Original Article

Analyzing United States Prescribing Information to gain insight into FDA-sponsor discussions

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ABSTRACT **The United States Prescribing Information (USPI) is a key vehicle for communicating the benefit-risk information of a Food and Drug Administration (FDA) approved prescription drug. The USPI is typically the last step of the drug development process and requires discourse between the FDA and the sponsor for a new drug application. The USPI may also be updated after obtaining FDA approval. As a social artifact of industry and FDA discussions, it is hypothesized that an analysis of a library of USPI records may yield insight into this dialog. Here, an analysis of DailyMed – a USPI data repository – reveals that structural language similarities (linguistic typologies) exist across USPI. Interestingly, these typologies describe labeling language that may not be explicitly described in FDA regulatory documentation. It is proposed that the methodology herein proposed may be leveraged to potentially facilitate USPI development and FDA dialogue (and therefore expedite the drug development paradigm). Several examples are used to showcase the approach. A discussion on limitations of the methodology and opportunities for development is also presented.**
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INTRODUCTION

Biopharmaceutical/biotechnology/pharmaceutical firms (also called sponsors or Marketing Authorization Holders (MAHs)) work with Food and Drug Administration (FDA) to co-navigate applicable regulatory guidelines and legal constructs,[1] interpretation of current scientific knowledge by external 'advisors',[2] and inferred outcomes (see, for example[3]) to develop and communicate pertinent and timely benefit-risk information for FDA-approved drugs that will enable the

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FDA to meet its mandate for protecting and promoting public health.[4] The United States Prescribing Information (USPI) is a key mechanism to communicate to prescribers such benefit-risk information in the form of codified claims of clinical efficacy, measures of safety and risk management, and guidelines on appropriate dosage (21 CFR 201[5]), and has been core component of the benefit-risk 'tool-box' since inception of the FDA.[6] The USPI is the result of discussions – typically performed at the end of the drug approval paradigm[7] – between the sponsor and the FDA, not infrequently with influence from external advisors.[2] The USPI – also known as the drug product label, prescription drug labeling, product insert, package insert, professional label, direction circular or package circular – may also refer to additional FDA-approved 'patient-friendly' labeling including the Patient Package Insert (PPI), Medication Guide (MG) and/or Patient Instructions for Use (PIU or IFU). Although the terminology may be considered imprecise, in this article and for the ease of the reader, the terms 'label' (21 U.S.C. 321(k)) and 'labeling' (21 U.S.C 321 (m)) are used interchangeably with a focus on prescriber information.

Although its function has been immutable since inception, the form of the USPI has recently undergone a transformation. Driven by the didactic 'to make information in prescription drug labeling easier for health care practitioners to access, read, and use … labeling to make prescribing decisions (FR Doc E9-4372[8])', the final rule (the so-called Physician's Labeling Rule (PLR)) was promulgated in 2006 enforcing a significant change to the face of the USPI.[5,9,10] This work seeks to reduce 'the number of adverse reactions resulting from medication errors because of misunderstood or incorrectly applied drug information,[11]' by requiring a general reorganization of the USPI structure (for example, the introduction of highlights and full prescribing information sections and table of contents), specific requirements surrounding formatting (for example, font size), reducing redundancy and a concomitant submission of an electronically formatted USPI. It may be recognized that the change in the structure of the USPI may facilitate readability, it is not clear, however, if it would influence compliance (see, for example,[12]). As with any such undertaking, it may take several years before the advantages and disadvantages of these changes are fully appreciated by the prescribing community.

The landscape by which the language of the USPI takes shape is seemingly simple in concept, but potentially challenging in implementation. For example, within post-marketing experience, the initiation of the USPI discussion is a change in the claim of the benefit or risk attributes of the drug that may be instigated by either the sponsor or the FDA (for example, as part of class labeling). Both parties leverage regulatory guidance and laws in their pursuit for labeling language that accurately reflects the data and/or clinical intent of the labeling topic.

On occasion, extant FDA guidance may define the appropriate labeling language. For example, in the post-marketing setting, should a sponsor receive a spontaneous safety report from their pharmacovigilence activities, FDA guidance (page 7/8 in[13]) suggests that the label language take the following form:

> The following adverse reactions have been identified during postapproval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Frequently, however, labeling text development is not straightforward, as is the case when guidance is new, non-existent, general, or the supportive data is interpretable. For example, it was only recently that the FDA introduced a section within the USPI termed 'pharmacogenomics' that would allow presentation concerning 'clinically relevant

information on the effect of polymorphic variation in drug metabolizing enzymes, transporters, receptors and other proteins on pharmacokinetics, pharmacodynamics and/or clinical responses (both safety and efficacy) (page 13 in[14]).' Interpretation of regulatory guidance may be seen as tedious for firms (both internally as they seek to ratify the firm's position) and the FDA as they try to find 'common' ground on labeling language.

