthetic process*

The main steps of the synthetic process are presented below:

Step 1 – Asymmetric hydrogenation (chemical step)

The starting material, reagents and catalyst are added to form eslicarbazepine. The reaction is monitored by IPC to ascertain the degree of conversion.

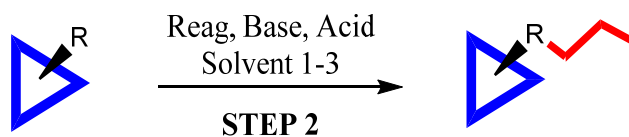
Reaction for step 1



Step 2 – Acetylation (chemical step)

Eslicarbazepine and reagents are charged into a vessel and eslicarbazepine acetate is isolated.

Reaction for step 2



Step 3 – Milling (physical step)

At this step, the active substance is micronised according to the specifications defined for the particle size and particles size distribution.

2.3.3.5 Specifications and impurities

The characterisation of the drug substance was part of the initial application, as per [case study I](#), and the information is applicable to the process described in this case. The potential impurities, by-products of the synthesis and degradation products have been discussed in detail.

The specifications of eslicarbazepine acetate were established according to the standards.

As for case study 1, the drug substance specification includes tests for appearance, particle size distribution (laser diffraction), identification (IR and HPLC), assay (HPLC), purity, including enantiomeric purity (HPLC), water content (Karl-Fisher), melting point, residue on ignition, heavy metals, residual solvents (GC), microbial purity and sulphated ash, as per ICH Q6A Guideline. Residual solvents and heavy metals are routinely controlled according to the applicable Guidelines (ICH Q3A and Q3C). All non-compendia analytical methods have been validated according to the ICH Q2 Guideline.

An assessment of the potential impurities that could be present in eslicarbazepine acetate was based on the chemical structures and purity of the starting materials, catalyst and intermediates, as well as the chemical reactions involved in the synthetic process. Standards of the potential impurities were purchased, synthesised or isolated by preparative chromatography for test purposes and characterised in terms of chemical structure by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy and UV spectroscopy. Specifications for the organic impurities, mainly unknown, and for the sum of known and unknown impurities) were set. All the organic impurities were studied and the corresponding maximum levels were established, either those impurities resulting from the synthesis or those originating from degradation.

Inorganic impurities were specified (heavy metals) in eslicarbazepine acetate as also residual solvents. The inorganic impurities are present in acceptable levels as well as the residual solvents.

The general characteristics of API from both manufacturers and synthetic routes (6-step method, described in [case study I](#) versus 3-step method, described in [case study II](#)) are aligned. The specifications of ESL manufactured by both synthetic processes are the same, except for the residual solvents and impurities specific of each process.

2.3.3.6 Impact on the company activity

In summary;

- the use of the starting material was duly justified, corresponding to an active substance authorised in Europe and marketed as medicine of well-established use;
- the applicant defined appropriate specifications for the starting material, intermediates and drug substance, and the analytical methods were suitably validated;
- the synthetic process consists of 2-chemical steps
- discussion on the potential impurities was presented;

During the assessment of the regulatory procedure, the Authority requested for the redefinition of the starting material justifying that 2-steps are not enough to guarantee process purging capability for the impurities and more cGMP steps should be added.

This fact had a negative impact on the company activity. A considerable delay for the availability of the API and increase of costs for the manufacturing process were two of the major aspects. A summary of the impact on the company activity is described in table 19.

Table 19: Impact on the company activity

Impact
- reassessment of the synthetic process to confirm which qualified SM manufacturer comply with GMP in the previous steps; - identification of the starting material to be proposed, assessing if it is adequate to be selected as redefined SM; - impact on the business continuity plan since the approval of the alternative API manufacturer was on hold and consequently delayed; - increase of costs (more steps under GMP; fees to Authorities).

2.3.4 Case Study III

2.3.4.1 Regulatory status

As a consequence of the assessment of the regulatory procedure described in [case study II](#), a redefinition of the starting material was requested. A new application was submitted in 2011.

2.3.4.2 Starting material

The starting material redefined is well characterised (chemically and structurally) and appropriate specifications were defined. It is commercially available.

Appropriate specifications for the starting material were established, stability data provided as well brief description of the synthetic process of the starting material proposed.

2.3.4.3 Considerations – synthetic process and control strategy

The use of the redefined starting material added three additional steps, carried out under cGMP, to the synthetic process of eslicarbazepine acetate initially proposed and as described in case study II. The synthetic process involves four chemical steps and one purification step to obtain eslicarbazepine acetate.

The steps of manufacture of eslicarbazepine acetate include in-process controls, as appropriate, to ensure the suitability of the process materials throughout the synthesis. The process steps were discussed in terms of the chemical reaction and summarising the in-process controls and the step-by-step manufacturing description. The analytical methods used to control the key intermediates were provided and the non-compendia methods were adequately validated.

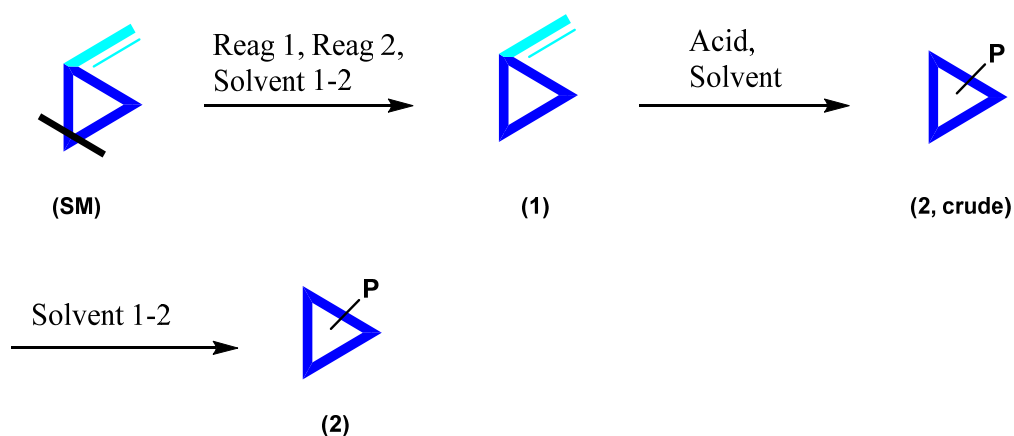
2.3.4.4 Description of main steps of the synthetic process

Below, a description of the synthetic process is included:

Step 1: Ammonisation and hydrolysis (chemical step)

The first step consists in the synthesis of a crude from the starting material.

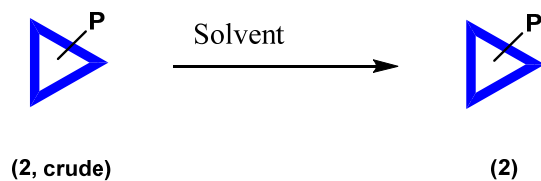
Reaction for step 1



Step 2: Crystallisation [chemical step]

The crude obtained in the first step is dissolved. The solution is then filtered and cooled down to getting the crystals.

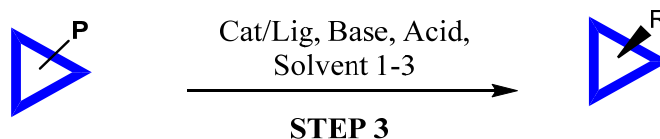
Reaction for step 2



Step 3: Asymmetric hydrogenation (chemical step)

The product obtained in the second step and reagents are charged to the vessel. The reaction is monitored by in-process control to ascertain the degree of conversion. When the conversion is complete, the solvent is removed.

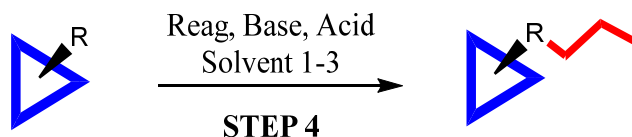
Reaction for step 3



Step 4: Acetylation (chemical step)

Eslicarbazepine, the intermediate resulting from step 3 and reagents are charged into a vessel. Finally, eslicarbazepine acetate, the API, is isolated.

Reaction for step 4



Step 5 – Milling (physical step)

At this step, the active substance is micronised according to the specifications defined for the particle size and particle size distribution.

2.3.4.5 Specifications and impurities

The drug substance resulting from the synthetic process described above presented the same general characteristics of the API synthesized by the synthetic process described in case studies I and II. The specifications are the same when compared to the API that results from synthetic process described in case study I, except for the residual solvents and impurities specific of each process.

The potential impurities which could be present in eslicarbazepine acetate were reassessed based on the redefinition of the starting material, but no change of the impurity profile was identified. The specifications defined for eslicarbazepine acetate remain unchanged.

2.3.4.6 Impact on the company activity

The redefinition of starting material which consisted in adding more 3 steps conducted under GMP, when compared to the synthetic process depicted in [case Study II](#), had as a direct consequence the increase of cost of goods. It will increase the complexity of the dossier by describing in more detail the synthetic process. The supply chain will be more complex and the redefinition of the starting material will impact the timelines to implement the alternative API manufacturer. In table 20 it is highlighted some of the more relevant aspects that impact negatively on the company activity:

Table 20: Impact on the company activity

Impact
- increased complexity/timelines to manufacture the API (in process-control, quality systems in place); - manufacturing chain/quality system more complex (additional audits, and quality agreements, qualified person declarations); - more demanding from a regulatory point of view (increased number of file variations, change control and compliance); - waste of the API manufactured before redefinition of the starting material; - synthetic process – higher costs - impact on the business continuity plan (the alternative API manufacturer took more time to be approved than planned);

2.3.5 Case study IV

2.3.5.1 *Regulatory status*

The case described were not yet submitted to any Regulatory Authority. It is similar to [case study II](#).

2.3.5.2 *Starting material*

The starting material proposed for the synthetic process consists in a well-established compound marketed worldwide as a well-established use medicine. A Certificate of European Pharmacopeia (CEP) was made recently available. The starting material proposed is considered an intermediate in the process described in case study III. The specifications established for the starting material are aligned with a set of specifications characteristic of an API. The synthesis of such starting material is performed according to the GMP requisites. Analytical results for the starting material are available for several batches demonstrating the consistency of the starting material quality.

