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A Prospective Study of Drug Approval Process in European Union Via Centralised Procedure (From 2015-2018)

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Abstract

The current scenario of this article mainly highlights about the medicinal products that are highly synchronized in European Union. Medicinal products undergo an elaborate system of approvals that governs how, when, where, and in what form such products will be authorised to be sold within European Union. The current marketing authorization procedures that are applicable to European Economic Area include 28 European member states and 3 European Free Trade Association states. This article mainly emphasizes on centralised marketing procedure, decentralized procedure, mutual recognition procedure, and national procedure in European Union.

Keywords

Centralised marketing procedure, decentralized procedure, mutual recognition procedure, and national procedure, medicinal products.

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INTRODUCTION:

Every country has its own basic legislations and regulatory requirements for approval of a medicinal product. The European Union is a political and economic union of 28 member states. They are Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK. The EU also has its own requirements and regulations.

The legal framework that governing the medicinal products for human use in EU:

The EU legal framework for medicinal products for human use sets some standards to ensure that a high level of public health protection and the quality, safety, and efficacy of approved medicinal products. It also supports the novelty. It mainly works on the principle that a medicinal product requires a marketing authorisation by the competent authorities before being placed on the market. This is the implemented legal framework. Behind this implementation there is a historical reason [1].

History:

Thalidomide disaster: (1950)

This incident occurred when the thousands of pregnant women taking the medicinal product (thalidomide derivatives). Because of that the babies were born with limb deformities.

After occurred this incident the general public and the public health authorities thought that their main aim is to safeguard the public health and no

medicinal product must ever again be marketed without the prior authorisation.

Drug approval process in European Union:

Regulating body: The European Medicines Agency (EMA) it regulates the medicinal products for both human and veterinary use. It was established in London in 1995 to coordinate the European Union member states in evaluating and supervising the medicinal products. It introduced a procedure for the development, consultation, finalization and implementation of pharmaceutical guidelines [2].

Approval process: it is accomplished in two phases.

1. Clinical trial
2. Marketing authorisation

1. **Clinical trial:** clinical trials are experiments or observations done in clinical research or testing the medicinal products. In which animals and humans are used as volunteers to test new treatments or tests as a means to prevent, detect, treat or manage various diseases or medical conditions. There are 5 types of clinical trials.
   i. Phase 0
   ii. Phase I
   iii. Phase II
   iv. Phase III
   v. Phase IV

Before doing clinical trials there is an application to be filed by the applicant i.e., clinical trial application. This is filed to competent authority of the state in which he wants to conduct the clinical trials within the European Union. The competent authority of that state evaluates the application. Then only he should conduct the clinical trials. After completing the 3 phases of clinical trials he should file for marketing authorisation application.

The rules and regulations governing the medicinal products in the EU are present in the pharmaceutical directives as volumes [3].

Volume 1: Pharmaceutical legislation for Medicinal Products for human use
Volume 2: Notice to applicants for Medicinal Products for human use
Volume 3: Scientific Guidelines for Medicinal Products for human use
Volume 4: Good Manufacturing Practices Guidelines for Medicinal Products for human and veterinary use
Volume 5: Pharmaceutical Legislation for Medicinal Products for veterinary use
Volume 6: Notice to Applicants for Medicinal Products for veterinary use
Volume 7: Scientific Guidelines for Medicinal Products for veterinary use
Volume 8: Maximum Residue Limits
Volume 9: Pharmacovigilance Guidelines for Medicinal Products for human and veterinary use
Volume 10: Clinical Trials Guidelines

2. **Marketing Authorisation:**
   - ✓ A license to sell a medicine
   - ✓ License granted by competent authorities
   - ✓ Assessment is benefit/risk based on:
     - Quality
     - safety
     - efficacy
   - ✓ Positive risk-benefit balance in favour of patients and users of products once they reach the marketplace.

Marketing authorisation application (MAA) to EU countries:

Marketing authorisation application modules:

In the EU, the approval of a medicinal product for human use are authorised by the EMA, European commission. At least seven months before submission applicant should notify the European medicines agency (EMA) of their intention to submit an application and give a realistic estimate of month of submission. MAA modules are shown in Table: 1

Table 1: Marketing authorisation application modules

Module	Content	Details
1	EU administrative & prescribing information	• Application form • Summary of product characteristics • Labelling text and make-ups • Information about the experts • Environmental risk assessments • Information relating to orphan market exclusivity • Description of the Pharmacovigilance system • Risk management plan
2	High level summaries	• Quality • Non-clinical overview • Non-clinical summaries (pharmacology, pharmacokinetic, toxicology) • Clinical overview

		• Clinical summary (biopharmaceutics, clinical pharmacology, efficacy, safety, study synopsis)
3	Quality documentation	• Body of data • references
4	Non-clinical documentation	• study report • references
5	Clinical documentation	• tabular listing of studies references

MAA can be filed through

- ❖ the centralised procedure or by
- ❖ national competent authorities through
  - ○ a mutual recognition,
  - ○ decentralised or
  - ○ national procedure

1) Centralised procedure:

The marketing authorisation which is granted under this procedure allows the marketing authorisation holder to market the medicines and make it available to patients and healthcare professionals throughout the EU [4].

