Healthcare information system engineering: AI technologies and open source approaches

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Chapter 4

Automatic Extraction of Adverse Drug Reactions from SmPC

The summary of product characteristics from the European Medicines Agency is a reference document on medicines in the EU. It contains textual information for clinical experts on how to safely use medicines, including adverse drug reactions. Using natural language processing (NLP) techniques to automatically extract adverse drug reactions from such unstructured textual information helps clinical experts to effectively and efficiently use them in daily practices. Such techniques have been developed for Structured Product Labels from the Food and Drug Administration (FDA), but there is no research focusing on extracting from the Summary of Product Characteristics. In this work, we built a natural language processing pipeline that automatically scrapes the summary of product characteristics online and then extracts adverse drug reactions from them. Besides, we have made the method and its output publicly available so that it can be reused and further evaluated in clinical practices. In total, we extracted 32,797 common adverse drug reactions for 647 common medicines scraped from the Electronic Medicines Compendium. A manual review of 37 commonly used medicines has indicated a good performance, with a recall and precision of 0.99 and 0.934, respectively.

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4.1 Introduction

Drug product labels are regulatory documents required as part of the marketing authorization of each medicine. They provide up-to-date and comprehensive information about the risks, benefits, and pharmacological properties of marketed medicines. As such, extracting the clinical knowledge stored in product labels and making it available in the form of computationally accessible knowledge bases would benefit several applications in the area of drug safety surveillance and assessment. For example, during post-marketing safety assessments, it is crucial to determine whether an investigated adverse drug reaction (ADR) is already labeled (Banda et al., 2016; Roberts et al., 2017).

There are two main versions of drug product labels around the world: Structured Product Labels (SPL) introduced by the Food and Drug Administration (FDA) in the US, and the Summary of Product Characteristics (SmPC) supervised by the European Medicines Agency (EMA) in the EU (Shekhani et al., 2020). Both product labels provide information in sections, and the content of each section is in free narrative texts. This study focuses on the undesirable side effect section of product labels which describes adverse drug reactions (ADRs).

To date, there are no structured machine-readable ADRs. Therefore, extracting ADRs from unstructured product labels becomes an interesting research topic. There are many studies focusing on transforming unstructured ADRs data into structured machine-readable data (Ly et al., 2018; Fung et al., 2013; Wu et al., 2019; Demner-Fushman et al., 2018; Kuhn et al., 2016). However, the majority of current studies focus on the US version of product labels. For example, systems such as SPLICER and SPL-X were developed to extract ADR terms from particular sections using various natural language processing (NLP) techniques, including named entity recognition, rule-based parsing, and NegEx (Ly et al., 2018). Fung et al. (2013) proposed to use open-source NLP tools to extract drug indication information from SPL. Wu et al. managed to fetch ADR terms using Oracle Text search from 1164 single-ingredient medicines (Wu et al., 2019). A variety of NLP techniques were designed to extract ADRs from SPL in the 2017 Text Analysis Conference track (Roberts et al., 2017).

However, the FDA SPL is the main data source used in such studies. Until now, the SmPC, as the European equivalent to SPL, has barely been investigated and no method has been developed solely for extracting ADRs from the SmPC. This study contributes to the field as a starting point.

In this study, the main research question we are addressing is how to utilize NLP techniques to automatically extract ADRs from standardized European product labels, namely SmPC. To answer the question, we first develop an NLP pipeline to extract adverse drug reactions from SmPC. A knowledge base is created from the extracted terms. The main characteristics of the NLP pipeline and the knowledge base are summarized as follows: (a) open-source and reproducible; (b) customizable for related ad hoc tasks; (c) knowledge base applicable for clinical studies.

The paper is structured as follows. section 4.2 defines a number of methods and materials used in our study. Then the results are presented in section 4.3. Discussions in section 4.4 summarize the main findings of this research and some limitations. section 4.5 concludes the study.

4.2 Materials and Methods

In this section, we describe the SmPC data source, elaborate on the various NLP techniques that are applied to extract ADRs from SmPC, and briefly explain the evaluation setup for validating our automatic ADR extraction approach. A conceptual overview of the ADR extraction pipeline is illustrated in Figure 4.1. The first step is to scrape the side effects data from the Electronic Medicines Compendium (EMC). Then the ADRs are extracted accordingly. Finally, the performance of our NLP method is evaluated by both NLP and clinical experts.

4.2.1 Dataset

All SmPCs were scraped from the EMC which provides the most recent and openly accessible regulated and approved information about medicines licensed in the UK (Electronic Medicines Compendium (EMC), 2020). The EMC was selected as our data source for two main reasons: (1) all information is in English; (2) it has more than 14,000 documents, all of which have been checked and approved by the European government agencies. Figure 4.2 shows an example of the side effects section of SmPC.