2.3.5.3 *Considerations – synthetic process and control strategy*

The synthetic process consists of 3 steps: 2 chemical steps consisting in a stereoselective asymmetric transfer hydrogenation of the starting material followed by the acetylation of eslicarbazepine, and a physical step, micronisation. The in-process controls were established based in the experience gained and are the same as described in case study II and in [case study III](#) if considered the last 3 chemical steps.

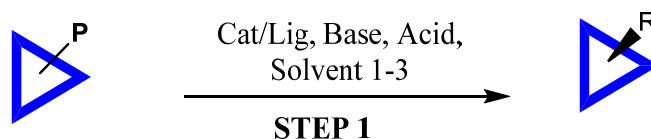
2.3.5.4 *Description of main steps of the synthetic process*

The main steps of the synthetic process are described below:

Step 1 – Asymmetric hydrogenation (chemical step)

The starting material, reagents and catalyst are added to form eslicarbazepine. The reaction is monitored by IPC to ascertain the degree of conversion.

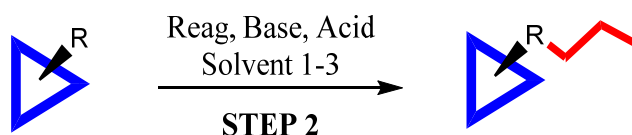
Reaction for step 1



Step 2 – Acetylation (chemical step)

Eslicarbazepine and reagents are charged into a vessel and eslicarbazepine acetate is isolated.

Reaction for step 2



Step 3 – Milling (physical step)

At this step, the active substance is micronised according to the specifications defined for the particle size and particle size distribution.

2.3.5.5 Specifications and impurities

An assessment of the potential impurities that could be present in eslicarbazepine acetate, will always be based on the chemical structures and purity of the starting materials, catalyst and intermediates, as well as on the chemical reactions involved in the synthetic process.

Standards of the potential impurities were purchased, synthesised or isolated by preparative chromatography for test purposes and characterised in terms of chemical structure by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy and UV spectroscopy. Specifications for the organic impurities, mainly unknown, and for the sum of known and unknown impurities) were set. All the organic impurities were studied and the corresponding maximum levels were established, either those impurities resulting from the synthesis or those originated from degradation.

Inorganic impurities were specified (heavy metals) in eslicarbazepine acetate as also residual solvents. The inorganic impurities are present in acceptable levels as well as the residual solvents.

The specifications of eslicarbazepine acetate were established according to the standards and are consistent with the set of specifications currently approved at the EMA

2.3.5.6 Impact on the company activity

The proposed starting material, that is considered an intermediate in [case study III](#) is of pharmaceutical grade quality, manufactured under GMP conditions. A CEP was recently issued by the European Pharmacopeia.

Assuming that an application to register this process is well succeeded, the complexity of the dossier, the control activities under responsibility of the applicant, as well as the number of post-approval variations that may need to be submitted will be less.

The table 21 highlights some of the most important aspects of the impact on the company activity.

Table 21: Impact on the company activity

Impact
- reduction of quality control activities under responsibility of the company; - assurance of quality of the starting material based on the “control” of an Authority (European Pharmacopeia); - decrease of costs of API; - decreased risk of shortage; - use of starting material of pharmaceutical ingredient quality.

3 Discussion

3 Discussion

3.1 Introduction

The purpose of this chapter is to discuss and evaluate, from a regulatory point of view, whether a specific synthetic process is approvable by a competent Regulatory Authority. The analysis is performed to synthetic routes described in the literature for three active pharmaceutical ingredients (eslicarbazepine acetate, lacosamide and retigabine) ([2.2. Cases described in the literature](#)) and for four case studies (practical examples) ([2.3 Case studies](#)).

To contextualise the discussion, the definitions and technical and scientific concepts previously mentioned in chapter [2.3.1 Case studies – Introduction](#) should be considered.

3.2 Cases described in the literature

3.2.1 Introduction

As mentioned in [2.2.1 Cases described in the literature - Introduction](#), four active pharmaceutical ingredients (API) were selected: *eslicarbazepine acetate*, *lacosamide*, *retigabine* and *zonisamide*. In case of zonisamide no relevant literature references were found, so it will not be conducted any analysis for this API. The discussion is then presented for the other APIs.

Considering that none of the synthetic routes described for the different APIs is providing information:

- on impurities and their carryover, at least in a satisfactory detail that allows a thorough assessment;

or

- on a control strategy,

the discussion for the different cases considers only two regulatory aspects:

- starting material designated;

and

- description of synthetic process - number and type (chemical or physical) of steps of the synthetic process.

Even taking in account that two aspects can be insufficient to conduct a proper and complete regulatory analysis, it was decided to conduct it just considering the available information.

The legislation and guidelines that are supporting the analysis and discussion were previously referred in [1.2 Introduction – Guidelines and legislation](#). For the cases described in the literature it was decided to consider the most recent guidelines since the intention is to conduct the assessment following the current scientific and regulatory knowledge. In that way, the one selected are summarised in [table 22](#).

Table 22: List of Legislation and Guidelines

Reference	Description	Date for coming into effect
EMA/CHMP/ICH/425213/2011 (ICH Q11)	On development and manufacture of drug substances (chemical entities and biotechnological/biological entities.	November 2012
Ares(2014)2674284	The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials.	September 2014
EMA/454576/2016	Guideline on the chemistry of active substances.	15 November 2016 ^(a)
EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1	Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances.	December 2016

^(a)(publication date) (date for coming into effect: 6 months after publication)

Hereinafter is presented the summary of the search conducted for each API and the discussion, focused on the starting material designated and the description of synthetic process.

3.2.2 Eslicarbazepine acetate

The results of the search conducted are summarised below.

Reference	Number of steps	Type of step	Starting material	Year of publication
Liu K-CK, <i>et al.</i>	2-steps	2-chemical steps	Oxcarbazepine	2011
Ravinder B, <i>et al.</i>	4-steps	4-chemical steps	10-methoxy-5 <i>H</i> -dibenzo[b,f]azepine	2013

The discussion, and as mentioned before, is about two aspects – the starting material designated and the description of synthetic process (number of steps).

3.2.2.1 Liu K-CK, Sakya MS, O'Donnell JC, Flick CA, Li Jin. *Synthetic approaches to the 2009 new drugs*. *Bioorg Med Chem* 2011; 19: 1136-1154.

3.2.2.1.1 Starting material designated

The starting material proposed by [Liu K-CK, et al., 2011](#) in a 2-step synthetic process, is oxcarbazepine.

Considering the principles of [ICH Q11](#) guideline, the aspects from a) to d) are outlined to justify oxcarbazepine as starting material. These aspects are also mentioned in the Guideline on the chemistry of active substances (EMA/454576/2016) as information to be provided in section Control of Materials (3.2.S.2.3) of the regulatory dossier to be submitted to a relevant Regulatory Authority.

a) A starting material should be a substance of defined chemical properties and structure

Oxcarbazepine is a well-known active substance, described in the literature and used as API itself. In that way is complying with the requisite.

b) The starting material is incorporated as a significant structural fragment

Comparing the chemical structure of the starting material proposed, oxcarbazepine, (Figure 17) and the final API, eslicarbazepine acetate (Figure 18), the requirement can be considered fulfilled.

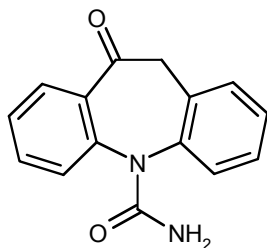


Figure 17: Oxcarbazepine

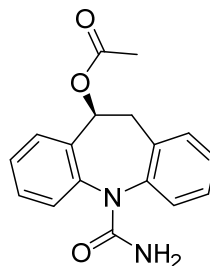


Figure 18: Eslicarbazepine acetate

According to the recent reflection paper ([EMA/CHMP/CVMP/QWP/826771/2016](#)) further justification may need to be included since oxcarbazepine can be considered as a “late intermediate” and the argument claimed can be applied to any intermediate in the manufacturing process.

c) Schematic synthetic process prior to the starting material may be useful

The information is not available, therefore in the perspective of [ICH Q11](#) it may not allow an adequate assessment of the suitability of starting material and its specification.

d) Complete specification of the starting material should be provided, including impurity profile

No information is provided, but it can be assumed that it is possible to get oxcarbazepine with a set of complete specifications, including impurity profile.

3.2.2.1.2 Description of synthetic process (number of steps)

The synthetic process described consists of 2-chemical steps: a reduction of oxcarbazepine followed by esterification. A crystallisation and filtration are mentioned (purification steps).

According to the Guideline on the chemistry of active substances (EMA/454576/2016), the description of the process and the scheme of the synthesis should include all the steps of the process. It is also mentioned that typically, multiple chemical transformation steps should separate the starting material from the final API. In the same way, the ICH Q11 determines that the Regulatory Authorities, expect a “commensurately high level of process understanding and control”. Even considering that the authors do not refer to a control strategy or provide enough detail concerning fate and purging capabilities of the process, it is not expected that it will be approvable. Short synthetic routes are not normally accepted by the Authority.

3.2.2.1.3 Conclusion

From the general principles recommended by the ICH Q11 guideline for the selection/designation of starting material only two were cumulatively verified – oxcarbazepine is a substance of defined chemical properties and structure and is incorporated as a significant structural fragment into the structure of the API. In that perspective, it will be difficult to justify that oxcarbazepine can be selected as starting material. The synthetic process described by the authors consists only of 2-chemical steps: a reduction of the starting material followed by esterification. According to the reflection paper recently published by the EMA on the requirements for selection and justification of starting materials ([EMA/CHMP/CVMP/QWP/826771/2016 Corr.1](#)) the possibility to propose a short synthetic process exists but that should be for clear scientific reasons. In that case, the Regulatory Authority is expecting that the applicant demonstrates that the steps of the synthetic process of the starting material are not critical

to the quality of the active substance. In any case, none of the steps described for the synthesis of eslicarbazepine acetate are purification steps (e.g. crystallisation, washing, etc). Ultimately, and despite oxcarbazepine is an API itself, the Regulatory Authority can consider oxcarbazepine as a “late intermediate”.