The application is assessed by the EMA and the authorisation is granted by the EC.

Benefits:

1. Medicines are authorised in all EU countries at the same time
2. Centralised safety monitoring
3. Product information available in all EU languages at the same time

Scope:

The centralised procedure is laid down in regulation (EC) NO 726/2004. Under this regulation this procedure is compulsory for:

4. Products derived from biotechnology
5. Orphan medicinal products
6. Medicinal products for human use which contain an active substance authorised in the Union after 20 May 2004 and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.

It can also apply to all medicinal products:

- ✓ That contain an active substance not authorised before 20 May 2004
- ✓ Constituting a significant therapeutic scientific or technical innovation
- ✓ For which an EU authorization would be in the interest of patients.

Under this centralised procedure, one marketing authorisation may only be able to get by a company per medicinal product. In specific cases only the company may apply for a duplicate marketing authorisation. For duplicate marketing authorisation they should submit the application to the commission.

The medicinal products approved under centralised procedure means it must be innovative and new. The increase in the number of medicinal products approvals under centralised means increase in the growth of innovation. From 2015 onwards there are rising in the number of assigned cases and number of assigned rapporteurs. Up to 2018 this rising continued and is shown in Figure: 1, 2, and 3,4,5,6,7,8,9 [5, 6, 7, and 8] in graphs format. Country wise information is shown in Table: 2

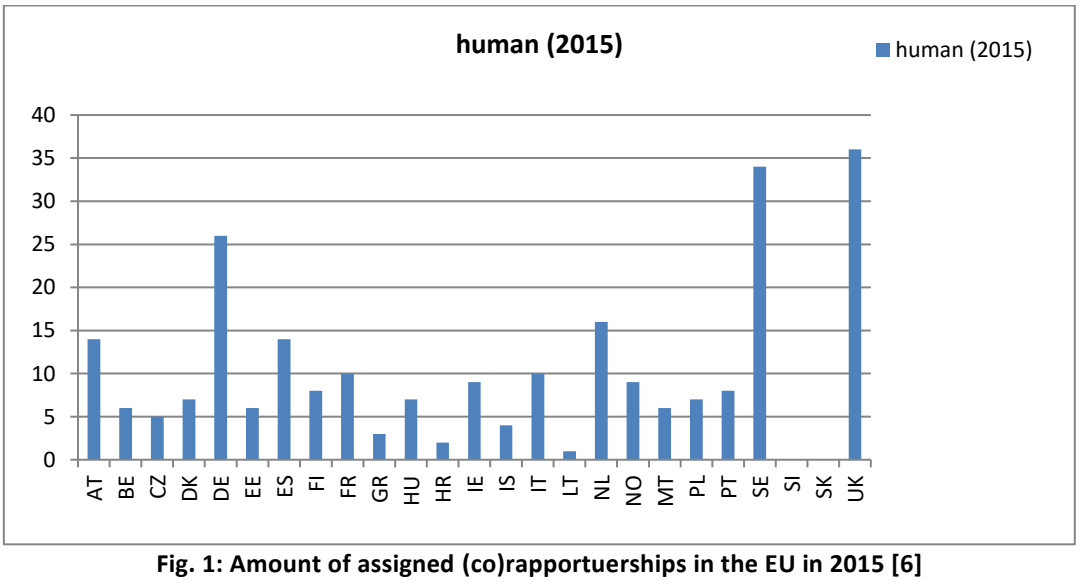

Fig. 1: Amount of assigned (co)rapportuerships in the EU in 2015 [6]