4.2.2 Scraping the Side Effects Section of SmPC

Since this study focuses on commonly used medications, we only scrape the SmPCs of a limited number of medicines in the EMC. As shown in Figure 4.1, the process of scraping side effects data starts with identifying active substances. Then, for

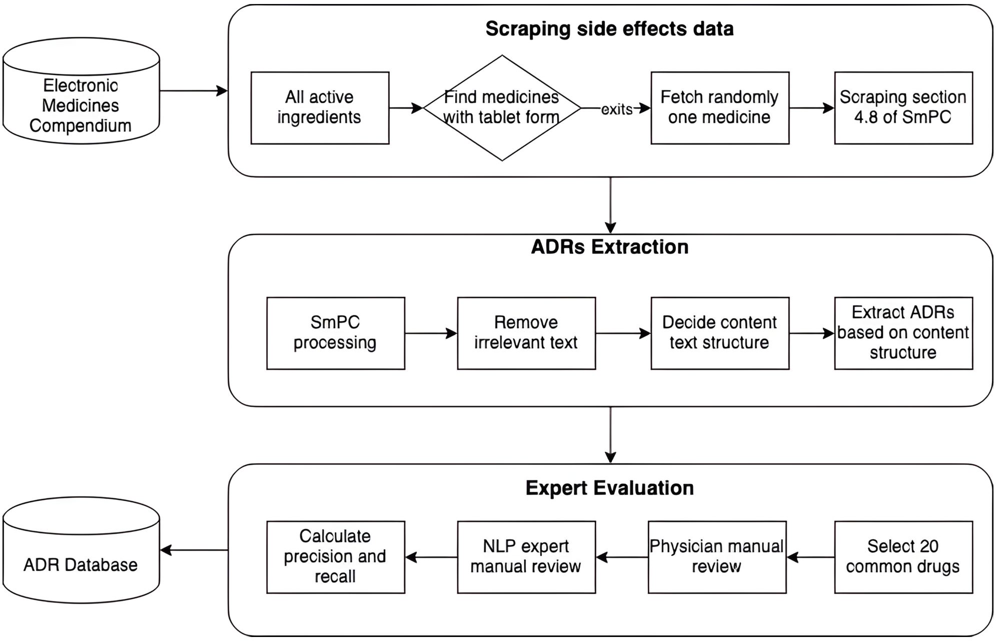

Electronic Medicines Compendium
Scraping side effects data
All active ingredients
Find medicines with tablet form
exits
Fetch randomly one medicine
Scraping section 4.8 of SmPC
ADRs Extraction
SmPC processing
Remove irrelevant text
Decide content text structure
Extract ADRs based on content structure
Expert Evaluation
Select 20 common drugs
Physician manual review
NLP expert manual review
Calculate precision and recall
ADR Database

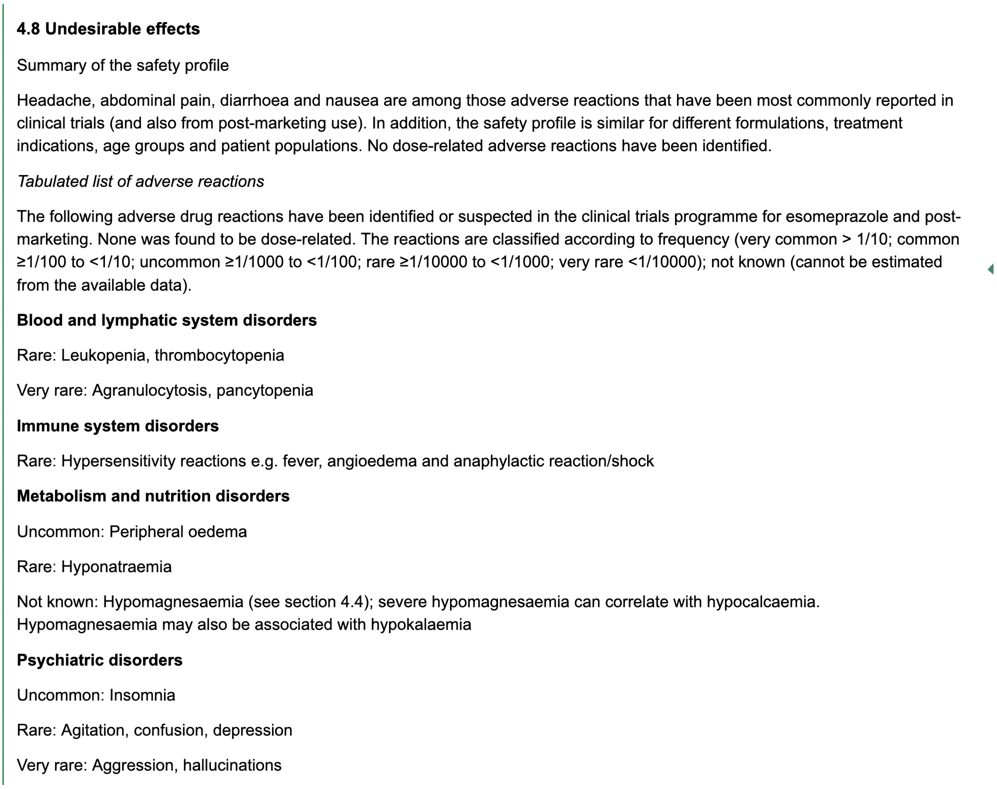
Figure 4.1: A conceptual overview of the automatic Adverse Drug Reactions (ADRs) extraction pipeline.