There is no additional information provided in the publication, namely about a control strategy, capability of purging of the synthetic process, synthetic process of the starting material, specifications of starting material, that helps to justify the selection of the starting material and a short synthetic process. It is unlikely, that the current process be well succeeded in regulatory terms.

3.2.2.2 Ravinder B, Reddy RS, Sridhar M, Mohan MM, Srinivas K, Reddy PA, et al. An efficient synthesis for eslicarbazepine acetate, oxcarbazepine and carbamazepine. Tetrahedron Lett 2013; 54: 2841-2844.

3.2.2.2.1 Starting material designated

In the example provided by [Ravinder B, et al., 2013](#) the starting material selected is 10-methoxy-5*H*-dibenzo[*b,f*]azepine, a chemical compound commercially available.

To discuss the justification for the starting material selected, the aspects from a) to d), as per the guidelines ICH Q11 and EMA/454576/2016, are considered.

a) A starting material should be a substance of defined chemical properties and structure

The 10-methoxy-5*H*-dibenzo[*b,f*]azepine is a chemical compound (CAS number 4698-11-7), commercially available. In that way, the requisite is fulfilled.

b) The starting material is incorporated as a significant structural fragment

Eslicarbazepine acetate is chemically designated as (S)-10-acetoxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carboxamide. It can be considered that the starting material having the chemical group “5*H*-dibenz[*b,f*]azepine” is incorporated as a significant structural fragment of the API.

c) Schematic synthetic process prior to the starting material may be useful

The information is not available, therefore in the perspective of ICH Q11 guideline, it may not allow an adequate assessment of the suitability of starting material and its specification.

d) Complete specification of the starting material should be provided, including impurity profile

No information is provided, but it can be assumed that it is possible to get that information from the manufacturer. The compound is described in the literature.

3.2.2.2.2 Description of synthetic process (number of steps)

The synthetic process described consists of 4-chemical steps: de-methylation, reduction, acetylation and urea formation. Information about reagents and reaction conditions is provided. No purification steps are mentioned. The expectation from the Regulatory Authorities, captured in the guidelines EMA/454576/2016 and ICH Q11, is that the applicant submits a synthetic process with multiple chemical transformation steps so that the generation, fate and control of impurities can be understood. In that way, the

information provided by [Ravinder B, et al., 2013](#) is not detailed enough to allow a conclusion about the feasibility of an approval of the synthetic process by a competent Regulatory Authority.

3.2.2.2.3 Conclusion

From a technical point of view, as mentioned by Ravinder B, *et al.*, 2013 the synthetic process is viable and efficient. The starting material selected seems to be adequate and able to comply with the principles stated in the ICH Q11 guideline. The synthetic process described, even consisting in 4-chemical steps, may not be enough to be considered for an application to a competent Authority. From a regulatory perspective, the information provided is not enough to allow a complete analysis of the feasibility of having this synthetic process approved by a Regulatory Authority. It will be necessary to make available details for the synthesis and the specification of the starting material and to define and justify the control strategy implemented.

3.2.2.3 Comparison of the two cases

The starting material selected by [Ravinder B, et al., 2013](#) seems to have more chance to be justified when compared to oxcarbazepine, the starting material proposed by [Liu K-CK, et al., 2011](#). For both examples was only possible to verify the compliance with two of the general principles recommended by the ICH Q11 guideline for the selection of the starting material – *substance of defined chemical properties and structure* and incorporated as a significant structural fragment into the structure of the API. Additional information about the synthetic process of the starting material as well the specifications, including impurities need at least to be available to conclude the analysis. Comparing the processes described by Liu K-CK, et al., 2011. (2-chemical steps) and Ravinder B, et al., 2013 (4-chemical steps), the second one is more likely to be well succeeded from a regulatory perspective, if additional information is available, in compliance with the ICH Q11 guideline.

3.2.3 Lacosamide

The information about the number of steps and results of the search conducted are summarised below.

Reference	Number of steps	Type of step	Starting material	Year of publication
Morieux P, <i>et al.</i>	5-steps	5-chemical steps	D-serine methyl ester	2008
Wadavrao BS, <i>et al.</i>	8-steps	8-chemical steps	acrylic acid	2013
Stecko S	8-steps	8-chemical steps	ethyl L-lactate	2014
Garg Y, <i>et al.</i>	5-seps	5-chemical steps	racemic butadiene monoepoxide	2015
Aratikatla KE, <i>et al.</i>	5-steps	5-chemical steps	<i>N</i> -Boc- <i>N</i> , <i>O</i> -isopropylidene-L-serinol	2015

The discussion, as mentioned in [3.2.1 Introduction](#), is focused in two aspects – the starting material designated and the description of synthetic process (number of steps).

3.2.3.1 *Morieux P, Stables PJ, Kohn H. Synthesis and anticonvulsant activities of N-benzyl (2R)-2-acetamido-3-oxysubstituted propionamide derivatives. Bioorg Med Chem 2008; 16: 8968-8975.*

3.2.3.1.1 Starting material designated

The starting material proposed is *D*-serine methyl ester, obtained from *D*-serine methyl hydrochloride (CAS 5874-57-7), commercially available.

The aspects below, from a) to d) are stated in guideline ICH Q11 and guideline EMA/454576/2016 and are the ones to be considered to justify the selected starting material.

a) A starting material should be a substance of defined chemical properties and structure

D-serine methyl ester has defined chemical properties and structure, so the requisite is fulfilled.

b) The starting material is incorporated as a significant structural fragment

D-serine methyl ester contributes to the final molecular structure of the API, lacosamide.

c) Schematic synthetic process prior to the starting material may be useful

D-serine methyl ester can be easily obtained from *D*-serine methyl ester hydrochloride. The paper describes the synthetic route with enough detail to allow the competent Authority to evaluate the suitability of the proposed starting material.

d) Complete specification of the starting material should be provided, including impurity profile

No information is provided, but it can be assumed that is possible to provide such information. The description of the synthetic route prior to the introduction of the starting material is considerably detailed, including details of reagents, solvents and reaction conditions.

3.2.3.1.2 Description of synthetic process (number of steps)

The synthetic process reported is a five-step stereospecific synthesis. The description of the process has enough detail to allow a comprehensive assessment. A considerable number of chemical steps is included, including purification steps. That will allow the Regulatory Authorities to have a high level of process understanding.

3.2.3.1.3 Conclusion

Considering the information provided for the starting material and about the synthetic process, a positive outcome of an assessment by a competent Authority is expected. Additional information will be needed to prepare the application, such as, specifications of the starting material, impurity profile, studies of purge capability. But, considering the information already provided and analysing the general principles recommended by the ICH Q11 guideline and the type of information required for the manufacture of active substances used in a medicinal product, that is set out by the guideline EMA/454576/2016, it can be concluded that there is a high probability of a well-succeed application.

3.2.3.2 Wadavrao BS, Narikimalli A, Narsaiah VA. *A non-infringing Route for Enantioselective Synthesis of Antiepileptic Agent Lacosamide*. *Synthesis* 2013; 45: 3383-3386.

3.2.3.2.1 Starting material designated

The starting material proposed is acrylic acid (CAS number 79-10-7). The compound is commercially available.

The aspects to be considered to justify acrylic acid as starting material are the ones mentioned below, a) to d). These aspects are according to the principles stated in ICH Q11 guideline and the type of information to be provided for the manufacture of active substance, as per the Guideline on the chemistry of active substances (EMA/45476/2016).

a) A starting material should be a substance of defined chemical properties and structure

Acrylic acid is a chemical compound with defined chemical properties and structure and it is commercially available, so the requisite is verified.

b) The starting material is incorporated as a significant structural fragment

This requisite is fulfilled. Acrylic acid is not a reagent or solvent and has defined chemical properties and structure.

c) Schematic synthetic process prior to the starting material may be useful

No information is available from the paper.

d) Complete specification of the starting material should be provided, including impurity profile

The compound is commercially available, so it is expected that complete specification and impurity profile can be provided.

3.2.3.2.2 Description of synthetic process (number of steps)

The synthetic process described consists in 8-steps using Sharpless asymmetric dihydroxylation as a key step. Considerable detail about the synthetic steps, including conditions of the reaction, reagents and solvents used, is provided. Purification steps are also described.

3.2.3.2.3 Conclusion

The Guideline on the chemistry of active substances has set out the type of information required for the manufacture that should be included in an application with a view to the

granting of a marketing authorisation for a medicinal product. According to this guideline, information from the synthetic process prior to the introduction of the starting material should be provided. In this case, the information is not provided, but it will be possible to get from the supplier of the starting material at least, information for the specifications and impurity profile, being a substance commercially available. Also, the guideline is referring that multiple chemical transformation steps should separate the starting material from the final API. The synthetic process is a quiet complex and with a considerable number of steps. The guideline ICH Q11 that describes the approaches to developing and understanding the manufacturing process of the drug substance, refers to general principles that should be followed for the selection and justification of starting material designated. Analysing such principles, it may be considered that some information is still missing to assure that an application of the synthetic process described will be well-succeeded. But, based on the detail provided so far for the synthetic process it can be concluded that there is high probability of support a successful application.

3.2.3.3 Stecko S. *Total Synthesis of Lacosamide*. J Org Chem 2014; 79: 6342-6346.

3.2.3.3.1 Starting material designated

The starting material proposed is the ethyl *L*-lactate.

a) A starting material should be a substance of defined chemical properties and structure

Ethyl *L*-lactate is a chemical compound (CAS number 687-47-8) commercially available with defined chemical properties and structure.

b) The starting material is incorporated as a significant structural fragment

Analysing the structures of ethyl *L*-lactate and lacosamide, it can be considered that the starting material designated contributes to the structure of lacosamide.

c) Schematic synthetic process prior to the starting material may be useful

It is not provided information about the synthetic process of the starting material.

d) Complete specification of the starting material should be provided, including impurity profile

The specification is not provided. Looking to the specification provided by one supplier, there was not information about impurity profile.

3.2.3.3.2 Description of synthetic process (number of steps)

The synthetic process described consists of 8-steps. The key step is stereospecific allyl cyanate-to-isocyanate rearrangement, which proceeds with chirality transfer. According to the description provided by the author some purification steps, such as washing, are included. It is a synthetic process with multiple chemical transformation steps separating the starting material from the final API. There is no information about a control strategy.