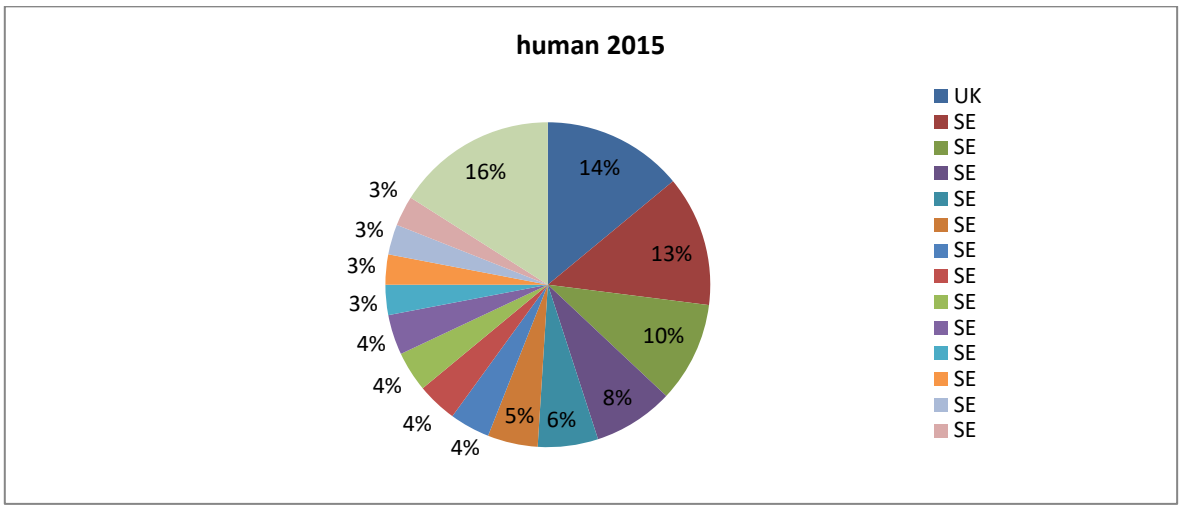

Fig. 2: Share of human Rap/Co-rap cases (2015) [6]

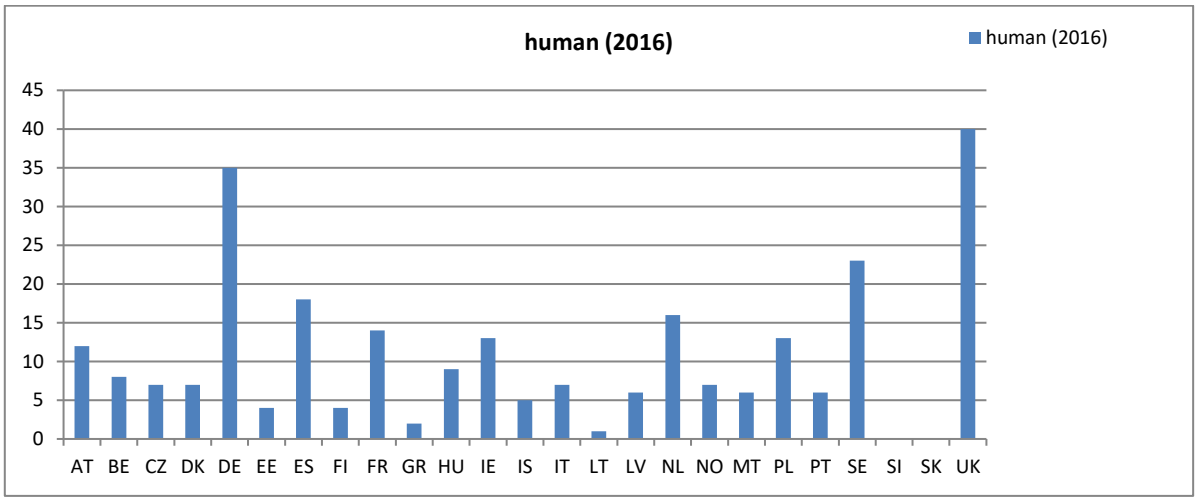

Fig. 3: Amount of assigned (co)rapportuerships in the EU in 2016 [7]