each active substance, only one medication in tablet form is included in the final list which contains 647 medicines, because the tablet form is the most common medication route. When there is no medicine in tablet form for a given active substance, none is selected. At last, section 4.8 Undesirable effects of the SmPC is obtained for all 647 medications in the final list. The 4.8 section consists of ADR information in both plain text and structured tables, we scraped the available information in HTML format so that the data structure is kept. All data is stored as a JSON file, which is used in the later steps.

4.2.3 ADR Extraction

SmPC Processing

In the second phase of our NLP pipeline is ADR extraction. It starts with processing the above-mentioned ADR relevant HTML excerpts. As we described before, the section 4.8 in the SmPC contains ADR information in diverse formats: plain text, structured text, and tables. Tables used in describing ADR information also come



4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency (very common > 1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥1/10000 to <1/1000; very rare <1/10000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: Leukopenia, thrombocytopenia

Very rare: Agranulocytosis, pancytopenia

Immune system disorders

Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: Peripheral oedema

Rare: Hyponatraemia

Not known: Hypomagnesaemia (see section 4.4); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia

Psychiatric disorders

Uncommon: Insomnia

Rare: Agitation, confusion, depression

Very rare: Aggression, hallucinations

Figure 4.2: An example of a Summary of Product Characteristics (SmPC) excerpt.

with different structural styles. Therefore, we classify the 4.8 section into separate categories in terms of its content structure. Figure 4.3 elaborates on the process of categorization. Each category has its own ADR extraction technique.

First, we identify a list of structural features in the HTML excerpts, for instance, the counts of '<table>', the counts and positions of some MedDRA terms (Mozzicato, 2007), such as the frequency and SOC (System Organ Classes) (MedDRA, 2020). Table 4.1 shows some specific examples of such words. Secondly, the features are engineered from the scraped HTML files. Based on the features, we obtain three main structural categories: structured text, free text, and tabular.

- Free-text: ADRs are explained in free-text, as shown in Figure 4.4a. ADRs are hidden in sentences, which thus requires named entity recognition (NER) to extract them.

- Structured text: ADRs are described in a structured text, as shown in Fig-

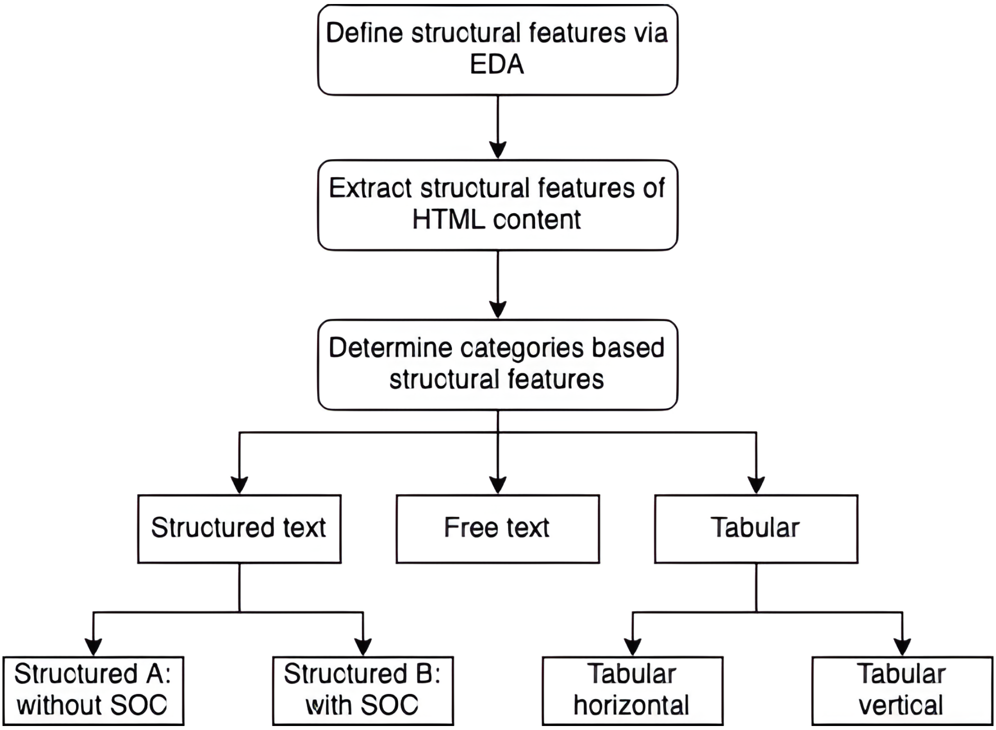

Define structural features via EDA
Extract structural features of HTML content
Determine categories based structural features
Structured text
Free text
Tabular
Structured A: without SOC
Structured B: with SOC
Tabular horizontal
Tabular vertical

Figure 4.3: A decision tree for classifying the ADR content during SmPC processing.

ure 4.4b. It depicts a list of ADRs and their frequencies in an organized format.