3.2.3.3.3 Conclusion

From the principles stated in the ICH Q11 guideline for the selection and justification of starting material, it was only possible to verify two of the principles – the commercial availability of the starting material and its contribution to the structure of the API.

The Guideline EMA/454576/2016 is describing the type of information that should be included in the quality part of an application to be submitted to a competent Authority with a view to the granting of a marketing authorisation for a medicinal product. Detailed information of the synthetic process should be provided, including schematic representation of the manufacturing process with chemical structures and molecular formulae of starting materials, intermediates and active substance as well as the reagents,

catalysts and solvents. The process described by [Stecko S, 2014](#) has multiple chemical transformation steps. There is a description of the process including reagents and conditions of the process. Also, purification steps are described. In that perspective, the synthetic process seems to be feasible to be included in a marketing authorisation application. The information available is not making possible to assess the formation, fate and purging capability of the process, one of the requisites stated in the ICH Q11.

In conclusion, the synthetic process described is promising and can be well succeeded from a regulatory point of view, if additional information about the starting material, namely impurity profile and synthetic process, and the purging capability of the synthetic process for the API, is available.

3.2.3.4 Garg Y, Pandey KS. **An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (R)-Lacosamide.** *J Org Chem* 2015; 80: 4201-4203.

3.2.3.4.1 Starting material designated

The starting material proposed to synthesise lacosamide is the racemic butadiene monoepoxide.

a) A starting material should be a substance of defined chemical properties and structure

Butadiene monoepoxide (3,4-Epoxy-1-butene) is commercially available (CAS number 930-22-3). It is a substance of defined chemical properties and structure.

b) The starting material is incorporated as a significant structural fragment

The butadiene monoepoxide is contributing to the final molecular structure of lacosamide.

c) Schematic synthetic process prior to the starting material may be useful

The author is mentioning that the starting material can easily be synthesised from silver-catalysed oxidation of 1,3-butadiene.

d) Complete specification of the starting material should be provided, including impurity profile

The specification of the starting material including impurity profile is not provided.

3.2.3.4.2 Description of synthetic process (number of steps)

The synthetic process is considered by the authors a short and highly efficient process (5-steps) and uses the palladium catalysed Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) as key step. A flow chart of the process is available and includes information of the reagents and conditions. Considerable detail for the description of the process is provided and several purification steps are also included.

3.2.3.4.3 Conclusion

The selected starting material seems to be adequate, but for a complete analysis more information need to be available. To be compliant with the ICH Q11, the specification and impurity profile should be provided. The synthetic process is of 5-chemical steps and includes also purification steps. No information for the purging capability of the process is provided and that information is relevant to assess the quality of the API.

From a regulatory perspective, it is not possible to conduct a thorough analysis of the feasibility of having a competent Authority approving it, but the odds are favourable.

3.2.3.5 Aratikatla KE, Bhattacharya KA. *Chiral pool approach for the synthesis of functionalized amino acids: synthesis of antiepileptic drug (R)-lacosamide*, *Tetrahedron Lett* 2015; 56: 5802-5803.

3.2.3.5.1 Starting material designated

The starting material proposed is N-Boc-N,O-isopropylidene-L-serinol. It is not commercially available.

a) A starting material should be a substance of defined chemical properties and structure

b) The starting material is incorporated as a significant structural fragment

N-Boc-N,O-isopropylidene-L-serinol is incorporated as a significant structural fragment into the structure of lacosamide.

c) Schematic synthetic process prior to the starting material may be useful

The synthetic process of the starting material is described as a four-step synthetic process starting from natural L-serine.

d) Complete specification of the starting material should be provided, including impurity profile

The information is not provided.

3.2.3.5.2 Description of synthetic process (number of steps)

The 5-chemical steps of the synthetic process are described, including reagents used and conditions of the reactions. There is no evidence of purification steps. A schematic flow chart is provided.

3.2.3.5.3 Conclusion

To assess if the starting material defined is adequate, information of the specification and impurity profile need to be available. The synthetic process prior the introduction of the starting material is of four-steps without the need of any purification of the intermediates. In that perspective, it will be critical for the justification of the starting material and for the assessment of such justification, that the description of the formation, fate and purge of impurities for the synthetic process of lacosamide is provided. The authors are referring that the synthetic process proposed is short and of high yield without the need of any kinetic resolution or the use of chiral ligands, making it commercially available. From a

regulatory point of view, if additional data is not possible to be provided, it will be difficult to register the process.

3.2.3.6 Comparison of the five cases

All the synthetic processes described are quite complex and with a considerable number of steps. Except for the last one (3.2.3.5), the description contains considerable detail for the different steps, including reagents used and conditions of the reactions. There are multiple chemical steps processes. Purification steps are also described and that information is relevant for the assessment of the feasibility, from a regulatory perspective, of the synthetic processes. The starting materials proposed for the first four cases are commercially available. There seems to be adequate. It is possible, from the information provided by the authors, to conclude that relevant principles of the guideline ICH Q11 for the selection of starting material and its justification are followed.

In conclusion, the synthetic processes provided for the first four synthetic processes described can be feasible to be proposed in an application to a competent Authority with the aim to obtain a marketing authorisation for a medicinal product, especially if additional information can be provided based on the principles of ICH Q11 guideline.

3.2.4 Retigabine

For retigabine, the information reported from the two publications selected is summarised in the table below.

Reference	Number of steps	Type of step	Starting material	Year of publication
Blackburn-Munro G, <i>et al.</i>	3-steps	3-chemical steps	2-Nitro-1,4-phenylenediamine and 4-fluorobenzaldehyde	2005
Ding XH, <i>et al.</i>	3-steps	3-chemical steps	4-fluorobenzaldehyde and 4-amino-2-nitroaniline	2013

The two aspects that are considered for the discussion, and as mentioned previously in the introduction to this chapter, are the starting material designated and the description of synthetic process (number of steps).

3.2.4.1 Blackburn-Munro G, Dalby-Brown W, Mirza NR, Mikkelsen JD, Blackburn-Munro RE. *Retigabine: Chemical Synthesis to Clinical Application*. CNS Drug Rev 2005; 11 (1): 1-20.

3.2.4.1.1 Starting material designated

The author proposes two starting materials, the 2-Nitro-1,4-phenylenediamine and the 4-fluorobenzaldehyde, in a 3-step synthetic process.

From the principles stated in the ICH Q11 guideline, the aspects from a) to d) are analysed to justify the selection of 2-Nitro-1,4-phenylenediamine and 4-fluorobenzaldehyde as starting materials.

a) A starting material should be a substance of defined chemical properties and structure

The starting material 2-Nitro-1,4-phenylenediamine is a compound commercially available (CAS number 5307-14-2). Also, the 4-fluorobenzaldehyde is commercially available (CAS number 459-57-4).

b) The starting material is incorporated as a significant structural fragment

Comparing the chemical structures of the starting materials proposed and the final API, retigabine, the starting materials are contributing significantly to the structure of the API. Since the synthetic process proposed is a 3-step synthetic process the starting materials proposed can be considered late intermediates. Other principles outlined in the ICH Q11 guideline should be used to justify the selection of the starting materials.

c) Schematic synthetic process prior to the starting material may be useful

There is no information about the synthetic process of the proposed starting materials.

d) Complete specification of the starting material should be provided, including impurity profile

The starting materials are commercially available. In that perspective, it may be possible to get the complete specification and impurity profile from the supplier.

3.2.4.1.2 Description of synthetic process (number of steps)

The synthetic process is of 3-steps. The description provided has not enough detail to allow a thorough analysis. It is mentioned the impossibility to isolate one of the intermediates. A crystallisation step is referred.

3.2.4.1.3 Conclusion

The information available is not enough to conclude about the feasibility of having a competent Authority approving the synthetic process.

3.2.4.2 Ding XH, Liu K-CK, Sakya MS, Flick CA, O'Donnell JC. *Synthetic approaches to the 2011 new drugs*. *Bioorg Med Chem* 2013; 21: 2795-2825.

3.2.4.2.1 Starting material designated

The starting materials selected are the 4-fluorobenzaldehyde and the 4-amino-2-nitroaniline (this compound corresponds to the 2-nitro-1,4-phenylenediamine). The starting materials are the same as the one proposed by Blackburn-Munro G, *et al.*, 2005 (3.2.4.1.1).

a) A starting material should be a substance of defined chemical properties and structure

Both starting materials are commercially available. The CAS number for 4-fluorobenzaldehyde is 459-57-4 and for 4-amino-2-nitroaniline is CAS number 5307-14-2.

b) The starting material is incorporated as a significant structural fragment

Comparing the chemical structures of the starting materials proposed and the final API, retigabine, the starting materials are contributing significantly to the structure of the API. Since the synthetic process proposed is a 3-step process, the starting materials proposed can be considered late intermediates. Other principles outlined in the ICH Q11 guideline should be used to justify the selection of the starting materials.

c) Schematic synthetic process prior to the starting material may be useful

It is not provided any information about the synthetic process of the starting materials.

d) Complete specification of the starting material should be provided, including impurity profile

The starting materials are commercially available. In that perspective, it may be possible to get the complete specification and impurity profile from the supplier.

3.2.4.2.2 Description of synthetic process (number of steps)

The synthetic process described is of 3-steps. It is not provided detailed information, that will allow a thorough analysis of the process and conclude about its feasibility from a regulatory point of view.

3.2.4.2.3 Conclusion

The information available is not enough to conclude about the feasibility of having an Authority approving the synthetic process.

3.2.4.3 Comparison of the two cases

The starting materials selected are the same in both processes as described by [Blackburn-Munro G, *et al.*, 2005](#) and [Ding XH, *et al.*, 2013](#) Also, the synthetic processes are similar.

Despite the starting materials are commercially available and in that perspective, the applicant does not need to justify their use as starting material, the synthetic processes as described are likely short and simple. An assessment of the feasibility of the synthetic processes to be registered would be only possible if more information is available.

3.3 Case studies

3.3.1 Introduction

It is proposed to discuss the case studies mentioned in [2.3 Case studies](#), considering the legal environment and the perspective of a regulatory affairs department for the selection of the starting material.