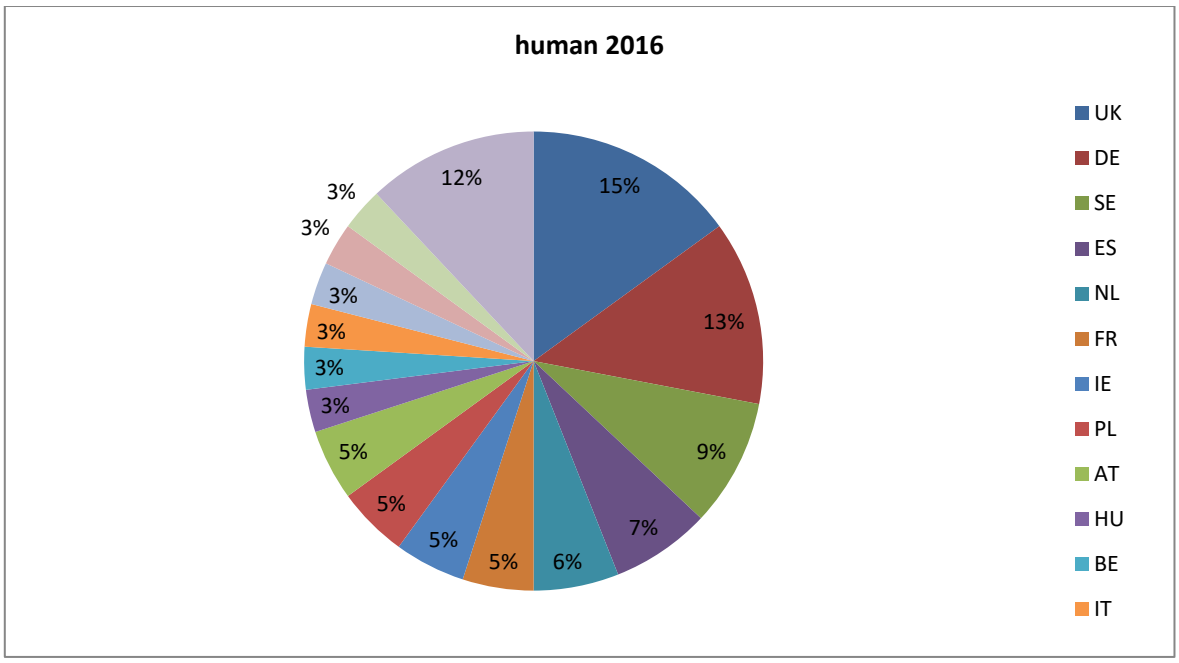

Fig. 4: Share of human Rap/Co-rap cases (2016) [7]

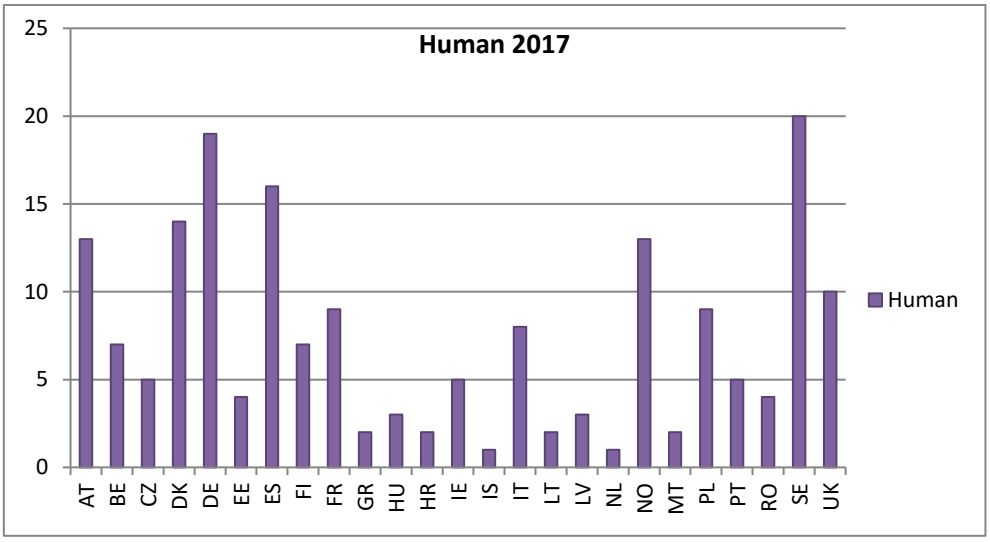

Fig. 5: Amount of assigned (co) rapportuerships in the EU in 2017 [8]