- Tabular: ADRs are presented in a very structured way, namely a table. Figure 4.4c shows an example of such tables. These tables are further split into two groups: tabular horizontal and tabular vertical.

ADR Extraction

In the previous section, we identify three main structural categories that require different ADR extraction techniques, respectively. An overview of the extraction pipeline for each category is illustrated in Figure 4.5.

To uncover the hidden ADRs in the free-text, entity extraction techniques are applied. Specifically, we simplify the extraction process by using the IBM Watson Natural Language Understanding API that offers sophisticated NLP techniques in extracting meta-data from content such as concepts, entities, keywords, and others.

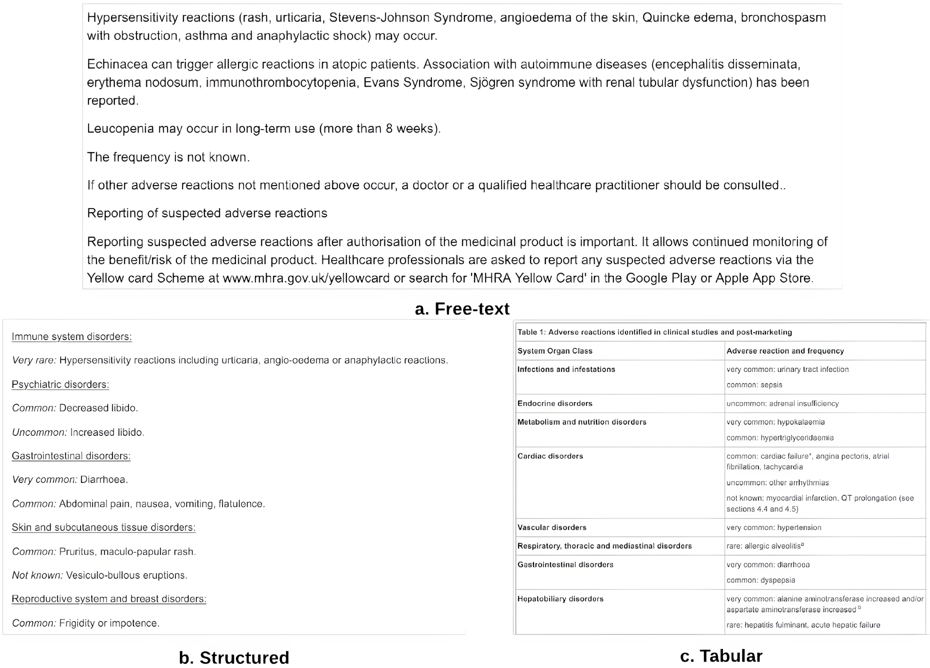
Term Type	Description	Examples
Frequency	Terms that describe how often an ADR happens	Very common Common Uncommon Rare Very rare Not known
SOC	The highest level of groupings in MedDRA. There are 27 groups which are defined by etiology (Electronic Medicines Compendium (EMC), 2020).	Immune system disorders Metabolism and nutrition disorders Nervous system disorders Eye disorders Cardiac disorders Gastrointestinal disorders Skin and subcutaneous tissue disorders General disorders and administration site conditions Investigations

Table 4.1: Examples of ADR-specific terminologies.

Benchmarking studies have shown that IBM Watson Natural Language Understanding API is a simple and useful NLP tool in solving various clinical NLP problems (Canonico and De Russis, 2018; Shen et al., 2019a). A demonstration of how the API works is available (IBM, 2021b). Since the number of ADR terms is relatively limited, we can use the API for free. It offers a lite account which can process 30, 000 items per month free of charge (IBM, 2021a). Frequencies of the extracted ADRs are assigned as unknown due to their absence in the free texts.

For the structured text, we extract ADR terms and their corresponding frequencies with syntax parsing. The syntactic structure of a structured HTML text is depicted by the occurrences and positions of SOC (System Organ Class) and frequency terms. With the identified positions of SOC and frequency terms, we can obtain the HTML elements that contain only ADR terms. In most cases, ADRs terms in an HTML element are separated by a comma. Thus, by splitting the string by comma, we extract several ADRs for a given SOC and frequency. An example of such ADR extraction is illustrated in Figure 4.6. The left is the structured text in HTML and the right side shows the extracted ADRs in JSON.

The tabular text refers to HTML tables that describe ADRs of a given medicine in a two-dimensional grid format. The first step of information extraction for HTML tables is to detect the structure. As mentioned above, we identify two types of struc-



Hypersensitivity reactions (rash, urticaria, Stevens-Johnson Syndrome, angioedema of the skin, Quincke edema, bronchospasm with obstruction, asthma and anaphylactic shock) may occur.