The legislation and guidelines considered to support the analysis were previously referred in [1.2 Introduction – Guidelines and legislation](#). For convenience and easy reference, the most relevant for the analysis are summarised in table 23.

Table 23: List of Legislation and Guidelines

Reference	Description	Date for coming into effect
3AQ5a (Note for guidance)	Chemistry of Active Substances.	October 1987 ^(a)
CPMP/ICH/4106/00 (ICH Topic Q7)	Good Manufacturing Practice for Active Pharmaceutical Ingredients.	November 2000
Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 (as amended)	Community Code Relating to Medicinal Products for Human Use.	6 November 2001 ^(b)
CPMP/QWP/130/96 Rev1	Guideline on Chemistry of New Active Substances.	February 2004 ^(a)
Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004	Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use.	31 March 2004
CHMP/QWP/297/97 Rev. 1 corr.	Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier.	1 February 2005
EMA/CHMP/ICH/24235/2006 (ICH Guideline Q9)	On quality risk management.	January 2006
PA/PH/OMCL (12) 51 3R	API Surveillance: Position Paper for OMCLs (OMCL Network of the Council of Europe, General Document.	September 2012
EMA/CHMP/ICH/425213/2011 (ICH Q11)	On development and manufacture of drug substances (chemical entities and biotechnological/biological entities.	November 2012
Ares(2014)2674284	The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human	September 2014

Reference	Description	Date for coming into effect
	and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials.	
Q11 Implementation Working Group - Development and Manufacture of Drug Substances	Questions and Answers (regarding the selection and justification of starting materials.	13 October 2016
EMA/454576/2016	Guideline on the chemistry of active substances.	15 November 2016 ^(c)
EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1	Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances.	December 2016

^(a)(replaced by "EMA/454576/2016 - Guideline on the chemistry of active substances adopted by CHMP on 21 July 2016)

^(b)date of the initial directive;

^(c)(publication date) (date for coming into effect: 6 months after publication)

In addition to legislation and guidelines it will be necessary to consider for the analysis the attributes of the API and the attributes of the starting material, the control strategy and the regulatory strategy/approach.

It is also relevant for the analysis to assume the following:

- Details about the starting material and quality, namely knowledge of synthetic process of SM;
- Information about the manufacturer;
- Complexity of starting material;
- Specifications of starting material.

The selection and justification of the adequate starting material is a challenge, firstly to the Pharmaceutical Industry and afterwards to the Regulatory Authorities.

According to the guideline CHMP/QWP/297/97 - Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier – full details of chemistry, manufacturing process, quality controls during manufacture and process validation for the active substance, as outlined in the 3AQ5a – Note for Guidance Chemistry of Active Substances or CPMP/QWP/130/96 – Note for Guidance the Chemistry of New Active Substance, may be submitted by the applicant as part of the Marketing Authorisation Application. The level of detail for information depends on the classification of the active substance:

- i) new active substances;
- ii) existing active substances not described in the Ph.Eur. or;
- iii) existing active substances described in the Ph.Eur.

Also, part of the detailed active substance information in the marketing authorisation application can be replaced by the Active Substance Master File (ASMF) or the Certification of Suitability to the Monographs of the European Pharmacopeia (CEP). The requisites are the same regardless of the route of submission (included in the marketing authorisation application or submitted as ASMF) of data on the active substance.

For the discussion, it was considered relevant to address the type and level of information to be provided in the following sections of the pharmaceutical documentation, Module 3.2.S.:

3.2.S.2.1 – Manufacturer(s)

3.2.S.2.2 – Description of Manufacturing Process and Process Controls

3.2.S.2.3 – Control of Materials

3.2.S.2.4 – Control of Critical Steps and Intermediates

3.2.S.3.2 – Impurities

For each of the above sections it is highlighted in table 24 the key aspects to be mentioned and/or discussed. The information is provided in tabular format for easy systematisation:

Table 24: Information to be included

CTD Section	Information
3.2.S.2.1 – Manufacturer(s)	To provide information of each production site or facility involved in manufacturing and testing of active substance for the production steps after introduction of the starting material(s) that includes: - name, address and responsibility of each manufacturer, including contractors.

CTD Section	Information
3.2.S.2.2 – Description of Manufacturing Process and Process Controls	- Adequate description of the active substance manufacturing process including special unit operations and process controls with emphasis on steps of the process considered as “critical”, i.e., having an impact on the quality of the active substance or intermediates. - Schematic representation of the manufacturing process. The molecular formulae of starting materials are included in the graphical representation. - Sequential procedure narrative that should include the quantities or ranges of materials, including for starting materials. - Control of critical steps.
3.2.S.2.3 – Control of Materials	- Materials used in the manufacture of active substance should be listed; - Adequate specifications should be provided - The specifications should address the characteristics of the material and its suitability for the intended use. - The information to be provided is applicable for the starting materials, solvents, reagents, catalysts, etc.
3.2.S.2.4 – Control of Critical Steps and Intermediates	- Tests and acceptance criteria performed at critical steps identified in section 3.2.S.2.2 (Manufacturing process).
3.2.S.3.2 – Impurities	- Provide information on impurities and their carryover - Includes related substances, residual solvents, elemental impurities, reagents and those derived from reagents. - A discussion of related substances considered as potential impurities arising from the synthesis and degradation products and a briefly description including an indication of their origin should be addressed.

Source: [EMA/454576/2016 – Guideline on the chemistry of active substances](#)

3.3.2 Discussion of Case Study I

Case study I considers as starting material a well-known active substance. The synthetic process to obtain the API is of 5-chemical steps and 1 physical step (micronisation). The name and address of the supplier was provided. No flow chart describing the synthetic process of the starting material was provided to the Regulatory Authority with the initial application.

Since the date of submission for the case study I was in 2008, to assess the adequacy of starting material selected and the justification provided it was considered, for the regulatory analysis, the following legislation/guidelines:

- 3A5a – Chemistry of Active Substances;
- CPMP/QWP/130/96 Rev. 1 – Guideline on Chemistry of New Active Substances;
- ICH Topic Q7 - Good Manufacturing Practice for Active Pharmaceutical Ingredients;
- ICH Topic Q9 – Guideline on Quality Management;
- Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, amending Directive 2001/83/EC on the Community code relating to medicinal products for human Use.

According to the ICQ Q7, an API starting material is *“a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or two more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure”*.

According to the guideline 130/96, the selection of SM should be justified (e.g. incorporated as a significant structural fragment into the structure of the active substance). The information provided for the starting material should include the description of the analytical controls applied to ensure that the starting material is correctly identified and is shown to be of a satisfactory quality (3A5a).

The level of significant impurities in the starting material should be given as well as the specifications for solvents used in the final stages of synthesis, crystallisation and/or washing. (3A5a).

The criteria for accepting or rejecting batches of starting material should be indicated and the control of SM should be designed to detect isomeric or other impurities which are potentially reactive and could be carried through to the final product of synthesis (3A5a; 130/96).

The name and address of the SM supplier should be provided as well as information in the form of flow chart, indicating the synthetic process prior to the introduction of the starting material, may be useful to evaluate the suitability of its specification(s) (130/96).

The starting material should be fully characterised to ascertain suitability for intended use and complete specifications should be provided, including an impurity profile (130/96).

A discussion of the potential carryover of impurities present in the starting material through the synthetic process should be discussed and should, if relevant be controlled in the SM by appropriate acceptance criteria with suitably validated methods.

The acceptance criteria should be established by the applicant based on evaluation of the fate of impurities present in the SM, when subjected to the normal synthesis process (130/96).

Since the GMP should be applied from the starting material onwards, the applicant should document the rationale to define this standard point, which would include the validation of critical process steps determined to impact the quality of the API (ICH Q7). As per the article 46 (f) of Directive 2001/83, as amended by Directive 2004/27, *“the holder of a marketing authorisation should at least be obliged to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials”*.

Based on the above and considering the information provided in the description of case study I (2.3.2 – Case studies – Case Study I), it can be confirmed that the starting material was appropriately defined and justification for the selection provided in a satisfactory manner.

Complete specifications for the starting material were provided, but a flow chart for the synthetic process of the starting material was not included in the initial submission. Information of control strategy, namely control of key intermediates, is described.

The impurity profile of the starting material was provided and a detailed discussion for the carryover of potential impurities was included. In the initial application, it was provided information of the supplier of starting material.

Despite the guideline 130/96 is only requesting information of the supplier, the Regulatory Authority requested, during the assessment, information of the manufacturer. Although the name of the manufacturer was not required at that time, it is mentioned in the description of the case that such detail was provided by the applicant to the Authority. Together with the name of the manufacturer, a flow chart of the synthetic process prior to the introduction of the starting material was provided as requested by the Regulatory Authority during the assessment.

In summary, the case study I corresponds to a well succeed regulatory application, after being addressed minor questions raised by the Authority during the assessment. In this case, and considering that all the other conditions supporting the application, according to the guidelines, were in general fulfilled, the request to provide the CEP resulted in additional burden to the applicant without any impact in the final quality of the API.

From a regulatory point of view, the Authority was more stricted than expected, considering the legislation and guidelines applicable.

The fact that the Authority requested the CEP for the starting material may imply additional costs for post-approval variations - e.g. each time that the CEP is renewed a regulatory variation to the initial application need to be submitted to the competent Regulatory Authority, in case of the EMA.

In case of FDA, the CEP is not a requisite and an amendment to the initial application only need to be submitted if the specifications of the starting material change. From this perspective, and bearing in mind that the same applicant may have the synthetic route registered at several Authorities, the differences of requisites always add complexity to the regulatory activities. In the case of the EMA and FDA, at least the ICH guidelines are a common guidance, but the approach, as can be demonstrated by a simple case as the one described, may be different.

3.3.3 Discussion of Case Study II

Case study II corresponds to a regulatory submission dated 2011. The legislation and guidelines applicable to this case are the same as described in case study I, since no new applicable guidelines or legislation came into force between 2008 and 2011. Of note, that the case study II corresponds to a variation of the synthetic process described in case study I.