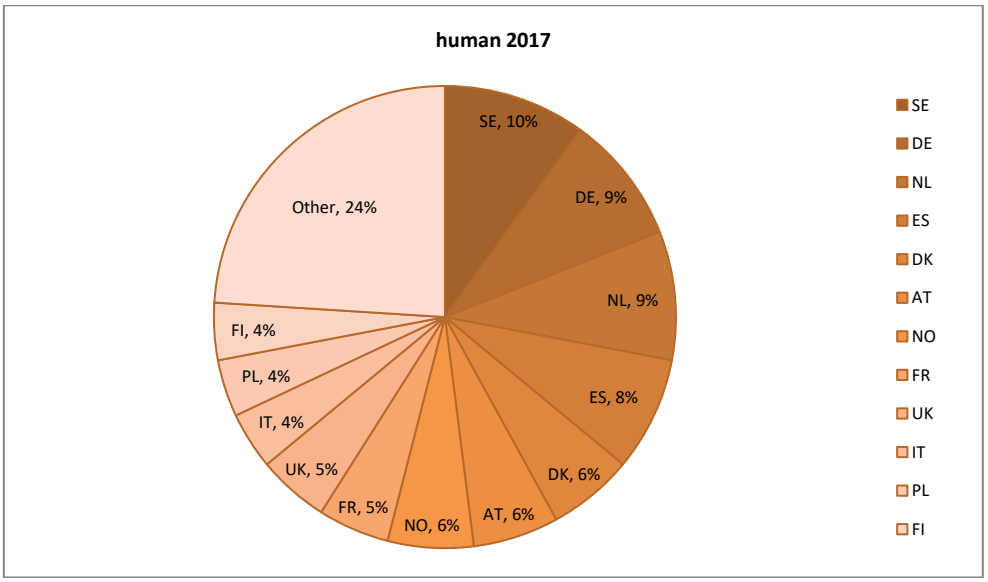

Fig. 6: Share of human Rap/Co-rap cases (2017) [8]

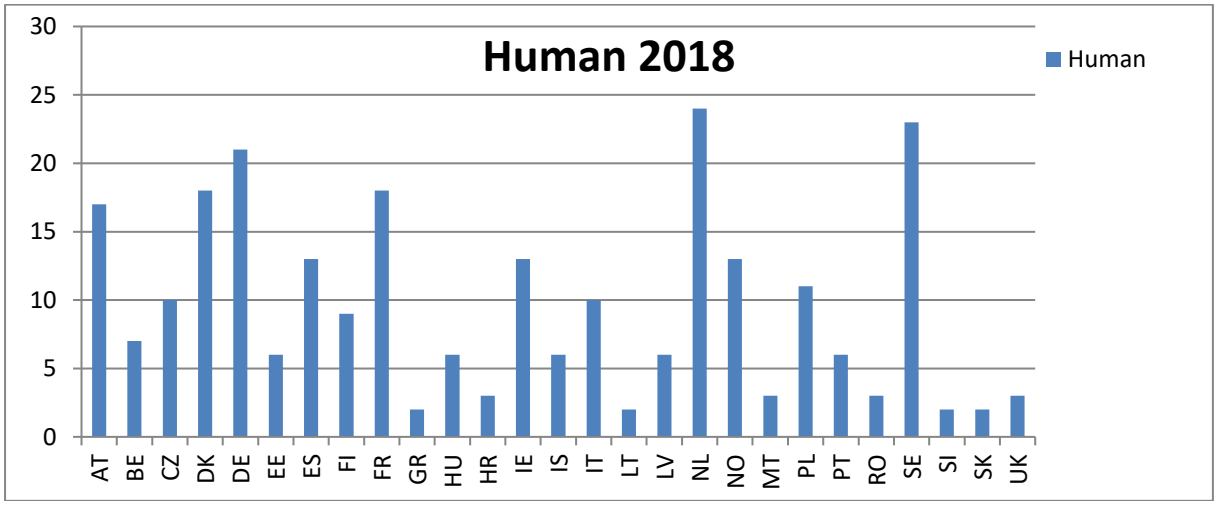

Fig.7: Amount of assigned (co)rapportuerships in the EU in 2018 [9]