Concomitant with the formatting change, a mandate for sponsors to supply product labeling in an electronic record – called Structured Product Labeling (SPL), a dialect of XML, – was promulgated. The SPL record of FDA-approved product labeling is displayed on DailyMed, a joint venture of the National Library of Medicine (NLM) and FDA. DailyMed is a freely accessible web database of USPI records built to facilitate access to prescribing information. DailyMed has been growing relatively rapidly since its launch in November 2005; as of 15 March 2010 (15:02 PST), it contained 7025 records, a jump from 4719 records on 29 July 2009 (14:00 PST). Each record represents either a pre- or a post-PLR-formatted USPI record. Further information concerning DailyMed may be found at http://dailymed.nlm.nih.gov/.

Given the dynamics of the USPI (as a socio-linguistic artifact of discussions), and the existence of DailyMed (as a repository of USPI records), it is the author's opinion that analysis of FDA-approved product labeling may provide valuable insight into a number of important questions, some of which have considerable practical utility. In this article, as DailyMed does not currently allow for facile searching (see Conclusions for discussion), labeling language is explored through analyzing the DailyMed USPI repository with a freely available search engine, google. As a means to showcase how the methodology may elucidate extant FDA thinking, as well as facilitate label language development, the following language hypotheses, based on experiential knowledge, were developed and investigated.

- Limitations of use;
- prophylaxis management;
- pharmacogenomics;
- comparison of incidence antibodies;
- presentation of pH language.

After reviewing the methods used to cull DailyMed, the results are presented and discussed. The article concludes with a discussion of both the opportunities and limitations of the approach, a proposal to enhance the usability of DailyMed, and a synopsis of how these findings may affect the labeling discussion process.

METHODS, RESULTS AND DISCUSSION

The DailyMed data repository was the sole source of the data. Unfortunately, currently (as of 16 June 2010; 11:50 PST), DailyMed only offers 'Search By Drug Name or NDC Code' search opportunities, strongly limiting searching the data repository. Given that the SPL (XML) records are contained in the online repository, the google (www.google.com) search engine was utilized as a free, user-friendly, publicly available means to qualitatively search DailyMed. The google search methodology developed allows viewing either or both pre- and post-PLR records as a means to expedite the contextualization of the common language. PLR records were resolved within DailyMed using the following google search string: '*keyword* "HIGHLIGHTS OF PRESCRIBING INFORMATION" site: www.dailymed.nlm.nih.gov/dailymed/druginfo', as PLR records idiosyncratically contain the 'Highlights' section. Removal of the term in the search string resolves the pre-PLR records. Alternatively, one may use a term such as '17. Patient' to elucidate PLR records, as these types of terms specify a section of the PLR record, such as Patient Counseling Information. Users are encouraged to explore the various capabilities that such

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search engines may have to further refine the search methodologies.

There are challenges with using an external searching capability to examine DailyMed, given the intrinsic tendencies of a given search routine. For example, as of 29 July 2009, the total number of pre- and post-PLR records from the available 4840 records were 4470 and 370, respectively. Interestingly, the total number as shown above is different from the 4719 records displayed on the DailyMed website. The discrepancy, while potentially showcasing the challenging of using a third-party web resource, does not affect the results presented as the ratios and the absolute values are not of interest. It is noted that DailyMed has grown rapidly since last year, nearly doubled to 7388 USPI records as of 13 April 2010.

As a means to investigate FDA thinking through the analysis of precedent labels, a series of search topics were developed. These search topics were determined experientially and may be mapped against FDA guidance, as available. In the following sections, the results are presented followed by a more theoretical discussion on the various contextual challenges that led to the selection of these search terms.

Example: Limitations of use

Understandably, as a prescription drug is approved for its intended use (as defined in 21 CFR 201.57 (B)(c)(2) and its subsections (i–v)), one may imagine that both sponsors and the FDA spend considerable time and resources codifying labeling language that best captures the patient population that would most benefit from receiving the prescription drug. For sponsors seeking regulatory authority approval of their proposed indications, it is of particular importance to understand the full spectrum of opportunities available to them to best describe the usefulness of a prescription drug. One particular dimension in labeling development that may be challenging to sponsors may be how to describe a potential limitation of use. Even though federal law provides description when such language is warranted, it may not provide enough information to allow label language development. For example, after a brief examination of 21 CFR 201.57 (B)(c)(2)(i)(B) (as presented below), a sponsor may not understand how to best present a 'succinct description' of a restriction indication statement and therefore is required to look at other FDA-approved labels to clarify potential label language opportunities:

> If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (eg, patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under 314.510 or 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the 'Clinical Studies' section for a discussion of the available evidence.

For sponsors, this is an ideal case for which precedent analysis of USPI may reveal insight into label development.

On 29 July 2009, the 'limitations of use' language was culled and analyzed through using the term 'limitations of use' as the google search criterion. Searching for Limitations of Use language within pre-PLR finds only one record: Chlormax (chlortetracycline) granule. The language on limitations of use in this record is presented as follows: 'Caution: For control and treatment of diseases caused by organisms susceptible to chlortetracycline as indicated. Observe the limitations of use and withdrawal periods as indicated.' However, searching with the same keyword 'Limitations of Use' finds 29 post-PLR formatted records; two entries were found to be invalid (one referred back to the DailyMed website, and the second was repetitive (Taclonex)). On 14 April 2010, the same search was performed that resulted in over 500 USPI records. For this work, because of the large number of 'hits' and a general notion that a subset of results may

reflect the greater set, only the first 20 records displayed from the search criterion were analyzed, and a summary of these findings are presented in the following tables. This is noted as an opportunity for additional work on this topic. The USPI for Chlormax as mentioned above was also elucidated in this search. Interestingly, within the Exalgo USPI record, the term 'limitations of use' appears exclusively in the Black Box, as 'warning: potential for abuse, importance of proper patient selection and limitations of use'.