Echinacea can trigger allergic reactions in atopic patients. Association with autoimmune diseases (encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Evans Syndrome, Sjögren syndrome with renal tubular dysfunction) has been reported.

Leucopenia may occur in long-term use (more than 8 weeks).

The frequency is not known.

If other adverse reactions not mentioned above occur, a doctor or a qualified healthcare practitioner should be consulted..

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

a. Free-text

Immune system disorders:

Very rare: Hypersensitivity reactions including urticaria, angio-oedema or anaphylactic reactions.

Psychiatric disorders:

Common: Decreased libido.

Uncommon: Increased libido.

Gastrointestinal disorders:

Very common: Diarrhoea.

Common: Abdominal pain, nausea, vomiting, flatulence.

Skin and subcutaneous tissue disorders:

Common: Pruritus, maculo-papular rash.

Not known: Vesiculo-bullous eruptions.

Reproductive system and breast disorders:

Common: Frigidity or impotence.

b. Structured

Table 1: Adverse reactions identified in clinical studies and post-marketing

System Organ Class	Adverse reaction and frequency
Infections and infestations	very common: urinary tract infection common: sepsis
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis^{a}
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased ^{b} rare: hepatitis fulminant, acute hepatic failure

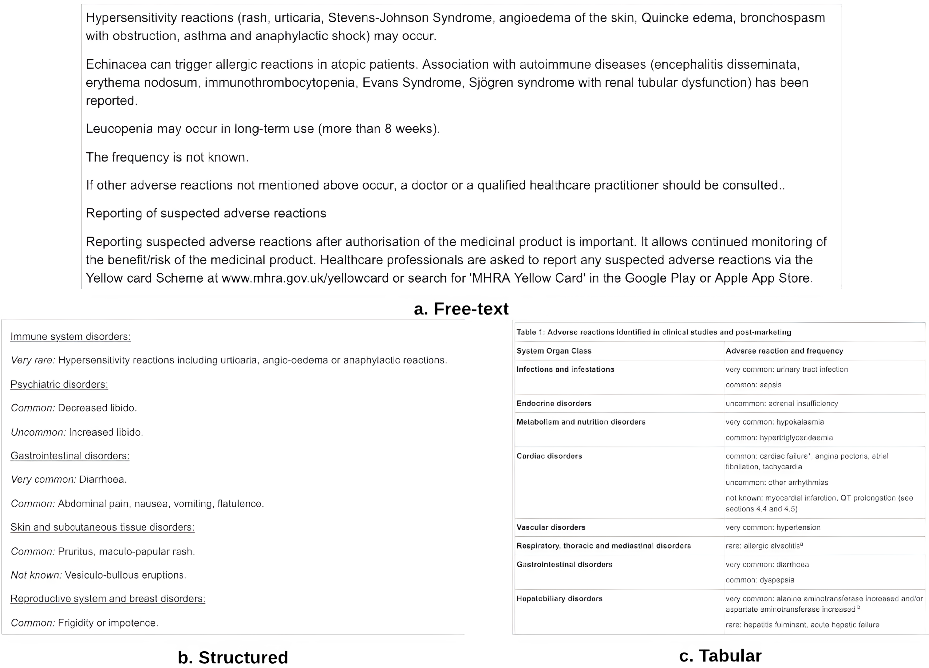
c. Tabular

Figure 4.4: Example fragments of the three main structural categories: **(a)** free text, **(b)** structured text, and **(c)** tabular text.

tures: vertical and horizontal. Similar to structured text, ADR extraction starts with getting the occurrences and positions of SOC and frequency terms. Then, with the position indexes of SOC and frequency terms, HTML table cells that contain ADR terms are fetched and processed. ADR terms in an HTML table cell are usually separated by a comma. An example is given in Figure 4.7.

4.2.4 Evaluation

An expert manual review is performed in the evaluation of ADRs extracted from the SmPCs in this study. To alleviate the burden of manual reviewing for our clinical experts, we only sample a small subset of common medicines. Moreover, an NLP expert is also involved in the manual review. The NLP expert specializes in processing the clinical text and has a sufficient clinical knowledge to properly review the extracted ADRS. In total, 37 medications were selected by the clinical expert for manual review.



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Echinacea can trigger allergic reactions in atopic patients. Association with autoimmune diseases (encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Evans Syndrome, Sjögren syndrome with renal tubular dysfunction) has been reported.

Leucopenia may occur in long-term use (more than 8 weeks).

The frequency is not known.

If other adverse reactions not mentioned above occur, a doctor or a qualified healthcare practitioner should be consulted..

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

a. Free-text

Immune system disorders:

Very rare: Hypersensitivity reactions including urticaria, angio-oedema or anaphylactic reactions.

Psychiatric disorders:

Common: Decreased libido.

Uncommon: Increased libido.

Gastrointestinal disorders:

Very common: Diarrhoea.

Common: Abdominal pain, nausea, vomiting, flatulence.

Skin and subcutaneous tissue disorders:

Common: Pruritus, maculo-papular rash.