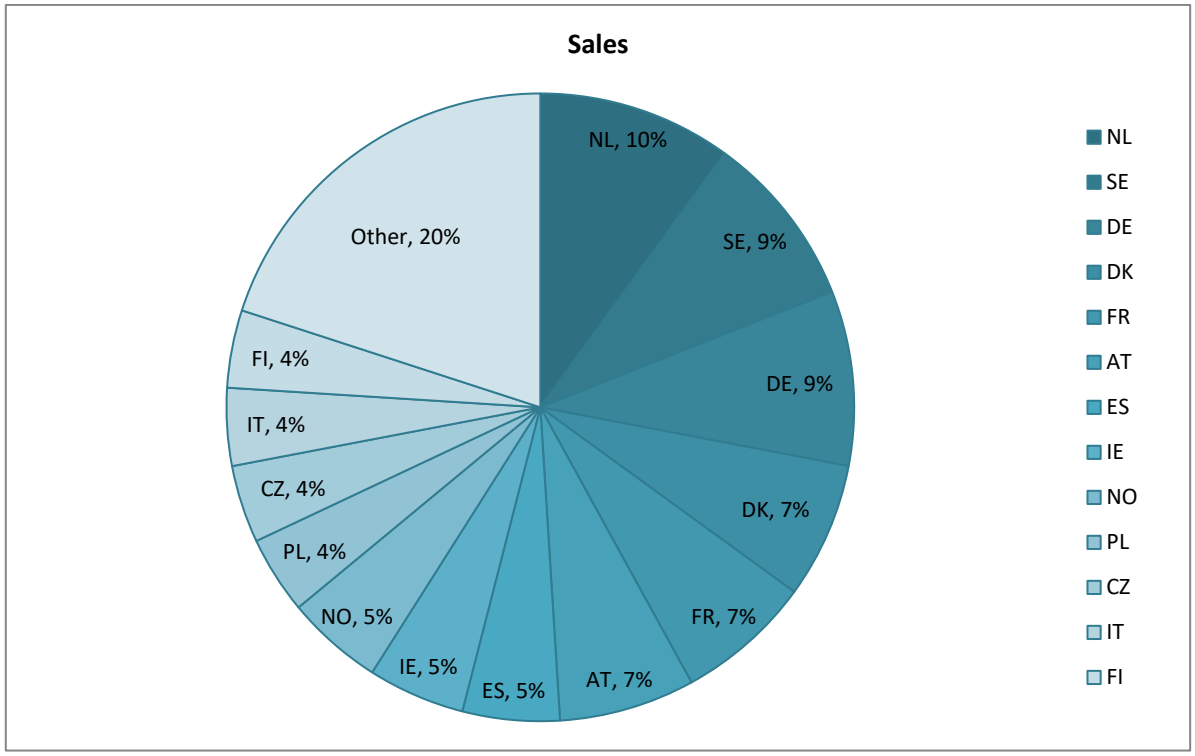

Fig. 8: Share of human Rap/Co-rap cases (2018) [9]

Comparison of 2015,2016,2017,2018:

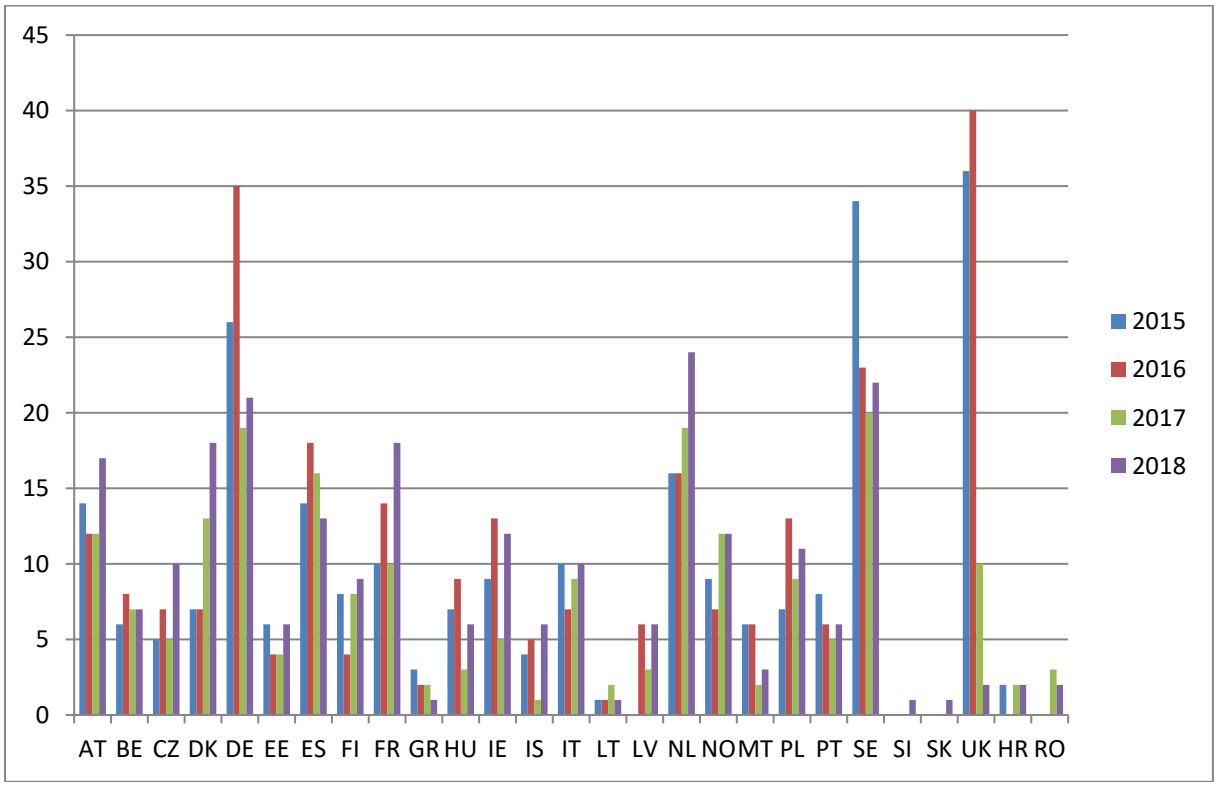

Fig. 9: comparison of Amount of assigned (co) rapportuerships in the EU in 2015, 2016, 2017, and 2018