The synthetic process presented consists in a two-step process and the starting material, even different from the one described for case study I, corresponds to a well-known active substance and authorised in several markets as a medicinal product.

The specifications of the starting material were characteristic of an API.

The discussion of impurity profile and details on the control strategy were included in the application.

It was performed comparability testing, including:

- (a) comparative physicochemical characterization,
- (b) impurities testing, stability testing,
- (c) qualification of impurities, and
- (d) appropriate comparability testing on the drug product.

The specifications of the drug product were the same using the API synthesised by the two different routes. The comparison was performed for four industrial scale batches of drug product (two industrial scale batches per API source).

The specifications of the API produced by the synthetic route approved, and described in case study I, and the proposed synthetic route (Case study II) are the same.

The impurity profile of the API, in both cases, is aligned.

Since the starting material in case study II is different, a new parameter was included corresponding to the selected starting material.

A comprehensive discussion for:

- (a) the list of impurities,
- (b) residual solvents, and
- (c) residual catalysts potentially present, was provided to the Authority.

The applicant, also provided results for batch analysis of 39 batches of starting material. Of relevance, the fact that the applicant provided information of the audit conducted by the manufacturer of the API to the manufacturer of starting material, stating the level of GMP compliance for its synthesis.

According to the guideline 130/96, if the description of the route of synthesis consists of only one step and the starting material is a substance described in the Ph.Eur., the substance should either have a CEP or proof of conformity with the monograph should be provided. Alternatively, such a starting material may already be authorised as an active substance in a marketing authorisation. In the present case, the starting material is already authorised as an active substance in a marketing authorisation, but no CEP or monograph was available at that time. Since the rationale behind the decision to propose the current starting material and a short synthetic process was mainly based on the same structural concept of both starting material proposed in case study I and case study II, it was not foreseen the impossibility to obtain an approval.

The process proposed is stereoselective using a catalyst and the specifications of the API, as mentioned above, were aligned between the processes of both cases.

Considering that additional information is available, namely a discussion of the carryover of impurities and details of the synthetic process of the starting material an approval should be possible. It was demonstrated that there was no significant carryover of impurities *i.e.*, no drug substance impurity greater than 0.1% traceable to the starting material.

In this case, the Authority requested a redefinition of the starting material considering that the starting material selected is too complex and the route of synthesis of the API consists only in two chemical steps. When compared the two processes the second one is more efficient and “greener”, since the yield is much higher when compared to the first one; no unwanted isomer is formed which would need to be incinerated. On the other hand, there is a huge reduction in the volume of organic solvents used in the process. The quality attributes of the API, as already mentioned were maintained unchanged when compared to the API manufactured by the process considered in case study I.

In summary, the similarities and differences between the two synthetic processes as described in case study I and case study II are tabulated below ([Table 25](#)):

Table 25: Similarities and differences between synthetic processes (case study I and case study II)

	Similarities		Differences	
Case Study I	SM well-defined (specifications, impurity profile)	Active substance, approved as medicinal product	CEP	5-chemical steps under GMP
Case Study II			No CEP or Ph.Eur. monograph	2-chemical steps under GMP

During the assessment, the Authority has recognised that the specifications of the API were well defined and are presented for all reagents and solvents, a comprehensive discussion for the impurities is provided, and the impurities have been identified and qualified in accordance with the ICH guidelines. Nevertheless, and despite the synthetic process proposed has considerable benefits from an environmental perspective, a major objection was raised by considering the selected starting material as not acceptable. The Regulatory Authority (in this case the EMA) based the assessment in two criteria:

- (a) complexity of starting material, and
- (b) a short synthetic process.

This example is showing how distinct can be the perspective of the applicant and the Regulatory Authority.

From a Regulatory Authority perspective, seems fair enough to questioning what was the added value of the redefinition of the starting material to the quality of the API.

From an applicant perspective, it was demonstrated that it would be possible to assure the quality of API as well as its quality consistency.

The redefinition of the starting material is giving to the Authority a better knowledge of the synthetic route of the proposed starting material, allowing a more detailed assessment of the impurity profile and specifications of the API defined by the applicant. The redefinition of the starting material is increasing the regulatory burden, implying increase number of variations post-approval, and for sure the costs of API.

3.3.4 Discussion of Case Study III

Case study III corresponds to a modification requested by the Regulatory Authority during the assessment of the previous process described in case study II (see [2.3.3 Case studies – Case Study II](#) and [3.3.3 Case studies – Discussion of Case Study II](#)). The synthetic process described in case study II was not approved by the Authority without a redefinition of the starting material.

Since the date of the resubmission with the redefined starting material was in 2011, the legislation and guidelines applicable were exactly the same as the ones considered in the discussion of case studies I and II.

The redefined starting material was commercially available and allowed the addition of three more steps to the synthetic process that need to be conducted under GMP.

The redefinition of the starting material did not impact anyway in the quality of the final API.

In the case study II it was demonstrated by the documentation submitted that the quality level, including impurity profile, of the starting material selected, now to be considered as an intermediate, was kept constant for all the suppliers (results for 39 batches of the starting material were presented and with consistent results). Also, the applicant, for the case study II, and as mentioned before, provided to the Authority the outcome of an audit conducted by the manufacturer of the API to the manufacturer of the starting material, that stated the level of GMP compliance for the manufacture of the starting material proposed in case study II. A considerable level of knowledge of the synthetic route of the starting material initially selected was disclosed to the applicant and to the manufacturer of the API.

Basically, there was a disagreement between the position of the Regulatory Authority and the applicant:

- (a) the Authority considered that the synthetic process was too short and the defined starting material too complex.
- (b) the applicant considered other aspects of the legislation and guidelines, namely the aspects related to a quality risk management, providing complete and comprehensive analysis of the quality of the starting material proposed initially and thorough analysis of the carryover of the impurities arising from the starting material.

In conclusion, the addition of one chemical step and one purification step to the synthetic route described in case study II did not change the specification of the API, or provided additional discussion to the carryover or impurity profile.

3.3.5 Discussion of Case Study IV

Case study IV is a hypothetical one. Since it has not yet been submitted to any Regulatory Authority, the discussion will consider the current legislation and guidelines. After the regulatory approval for the process described in case study III, in December 2011, new guidelines were issued. To support the regulatory analysis of case study IV were considered relevant the ICH Q11 guideline and the Reflection Paper issued by the EMA in December 2016 ([EMA/CHMP/CVMP/QWP/826771/2016](#)).

The starting material proposed is *per se* an API. Recently the Ph.Eur. monograph for this API was approved. One manufacturer was identified as holding a valid CEP.

The starting material can be considered as too complex, but the fact that a Ph.Eur. monograph exists could be part of the justification, from a regulatory perspective, to the selection of it as starting material.

According to the “Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical substances” (EMA/CHMP/CVMP/QWP/826771/2016) it is clarified that “If an intermediate in the proposed synthesis of the active substance is itself an active substance covered by a monograph of the European Pharmacopoeia (Ph. Eur.) covered by a valid CEP, then the CEP can be submitted as an alternative to submitting its process description”.

From a regulatory perspective, it may be interesting to prepare and submit an application reflecting this case study. It is still expected that questions may arise from the Authority, but if a comprehensive discussion for the impurity profile, carryover of potential impurities and a demonstration of an enough knowledge of the starting material synthetic process are included, it is not foreseen any reason for a negative outcome of such application.

4 Conclusions

4 Conclusions

The definition of starting material has been shown, along the time, as a complex topic. From the analysis of the guidelines and legislation related, directly or indirectly, to the starting material, it can be concluded that there is no harmonised language for the definition of starting material. It can be found more simple or complex definitions and such definitions are associated, indistinctly to “API starting material” or simply “starting material” and more recently, “active substance starting material”. That does not mean *per se* differences in the meaning, but can difficult the interpretation and reflects the complexity of establishing a clear definition. Therefore, the harmonisation of the language used to defined the starting material is one of the recommendations ([4.5 Recommendation for the definition of starting material](#)).

The current guidelines are more focused in addressing what can be defined as starting material instead of giving guidance or establishing the criteria for the selection of a starting material. Each synthetic process has specific characteristics and different variables and this aspect may be enough reason to justify the absence of guidelines. Looking for a definition of the clearly criteria to be applied for the selection of the starting material or for the identification of the adequate information to be provided to the Authority, may be desirable. The decision about the selection of the adequate starting material is of utmost relevance for the Industry, since it will be the starting point from which the synthetic process needs to comply with the GMPs. Other aspects such as the number of steps from the starting material to the final API, the isolated intermediates, the impurity profile and specifications of starting material, intermediates and API, should also be considered for the selection of the starting material. The conditions and type of chemical reactions for each synthetic process, the characteristics of raw materials, purging capability of the synthetic process, type of impurities and respective carryover, as well as, the control of quality attributes and in-process controls of critical parameters applied, are factors that should be taken in account at the time of the overall analysis of the synthetic process. Due to all this complexity, the selection of the starting material is key for the success of the marketing authorisation application.

The main objective of the different stakeholders is the same - make available to the patients a medicinal product of quality, safe and efficacious, although the perspectives of each of them, Pharmaceutical Industry and Regulatory Authorities may be different.

From an Authority perspective, it should be expected that the applicant submits a complete and comprehensive package, which includes a sufficient number of chemical

steps from the starting material until the API, information about the synthetic process of the starting material (earlier synthetic steps), details about the controls applied to the API and its manufacturing process, discussion about the impurity profile, purging capability of the process and control strategy adopted. And it seems that the tendency is for the Authority to require even more detail in the applications.

On the Industry view, the aspects listed above are also considered as key and should be comprehensively studied, supported and documented. But, there are also other pieces that should be put on the equation, since the marketing authorisation holder is responsible for the availability of the medicinal product to the patient, namely the flexibility and assurance of the supply chain, timely availability of the API and its costs. So, without disregard any requisite and concern from the Authority, different pathways should be discussed also to accommodate the Industry needs.

The regulatory affairs perspective is very pragmatic and more detail in the marketing authorisation application consequently implies additional burden on the process, with potential delays as well as the need to submit more post-approval variations.