Not known: Vesiculo-bullous eruptions.

Reproductive system and breast disorders:

Common: Frigidity or impotence.

b. Structured

Table 1: Adverse reactions identified in clinical studies and post-marketing

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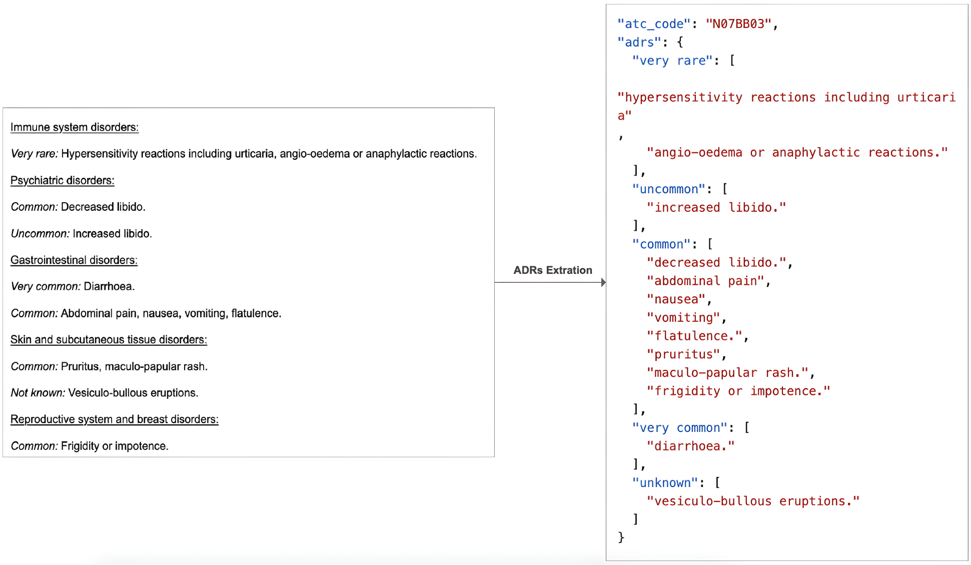
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased [b] rare: hepatitis fulminant, acute hepatic failure

c. Tabular

Figure 4.5: An Overview of the ADR Extraction Pipeline.

The clinical expert provided a list of top 50 commonly used medicines in Dutch primary care, and 37 of 50 were available in our scraped drug list. At the beginning of the evaluation, both clinical and NLP experts are requested to review five identical medicines to align the manual reviews of different experts. Following that, due to time constraints, the clinical expert is asked to review five more medicines, whereas the NLP expert continues to review 32 more medicines.

For each medicine, all extracted ADRs are examined and labeled as 'correct', 'near', or 'incorrect'. Furthermore, the number of missing ADRs is counted by comparing the extracted ADRs with the original SmPC. Subsequently, we obtain the numbers of true positives (TP), false positives, and false negatives (FN). The ADR terms with only 'correct' label are considered as TP, both 'near' and 'incorrect' are FP, and the missing ADRs are FN. The standard metrics of recall, precision, and F-score are calculated to measure the performance of the proposed automated approach.



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Psychiatric disorders:

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Gastrointestinal disorders:

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Common: Abdominal pain, nausea, vomiting, flatulence.

Skin and subcutaneous tissue disorders:

Common: Pruritus, maculo-papular rash.

Not known: Vesiculo-bullous eruptions.

Reproductive system and breast disorders:

Common: Frigidity or impotence.

```
"atc_code": "N07BB03",
"adrs": {
  "very rare": [

"hypersensitivity reactions including urticari
a"
,
    "angio-oedema or anaphylactic reactions."
  ],
  "uncommon": [
    "increased libido."
  ],
  "common": [
    "decreased libido.",
    "abdominal pain",
    "nausea",
    "vomiting",
    "flatulence.",
    "pruritus",
    "maculo-papular rash.",
    "frigidity or impotence."
  ],
  "very common": [
    "diarrhoea."
  ],
  "unknown": [
    "vesiculo-bullous eruptions."
  ]
}
```

Figure 4.6: An example of ADR extraction for the structured text.

4.3 Results

This section presents the results of our proposed ADR extraction method and the manual evaluation results.

4.3.1 Overview

This study scrapes the SmPC documents of a total number of 647 marketed medicines, from which 32,797 ADR terms and their frequencies are extracted. Among all extracted ADR terms, 8069 are unique. The average number of ADR terms per medicine is 51. Table 4.2 offers a statistical overview of the extraction results from our selected medicines.