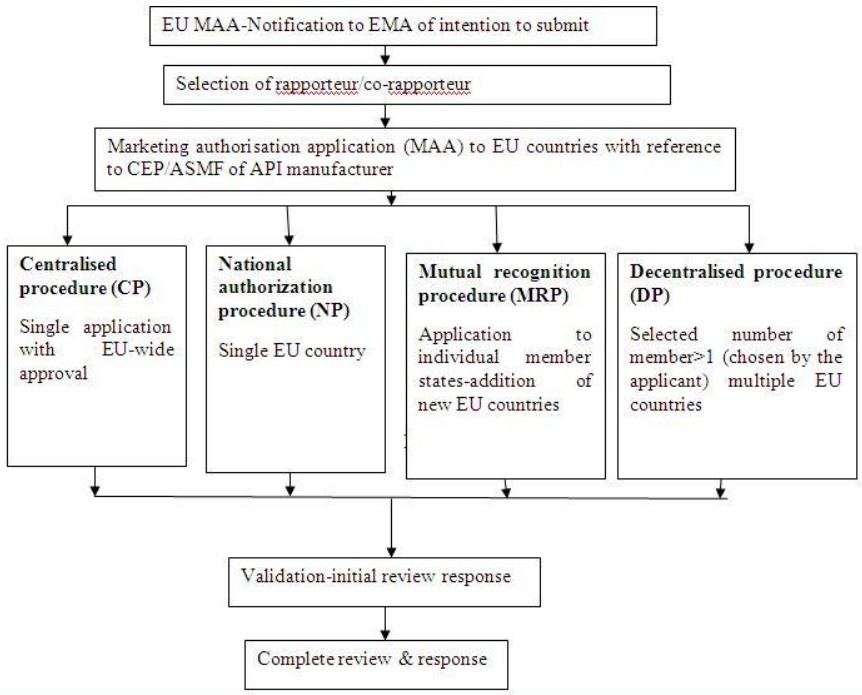

Fig: 10 EU: MAA Regulatory Submissions-General Process Flow chart

Table 2: Country wise assigned cases to co-Rapporteurship (year wise)

S.No	Country name	Country name-shortcut	Number of cases assigned to co-Rapporteurship (year wise)			
			2015	2016	2017	2018
1	Austria	AT	14	12	12	17
2	Belgium	BE	6	8	7	7
3	Czechia	CZ	5	7	5	10
4	Denmark	DK	7	7	13	18
5	Germany	DE	26	35	19	21
6	Estonia	EE	6	4	4	6
7	Spain	ES	14	18	16	13
8	Finland	FI	8	4	8	9
9	France	FR	10	14	10	18
10	Greece	GR	3	2	2	1
11	Hungary	HU	7	9	3	6
12	Croatia	HR	2	-	2	2
13	Ireland	IE	9	13	5	12
14	Icelandic	IS	4	5	1	6
15	Italy	IT	10	7	9	10
16	Lithuania	LT	1	1	2	1
17	Latvia	LV	-	6	3	6
18	Netherlands	NL	16	16	19	24
19	Norway	NO	9	7	12	12
20	Malta	MT	6	6	2	3
21	Poland	PL	7	13	9	11
22	Portugal	PT	8	6	5	6
23	Romania	RO	-	-	3	2
24	Sweden	SE	34	23	20	22
25	Slovenia	SI	-	-	-	1
26	Slovakia	SK	-	-	-	1
27	United Kingdom	UK	36	40	10	2
Total			246	263	201	247

Union register:

The union register lists all medicinal products for human and veterinary use as well as orphan medicinal products that have received a marketing authorisation by the commission through the centralised procedure.

Access to the Union Register: [9]

The information provided in the register can be accessed either by searching for the name of the product, the name of the active substance (INN), or the EU registration number.

The information includes the name of the medicinal product, the EU registration number, the name and address of the marketing authorization holder, the active substance, the international non-proprietary name, the anatomical therapeutic chemical (ATC) code and the therapeutic indication together with relevant documents.

In addition to medicinal products that are currently on the EU market, the register includes information on:

1. Medicinal products that were suspended or withdrawn, or for which a marketing authorization was refused.
2. Medicinal products for human and veterinary use adopted nationally for which a commission decision was necessary.
3. Commission decisions adopted in the last six months.
4. Medicinal products authorised by individual EU countries under article 126a of directive 2001/83.
5. A general index of active substances covered by commission decisions.
6. A general index of medicinal products listed by the brand name covered by commission decisions.