Bearing in mind that the selection of the adequate starting material was identified as a potential and sometimes, unexpected burden in the assessment of a marketing authorisation application, it will be recommended, as early as possible, an engagement of the Regulatory Authority, through scientific advice consultations, as well as the involvement of regulatory affairs in the discussion of the selection of the starting material. The FDA recommends the companies to request End-of-Phase 2 meetings to discuss CMC aspects but it is quite common in Europe as also in Japan, that the CMC discussion is only taking place during the assessment of a marketing authorisation. The need to redefine the starting material in a late stage of the development of a drug may have huge impact from a time and cost perspectives, and can even jeopardize the approval of the medicinal product. The criticism will increase dramatically if such redefinition happens during the assessment of the marketing authorisation application. Apart the direct impact on costs, since all the development activities were concluded, delay in reaching the market can be one of the indirect and most negative consequences.

Despite an improvement and effort from the different stakeholders to clarify the aspects related to the starting material along the time, as reflected by the [ICH Q11](#), the Guideline on the chemistry of active substances, from November 2016 and the recent reflection paper from the EMA ([EMA/CHMP/CVMP/QWP/826771/2016](#)), no clear concept of starting material was achieved or detailed guideline issued of how to select a starting material. Indeed, the Reflection paper contributed positively to reduce the risk of disagreement

between Pharmaceutical Industry and Regulatory Authorities but is limited in providing just clarifications about some expectation of the EU competent Authorities arising from the [ICH Q11](#). On the other hand, the reflection paper is touching aspects behind the technical ones, such the tendency of the companies to propose complex custom-synthesized starting materials and to outsource the manufacture of API. With the globalisation and considering the possible impact on the patient, it is of utmost relevance that the different Regulatory Authorities have a common understanding of the technical and scientific questions related to the starting material, and achieve an agreement, namely on the requisites to be complied with.

If a recommendation can be made, it would be to develop a concept paper addressing the criteria to select the starting material, that could be the starting point for a discussion between the different stakeholders ([4.6 Recommendation for the criteria for selection of starting material](#)).

The above conclusions were supported by the different aspects detailed and analysed along the document and as summarised below in [4.1](#), [4.2](#), [4.3](#) and [4.4](#).

4.1 Guidelines, position papers and legislation available

An extensive review of guidelines, position papers and legislation relevant to the definition of starting material and concepts of starting material was done. Twenty-one guidelines, four legislation pieces (Directives or Regulations) and two position papers were consulted and analysed. As a results, it was verified that the language used to define a starting material is not harmonised along the documents. That aspect triggered the need to suggest a recommendation for a definition of starting material to be used across the documents ([4.5 Recommendation for the definition of starting material](#)).

Conclusion 1

- The language used to define a starting material is not harmonised along the documents.

4.2 Retrospective analysis of assessment reports

The assessment reports that were made available by the EMA and FDA, for the medicinal products for which a marketing authorisation was granted by both Regulatory Authorities, between 01 January 1999 and 12 April 2015, were retrospectively analysed.

The assessment reports analysed correspond to thirty-three medicinal products. The cut-off considered for the documents analysed was 31 July 2017. It was collected and treated the information about:

- i) the identification and commercial availability of starting material,
- ii) number of steps of the described synthetic process of the API,
- iii) submission of ASMF/DMF.

Post-approval variations related to the synthetic process of API and/or synthetic process were systematised for the regulatory procedures handled by the EMA for the thirty-three medicinal products. After systematisation of the information collected a statistical analysis was performed, using the Chi-Square test. The statistical analysis was run in an attempt to establish a relationship between the data collected and the evolution of legislation. The variables selected for the analysis were:

- i) Interval of time,
- ii) identification of starting material,
- iii) commercial availability of the starting material,
- iv) information about the API covered by a ASMF/DMF and,
- v) number of steps of the synthetic process.

The variable “interval of time” was common to all the analysis and it was possible to establish a relationship between the date of approval of the marketing authorisation and the different variables selected, except for the variable “information about the API covered by a ASMF/DMF. In conclusion, it can be stated that the level of detail in the assessment reports about the identification of the starting material is decreasing along the time. Maybe this is related to intellectual property and commercially sensitive information aspects. In

the opposite side, it is noted an increase of number of steps described for the synthetic processes of the API. As an example, for the interval of time between 2012 and 2015, from the fifteen medicinal products included, eleven described a synthetic process with 4 or more steps. This conclusion can be a reflex of the increase of complexity of the regulatory environment and the application of the ICH Q11.

When analysed the type of post-approval variations approved by the EMA for the thirty-three medicinal products, a total of ninety-nine variations related to changes in the synthetic process or to the manufacturer were identified. From that, forty-four were related to changes in the manufacturing process, being eight of that considered substantial changes to the synthetic process. It was concluded that the number of variations substantially affecting the synthetic process is quite low when compared to other type of variations affecting the manufacturing process. The low figure can reflect how complex it is to develop, support and get the approval of new synthetic processes as lifecycle management activity.

Conclusion 2

- The level of detail about the identification of the starting material made publicly available is decreasing along the time;
- The number of steps described for the synthetic processes is increasing along the time;
- The number of post-approval variations related to substantial changes in the synthetic process is quite low when compared to other type of variations affecting the manufacturing process.

4.3 Cases described in the literature

Four active substances, eslicarbazepine acetate, lacosamide, retigabine and zonisamide, were selected for the analysis of synthetic processes described in the literature. The criterion for the selection is stated in [2.2. Cases described in the literature](#). The information collected from the literature was organised by:

- i) information on the starting material,
- ii) considerations and information about the synthetic process and control strategy, and
- iii) description of main steps of the synthetic process.

It was concluded that there is lack of detail in the publications to determine in accurate way the feasibility of such to come through a successful regulatory assessment. Nevertheless, from the nine publications analysed it was considered that four synthetic processes have high probability of going through successful submissions and one was considered likely to be approvable.

Conclusion 3

- The level of detail of the information included in the publications for the different synthetic approaches is not enough to allow a proper and complete analysis of their feasibility from a regulatory point of view.

4.4 Case studies

The practical case considered for the thesis comprises four case studies, with three of them already assessed by different Regulatory Authorities. The fourth case is an hypothetical one. From the analysis of these cases, it can be concluded that the selection of the adequate starting material is a key aspect of the development of a medicinal product. Redefinition of starting material during the assessment can create additional burden to the Pharmaceutical Industry, resulting in additional costs but, more important, in delays of the optimisation of supply chain with as potential consequence, shortage of medicines. It can be also concluded that a previous consultation to the relevant Regulatory Authority may help to reduce the risk of the selection of the starting material.

Conclusion 4

- Selection of adequate starting material is a key aspect to be considered during the development of a synthetic process;
- Redefinition of starting material during the assessment creates additional burden by increasing costs, delays in the assessment to the market and increasing the risk of shortages;
- Previous consultation with the relevant Regulatory Authority may help to reduce the risk inherent to the selection of starting material:

4.5 Recommendation for the definition of starting material

Instead of using indistinctly “API starting material”, “starting material” “Active substance starting material” and different definitions, the proposal is to adopt the following definition:

Starting material: any substance of defined chemical properties and structure used for the synthesis of an active substance. A starting material can be an article of commerce, a material purchased from one or more manufacturers under contract quality agreement, or produced in-house.

4.6 Recommendation for the criteria for selection of starting material

Due to the need to concretely address the challenges of selecting the adequate starting material and define an appropriate process to be implemented, it was considered relevant to propose the development of a position paper to address the following aspects:

- How to select a starting material?
- What should be the Applicant's responsibility?
- What documentation should be submitted to the Regulatory Authority regarding the starting material?
- What should be the Regulatory Authority role?

The approach proposed is based on flexibility of the process, without disregarding the Authority concerns and requirements, but simultaneously increase Industry responsibility and commitment with the starting material aspects.

This position paper intends also to promote brainstorming between the different stakeholders and achieve, as possible, the same understanding from the different Regulatory Authorities.

4.6.1 How to select a starting material?

The criteria to select a starting material should consider technical and supply chain aspects.

4.6.1.1 *Technical aspects*

The starting material should be any substance:

- of defined chemical properties and structure;
- with adequate set of specifications, including acceptance criteria for impurities.
- with suitable stability;
- should be different from raw materials, reagents and solvents;
- with available synthetic scheme;
- commercially available or manufactured in-house.

The number of steps to be conducted under GMP should consider the following cumulative conditions:

1. report of specifications defined for the starting material, namely acceptance criteria for impurities;
2. purging capability of the process (for example, reactivity and solubility studies), taking into account the type of steps;
3. identification of isolated intermediates and respective specifications, namely acceptance criteria for impurities;
4. in-process controls along the process, including justification of the critical parameters and process conditions;
5. impurity profile generated during the process and respective control strategy, also considering the ICH M7 Guideline.

4.6.1.2 *Supply chain aspects*

The following aspects related to the supply chain should be addressed:

- the manufacturer of the starting material should be previously qualified according to the ISO requirements. Periodicity as well as type of audits (audit *in situ*,

documental) to be conducted by the manufacturer of the API and the medicinal product manufacturer should be defined based on a risk assessment approach;

- the manufacturer(s) of both API and medicinal product should have in place transparent and well documented quality systems that can assure consistency on the quality of the API;
- description of oversight of the API and medicinal product manufacturers of the quality management system in place for the manufacturer of the starting material should be detailed;
- robust contract quality agreements between the API manufacturer, the manufacturer of medicinal product and the starting material manufacturer should be in place;
- implementation of quality metrics by the manufacturers of the API in the same way as defined already in the recent FDA Guidance for Industry for the manufacturers of medicinal products. This set of measurements is designed to confirm that pharmaceutical manufacturers produce quality medicines and drive continuous improvement throughout a product's lifecycle.

4.6.2 What should be the Applicant's responsibility?

The applicant's responsibility should be framed in a scenario of more flexibility but increasing responsibility.

The applicant is responsible for:

- having comprehensive knowledge of the synthetic process, including information regarding the starting material;
- having in place quality systems and quality policies that guarantee the quality of the API as well as the complete manufacturing chain, including starting material manufacturer;
- document all the changes, including the ones impacting the starting material, through a robust change control system;
- comply with all requirements from the Authority and archive the required quality documents.