4.3.2 The Manual Evaluation Results

Clinical experts chose 37 commonly prescribed medicines for manual reviews. Appendix A in the section 4.6 provides a complete list of the 37 reviewed medicines. Among these chosen medicines, there are 28 tabular texts, 7 structured texts, and 2 free texts. As explained before, two experts participated in the manual evaluation. Table 4.3 shows the results of the manual review, including some important perfor-

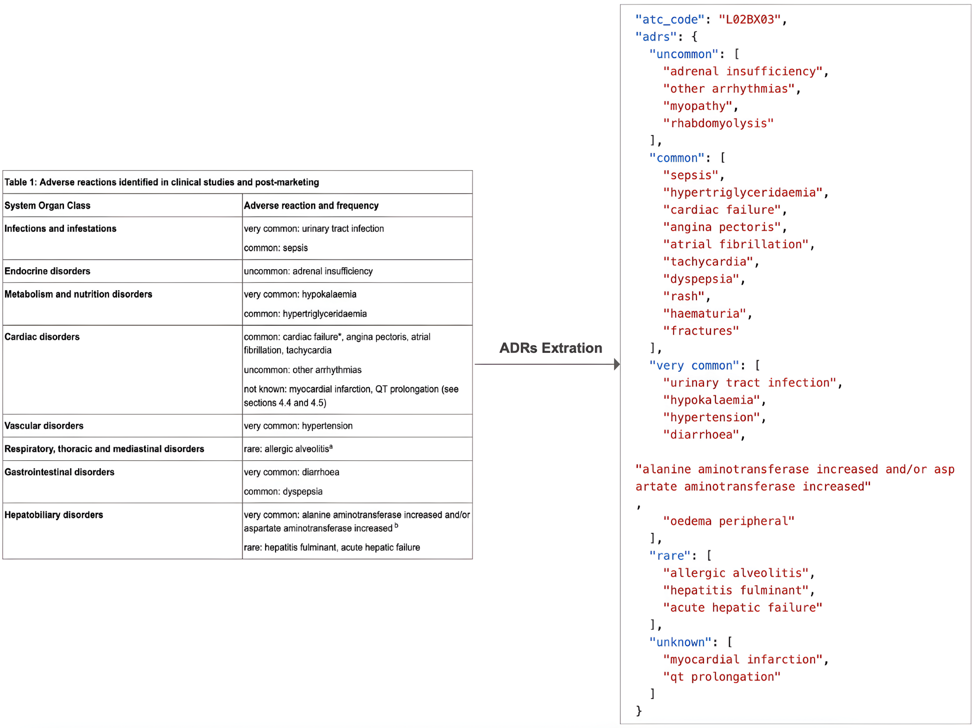

Table 1: Adverse reactions identified in clinical studies and post-marketing	
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Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased [b] rare: hepatitis fulminant, acute hepatic failure

```
"atc_code": "L02BX03",
"adrs": {
  "uncommon": [
    "adrenal insufficiency",
    "other arrhythmias",
    "myopathy",
    "rhabdomyolysis"
  ],
  "common": [
    "sepsis",
    "hypertriglyceridaemia",
    "cardiac failure",
    "angina pectoris",
    "atrial fibrillation",
    "tachycardia",
    "dyspepsia",
    "rash",
    "haematuria",
    "fractures"
  ],
  "very common": [
    "urinary tract infection",
    "hypokalaemia",
    "hypertension",
    "diarrhoea",

"alanine aminotransferase increased and/or asp
artate aminotransferase increased"
,
    "oedema peripheral"
  ],
  "rare": [
    "allergic alveolitis",
    "hepatitis fulminant",
    "acute hepatic failure"
  ],
  "unknown": [
    "myocardial infarction",
    "qt prolongation"
  ]
}
```

Figure 4.7: An example of ADR extraction for the tabular text.

mance scores, such as recall and precision. For each medicine, the number of true positives, false positives, and false negatives are counted. An extracted term is considered as true positive only when it is reviewed as a correct ADR compared with the original text. False positives refer to the extracted terms that are not ADRs. The missing ADRs are labeled as false negatives. The overall recall and precision of all reviewed medicines are 0.99 and 0.932, respectively, which shows the effectiveness of our ADR extraction approach and the reliability of its outputs.

4.3.3 Error Analysis

Three main types of errors are identified among the 116 incorrect extracted ADRs of Reviewer 1 (false positives). Table 4.4 summarizes the error analysis of incorrectly extracted ADRs. Our approach encountered issues with splitting multiple ADR terms that are joined by a colon or semicolon. For instance, two ADR terms (agitation and aggression) could be extracted from ‘Agitation, aggression’. However, if multiple

Characteristics	Statistics
# of selected marketed medicines	647
# of medicines with structured text	141
# of medicines with tabular text	419
# of medicines with free text	87
Average ADRs per medicine	51
25% percentile ADRs per medicine	21
50% percentile ADRs per medicine	38
75% percentile ADRs per medicine	67
Top medicines in terms of extracted ADRs	1.Topamax 100 mg Tablets (269) 2. Revolade 25 mg film-coated tablets (255) 3.Capecitabine Accord 150 mg film coated tablets (240) 4.Glivec 100 mg film-coated tablets (232) 5.Risperdal 0.5 mg Film-Coated Tablets (218) 6.Xadago 50 mg film-coated tablets (215) 7.Invega 12 mg prolonged-release tablets (207) 8.LUSTRAL 100 mg film coated tablets (207) 9.Isentress 100 mg chewable tablets (191)

Table 4.2: Overview of the ADR extraction results.