2) National authorisation procedures:

- ❖ In order to obtain a national marketing authorisation, an application submitted to the competent authority of the member state.
- ❖ Each EU member state has its own procedures for the authorisation, within their own territory.
- ❖ The competent authorities of the member states are responsible for granting marketing authorisations for medicinal products which are placed on their markets, except for medicinal products which are authorised under regulation (EC) NO 726/2004.
- ❖ MA applications should be within 210 days.
- ❖ If any organisation wishes to market their product only in one EU country then this is preferred procedure. No need to book the slot, only need to book the slot, only needs to inform relevant authority prior filing.
- ❖ In recent years, a national application is made in very limited number of cases.eg. Inability to get a slot with any RMS to run a DCP or complex product which any RMS does not wish to assess as part of DCP. In such cases the company is left with the option of getting it approved in a single country first and then take support of this approval to extend authorisation in other countries by mutual recognition procedure.

3) Mutual recognition procedure:

- ❖ Companies that have a medicine authorised in one EU member state (which would be through a national procedure) can apply for this authorisation to be recognised in other EU countries.
- ❖ Authorisation of the medicines in several countries simultaneously
- ❖ Quicker to first market
- ❖ Can withdraw application from critical CMS
- ❖ Second wave possible
- ❖ Different trade names possible
- ❖ 6/10 years data protection from first date

4) Decentralised procedure:

- ❖ For products that fall outside the scope of the European medicines agency with regard to centralised procedures, a sponsor can submit under the decentralised procedure.
- ❖ Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorised in any EU country.
- ❖ Need to book slot with choice of RMS via slot booking procedure.
- ❖ Once slot granted application needs to be submitted to RMS & all CMS

EU: MAA Regulatory Submissions-General Process Flow chart is shown in Figure: 10

Fees payable for medicinal products marketing authorisation in EU is shown in Table: 3 [10]

Table 3: Fees payable for medicinal products marketing authorisation in EU

Fee type	Human medicines	Veterinary medicines
Marketing authorization application (single strength, one pharmaceutical form, one presentation)	From €291,800	From €146,100
Extension of marketing authorization (level I)	€87,600	€36,500
Type-II variation (major variation)	€87,600	€43,700
Scientific advice	From €43,700 to €87,600	From €14,400 to 43,700
Annual fee (levelI)	€104,600	€35,000
Establishment of MRLs	-	€72,600

CONCLUSION:

European Union has established and harmonized regulations in the aspects of production, distribution, and use of medicines. EU has different types of procedures and different types of applications which will specify the product and time frame required for the approval of the drug which helps in tracking of life of the respective product. From 2015-2018 the innovation is increased under centralised procedure and at some point, the assigned cases decreased under centralised procedure.

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AUTHORS' CONTRIBUTION:

Navya Sri. B was involved in design and planning, execution and manuscript preparation. Sai Sindhu. P, Koushik. Y were involved in the manuscript preparation.

CONFLICTS OF INTEREST:

All authors approved the manuscript and this submission. The authors reported no conflicts of interest and no funding was received for this work.

REFERENCES:

1. https://ec.europa.eu/health/human-use/legal-framework en.
2. The European regulatory system for medicines [internet]. EMA; 2019 [cited 2019 Jan 02]. Available from: www.ema.europa.eu/en/documents/leaflet/european regulatory system medicines European medicines agency consistent approach medicines en.pdf.
3. European Medicines Agency (EMA) [internet]. London (UK) Volume 2 Mutual Recognition and decentralized procedure [cited 2019 Feb] Available from http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a/chap 2 2007- 2 en.pdf
4. https://ec.europa.eu/health/authorisation procedure-centralised en
5. https://laegemiddlestyrelsen.dk/en/licensing/licensing-of-medicines/case-statistics-and-order-books/numebr-of-cases-on-the-authorisation-of-medicinal-products/centralised-authorisation-procedure-2015/
6. https://laegemiddlestyrelsen.dk/en/licensing/licensing-of-medicines/case-statistics-and-order-books/numebr-of-cases-on-the-authorisation-of-medicinal-products/centralised-authorisation-procedure-2016/
7. https://laegemiddelstyrelsen.dk/en/licensing/licensing-of-medicines/case-statistics-and-order-books/number-of-cases-on-the-authorisation-of-medicinal-products/centralised-authorisation-procedure-2017/
8. https://laegemiddelstyrelsen.dk/en/licensing/licensing-of-medicines/case/statistics-and-order-books/number-of-cases-on-the-authorisation-of-medicinal-products/centralised-authorisation-procedure-2018/
9. https://ec.europa.eu/health/documents/community-register en
10. https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency#fees-for-marketing-authorisations-section