4.6.3 What documentation should be submitted to the Regulatory Authority regarding the starting material?

Considering the aspects discussed above and aiming a more flexible but simultaneously well controlled process, the documentation regarding the starting material to be assessed by the Regulatory Authority can be classified as follows:

- *List of documentation concerning the starting material to be submitted to the Regulatory Authority in the scope of an authorisation application:*
 - a) name and structure of the starting material;
 - b) specifications, including impurity acceptance criteria;
 - c) declaration confirmation that the starting material manufacturer was properly qualified.

- *List of documentation concerning the starting material that applicant should kept for in situ:*
 - a) name and address of the starting material manufacturer;
 - b) details on the starting material synthetic process;
 - c) justification of starting material specifications, namely rational to address impurities carry-over;
 - d) description of the analytical methods and respective validation, as applicable;
 - e) batch analysis, representative certificate of analysis and TSE/BSE declaration;
 - f) stability studies;
 - g) documents listed above in **4.6.1.2 Supply chain aspects**, namely quality agreement in place;

4.6.4 What should be the Regulatory Authority role?

The Regulatory Authority should be keen to accept this approach, which, in some extent, could be considered as a change on the stakeholders behaviour.

The Authority should be prepared to:

- give upfront support to the applicant on the starting material selection process (CMC scientific advice, for example);
- have a pedagogic approach by organising periodically workshops about this topic and discuss with the Industry about their expectations;
- periodically inspect the applicant to assure compliance with the defined rules.

4.7 Final remarks

The definition and selection of the adequate starting material are a challenge for both Regulatory Authorities and Pharmaceutical Industry. The reflection made about these aspects are based in my professional experience gained along 20 years in the Regulatory Affairs role and represents my personal view. Hopefully, this reflection will contribute to stimulate the discussion among the stakeholders.

5 References

5 References

- Aratikatla KE, Bhattacharya KA. Chiral pool approach for the synthesis of functionalized amino acids: synthesis of antiepileptic drug (R)-lacosamide. *Tetrahedron Lett* 2015; 56: 5802-5803.
- Argentine MD, Owens PK, Olsen BA. Strategies for the investigation and control of process-related impurities in drug substances. *Adv Drug Deliv Rev* 2007; 59: 12-28.
- Blackburn-Munro G, Dalby-Brown W, Mirza NR, Mikkelsen JD, Blackburn-Munro RE. Retigabine: Chemical Synthesis to Clinical Application. *CNS Drug Rev* 2005; 11 (1): 1-20.
- Challenger CA. API Custom manufacturing outlook: More growth in 2015. *API Synthesis & Manufacturing. PharmTech Europe* 2015 Jan: 36-38. (issue online).
- Diego IO, Fake A, Stahl M, Rågo L. Review of Quality Deficiencies Found in Active Pharmaceutical Ingredient Master Files Submitted to the WHO Prequalification of Medicines Programme. *J Pharm Pharm Sci* 2014; 17 (2): 169-186.
- Ding XH, Liu K-CK, Sakya MS, Flick CA, O'Donnell JC. Synthetic approaches to the 2011 new drugs. *Bioorg Med Chem* 2013; 21: 2795-2825.
- EMA. CPMP/QWP/130/96 Rev.1. Guideline on Chemistry of New Active Substances. 17 December 2003.
- EMA. CPMP/QWP/1529/04 Guideline on Control of Impurities of Pharmacopeial Substances: Compliance with the European Pharmacopeia General Monograph "Substances for Pharmaceutical Use" and General Chapter "Control of Impurities in Substances for Pharmaceutical Use. April 2004.
- EMA. CHMP/QWP/297/97 Rev.1. Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier; 1 February 2005.
- EMA. EMA/CHMP/CVMP/QWP/450653/2006. Recommendation on the Assessment of the quality of medicinal products containing existing / known active substances. 9 February 2009.
- EMA. CHMP/QWP/227/02 Rev.3/corr. Guideline on Active Substance Master File Procedure. 1 October 2012.
- EMA. EMA/CHMP/QWP/752676/2013. Concept paper on the need for a single note for guidance on the chemistry of active substances. 19 December 2013.
- EMA. EMA/454576/2016 - Guideline on the chemistry of active substances. 21 July 2016.
- European Parliament. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use. (OJ L 311. 28.11.2001: 67); as amended.
- European Pharmacopeia 9.0. General Text: 5.10. Control of Impurities in Substances for Pharmaceutical Use; 2016.

- Faul MM, Argentine MD, Egan M, Eriksson MC, Ge Z, Hicks F, et al. Part 3: Designation and Justification of API Starting Materials: Proposed Framework for Alignment from an Industry Perspective. *Org Process Res Dev* 2015; 19: 915-924. (a)
- Faul MM, Busacca CA, Eriksson MC, Hicks F, Kiesman WF, Smulkowski M, et al. Part 2: Designation and Justification of API Starting Materials: Current Practices across Member Companies of the IQ Consortium. *Org Process Res Dev* 2014; 18: 594-600.(b)
- Faul MM, Kiesman WF, Smulkowski M, Pfeiffer S, Busacca CA, Eriksson MC, et al. Part 1: A Review and Perspective of the Regulatory Guidance to support Designation and Justification of API Starting Material. *Org Process Res Dev* 2014; 18: 587-593.(c)
- Garg Y, Pandey KS. An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (R)-Lacosamide. *J Org Chem* 2015; 80: 4201-4203.
- Gavin PF, Olsen BA, Wirth DD, Lorenz KT. A quality evaluation strategy for multi-sourced active pharmaceutical ingredient (API) starting materials. *Journal of Pharmaceutical and Biomedical Analysis* 2006; 41: 1251-1259.
- ICH. ICH Topic Q7. (CPMP/ICH/4106/00). Good Manufacturing Practice for Active Pharmaceutical Ingredients (Note for Guidance on Good Manufacturing Practice for Active Pharmaceutical Ingredients); November 2000.
- ICH Topic Q3B (R2) Impurities in New Drug Products. Step 5. (CPMP/ICH/2738/99). August 2003 (June 2006 – Revised Attachment 2).
- ICH. ICH Topic Q3A (R2). (CPMP/ICH/2737/99) Impurities in new Drug Substances (Note for Guidance on Impurities Testing: Impurities in New Drug Substances). October 2006.
- ICH guideline Q3C (R5) on impurities: guideline for residual solvents. Step 5. March 1998 (part I); February 2009 (Part II and Part III); August 2011 (Part IV).
- ICH. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities). November 2012.
- ICH. ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (EMA/CPMP/ICH/83812/2013). 25 August 2015.
- ICH. ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013). 25 July 2016.
- ICH. ICH Topic Q8 (R2). (EMA/CHMP/ICH/167068/2004) Pharmaceutical Development (Note for Guidance on Pharmaceutical Development). 22 June 2017.
- Information Exchange System Alert No. 126, 24 January 2013. Available at http://www.who.int/medicines/publications/drugalerts/Final_Alert_126_Information_on_Dextromethorphan.pdf [accessed on 28 Dec 2017].

- Jiménez-González C, Poechlauer P, Broxterman QB, Bing-Shiou Y, am Ende D, Baird J, et al. Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacture. *Org Process Res Dev* 2011; 15: 900-911.
- Liu K-CK, Sakya MS, O'Donnell JC, Flick CA, Li Jin. Synthetic approaches to the 2009 new drugs. *Bioorg Med Chem* 2011; 19: 1136-1154.
- Matsuhama M, Takishita T, Kuribayashi R, Takagi K, Wakao R, Mikami K. Similarities and Differences of International Practices and Procedures for the Regulation for Active Substance Master File/Drug Master Files of Human Use: Moving Toward Regulatory Convergence. *J Pharm Pharm Sci* 2016; 19(2): 290-300.
- Morieux P, Stables PJ, Kohn H. Synthesis and anticonvulsant activities of N-benzyl (2R)-2-acetamido-3-oxysubstituted propionamide derivatives. *Bioorg Med Chem* 2008; 16: 8968-8975.
- Notice to Applicants. Medicinal Products for Human Use. Presentation and Format of the Dossier. Common Technical Document. Module 3. Ed. July 2004. Eudralex.
- MarketLine Industry Profile, Pharmaceuticals in India. Available at www.marketline.com. Reference code:0102-0372. April 2014 [accessed on 17 Jan 2016].
- Panzitta M, Ponti M, Bruno G, Cois G, D'Arpino A, Minghetti P, et al. The strategic relevance of manufacturing technology: An overall quality concept to promote innovation preventing drug shortage. *Int J Pharm* 2017; 516: 144-157.
- Ravinder B, Reddy RS, Sridhar M, Mohan MM, Srinivas K, Reddy PA, et al. An efficient synthesis for eslicarbazepine acetate, oxcarbazepine and carbamazepine. *Tetrahedron Lett* 2013; 54: 2841-2844.
- Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances (EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1.). December 2016.
- Seevers RH, Kluttz WF. Regulatory Strategy for Starting Material Designation. *Pharmaceutical Outsourcing*. 2010 Jan; 1 (11). Available at <http://www.pharmoutsourcing.com> [accessed on 11 June 2014].
- Shanley A. Pharma APIs: It's Still a Small World. *PharmTech Europe* 2015 May: 18-22. (issue online).
- Shanley A. Specialty Markets and Services Drive API Growth. *PharmTech Europe* 2016 May: 24-27. (issue on line).
- Spadoni C. How the pharmaceutical R&D crisis is reshaping the contract research and manufacturing services (CRAMS) industry. The rise of India as top spot for chemistry outsourcing. *Supplement to chimica oggi/Chemistry Today* 2011; 29 (4).
- Stecko S. Total Synthesis of Lacosamide. *J Org Chem*. 2014; 79: 6342-6346.

- Wadavrao BS, Narikimalli A, Narsaiah VA. A non-infringing Route for Enantioselective Synthesis of Antiepileptic Agent Lacosamide. *Synthesis* 2013; 45: 3383-3386.
- Wells AS, Finch GL, Michels PC, Wong JW. Use of Enzymes in the Manufacture of Active Pharmaceutical Ingredients – A Science and Safety-Based Approach to Ensure Patient Safety and Drug Quality. *Org Process Res Dev* 2012; 16: 1986-1993.