ADR terms are joined by 'or', 'and', or semicolon, such as the examples shown in Table 4.4, our extraction method fails to properly address this. The second type of false-positive results is related to the data cleaning of our approach. The extracted ADRs contain noises such as unrelated words or special characters. As shown in the examples, to get the correct ADRs, we need to clean up noises like '2̌020', and 'in combination with insulin or sulphonylurea'. Lastly, a small number of extracted terms are not ADRs at all. For example, 'skin and subcutaneous tissue disorders' is an SoC term

	Reviewer 1 (NLP Expert)	Reviewer 2 (Clinical Expert)	Totals
# of reviewed medicines	32	5	37
# of extracted ADRs terms	1700	118	1824
# of correct ADRs (TP)	1590	110	1703
# of incorrect ADRs (FP)	116	8	124
# of missing ADRs (FN)	7	11	18
Recall	0.996	0.909	0.99
Precision	0.932	0.932	0.932

Table 4.3: Final results of the manual expert reviews.

that should be excluded from our final ADR lists. Since other incorrect extractions do not belong to any specific group, it is difficult to exclude them. However, the number of such errors is so small that its impact is limited.

Type of Error	Examples	Extracted Terms	Counts
Unsplit multiple ADTs	"angio-oedema or anaphylactic reactions"	- angio-oedema - anaphylactic reactions	81
ADR with noise	- 'retinal detachment' - 'hypoglycaemia in combination with insulin or sulphonylurea'	- retinal detachment - hypoglycaemia	22
Non-ADR	- 'all causality frequency' - 'general disorders:' - 'skin and subcutaneous tissue disorders'	Not ADR	13

Table 4.4: Error analysis for false positives.

Since there are only seven missing ADRs out of 1706 extracted ADRs, false-negative (missing ADR) is not a common error. However, we found that such an error is more likely to happen to medicines using free text to describe their ADRs. Since only 87 out of the selected 647 medicines summarize their ADRs in free-text, and the number of unstructured reported medicines has been steadily decreasing with recent SmPC updates, the false-negative error has a relatively limited and decreasing impact on the performance of our approach.

4.4 Discussion

Many studies investigated the extraction of ADRs from SPLs from the FDA in the USA, and some effective methods have been developed. However, as an equivalent in Europe, the SmPC from the European Medicines Agency receives very little attention in the field of NLP. In this study, we fill the research gap with the development of an automated ADRs extraction method for the SmPC.

The manual experts review results demonstrate that our proposed method is effective and has the potential of being used to solve ADR related clinical problems. Specifically, our method achieves an overall recall of 0.990 and a precision of 0.932. Such high performance has never been reported in previous studies focusing on extracting ADRs from SPLs (Wu et al., 2019; Pandey et al., 2019).

As discussed in the error analysis, there are a few ways to further improve the performance of our method. For example, noise in the extracted terms can be cleaned with regular expressions. When it comes to the unsplit multiple ADRs, we can extend the split function with more options so that it allows strings to be split by 'or', 'and', or semicolon. Furthermore, encoding extracted ADR terms into MedDRA Preferred Terms could reduce the non-ADR errors, thus further improving the performance.

Our study has some limitations. First, there are no standardized ADR annotations based on the SmPC available to benchmark ADR extraction methods. It is difficult to reproduce the performance of this study. Manual reviews from different experts might present different performance scores.

Another limitation lies in the manual review process of this study. Involving clinical experts in the manual review process is always challenging given their busy schedule. The coronavirus has made the situation even worse. Therefore, the manual process in this study only included one clinical expert. To compensate for this, we added one clinical NLP expert as another reviewer. The NLP expert is familiar with this topic and was trained for the task by the clinical expert. To address this, we plan to expand the manual review to a larger size of samples and a bigger group of clinical experts in a post-COVID world.

The proposed ADR extraction method is developed based on data from the EMC in UK. However, due to Brexit, product labels in UK might changes. Then the method will not perform the same as shown in this study. Further development of this method should focus on using the SmPCs from the EMA.

4.5 Conclusions

The contributions of this study are two-fold. First, it contributes to the field of clinical NLP by introducing an open-source and reproducible method that extracts ADR terms from the SmPC. The high-performance scores (recall: 0.99 and precision: 0.934) indicate our approach is very effective, which leads us to believe that the method could be useful in the processing and coding of ADRs in the SmPC. The second contribution lies in the clinical field. The results of our extraction method are structured data that describes marketed medicines and their recorded ADRs and frequencies. Such a knowledge base could be applied to address practical clinical problems, ranging from ADR assessment in clinical trials to assisting the detection of ADRs in patients.

4.6 Supplementary Materials

The following materials are available online at https://github.com/ianshan0915/ade-extraction/paper, Appendix A: Appendix A-manual review results.xlsx. Source code of the project is available on https://github.com/ianshan0915/ade-extraction.