Tables 1a and 1b presents a classification of these findings within a pertinent typology. Altogether five typologies are found with very similar to exact verbiage among members of that class.

Example: Prophylaxis management

Alternatively, when there is no FDA guidance whatsoever concerning putative topics, then the search technique developed herein may be useful to understand if FDA has any thinking on a particular topic. As an illustrative example, and as a means to examine and potentially leverage precedent examples, the topic of prophylaxis management, which to the author's knowledge is not presented in any labeling specific guidance documentation, was examined. As described in Table 2, a keyword search using the term 'prophyla,' as the stem for 'prophylaxis' and 'prophylactic', was performed (at 16:00 PST on 25 Jan 2010), and results (from an analysis of the first 20 labels retrieved from approximately 290 PLR-formatted USPI) suggest that, although there potentially are several components of the label affected, sponsors purporting prophylaxis management techniques should provide enabling language within the dosage and administration, and respective safety sections of their respective labels.

Example: Comparison of incidence antibodies

In some circumstances, non-labeling specific FDA guidance provides the agency's thoughts on various subjects, but it is not clear if the concept is extendable to labeling language. Precedent analysis may therefore be a critical

Table 1a: PLR formatted USPI records: Proposed typologies of 'limitations of use' (see text for search criterion; data culled on 29 July 2009)

Typology	*Examples: product name*[a] *and USPI text*
Explicit forbidden use ('should not be used'; 'not indicated')	• Vectical (calcitriol) ointment: 'Vectical ointment should not be applied to the eyes, lips or facial skin'
Explicit risk of use ('may cause')	• Fusilev (levoleucovorin calcium) injection, powder, lyophilized, for solution: 'Fusilev is not approved for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. Improper use may cause a hematologic remission while neurologic manifestations continue to progress'
Explicit lack of evidence ('not established'; 'not evaluated'; 'not studied'; 'not determined')	• Veregen (sinecatechins) ointment: 'The safety and effectiveness of Veregen have not been established for treatment beyond 16 weeks or for multiple treatment courses. The safety and effectiveness of Veregen in immunosuppressed patients have not been established'
Implicit forbidden use ('not recommended'; 'failed to demonstrate efficacy')	• Aldara (imiquimod) cream for topical use: 'Aldara Cream has been evaluated in children in the age group from 2 to 12 years with molluscumcontagiosum and these studies failed to demonstrate efficacy. (see Use in Specific Populations (8.4))'
Hybrid	• Avandaryl (rosiglitazone maleate and glimepiride) tablet, film coated: 'because of its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, Avandaryl should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. The use of Avandaryl with nitrates is not recommended. The coadministration of Avandaryl and insulin is not recommended'

[a]Product names may be registered trademarks owned by their respective manufacturers.

Table 1b: PLR formatted USPI records: Proposed typologies of 'limitations of use' (see text for search criterion; data culled on 14 April 2010)

Typology: intention of limitation of use	*Examples: product name[a] and USPI text*
Explicit forbidden use ('should not be used'; 'not indicated')	• Exalgo (hydromorphone hydrochloride) table, extended release ○ No sub-section, 'limitations of use' appears in the black box ○ The following language appears in the indication text: 'Exalgo is NOT intended for use as an as-needed analgesic. Exalgo is not indicated for the management of acute or postoperative pain'
Explicit risk of use ('may cause')	• Fusilev (levoleucovorin calcium) injection, powder, lyophilized, for solution (see Table 1a)
Explicit lack of evidence ('not established'; 'not evaluated'; 'not studied'; 'not determined')	• Veregen (sinecatechins) ointment (see Table 1a)
Implicit forbidden use ('not recommended'; 'failed to demonstrate efficacy')	• Avandaryl (rosiglitazone maleate and glimepiride) tablet, film coated: 'because of its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, Avandaryl should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. The use of Avandaryl with nitrates is not recommended. The coadministration of Avandaryl and insulin is not recommended'
Hybrid	• Byetta (exenatide) injection: 'Byetta is not a substitute for insulin. Byetta should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Byetta with insulin has not been studied and cannot be recommended. On the basis of post-marketing data Byetta has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Byetta has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Byetta. Other antidiabetic therapies should be considered in patients with a history of pancreatitis'

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component for sponsors interested in understanding FDA's expectations in such a case. For example, in the draft FDA guidance for assay development for immunogenicity testing of therapeutic proteins, the following guidelines are presented:

> FDA believes that such assays enable a true understanding of the immunogenicity, safety, and efficacy of important therapeutic protein products. The detection of antibodies is dependent on key operating parameters of the assays (eg, sensitivity, specificity, methodology, sample handling) which vary between assays. Therefore, in the product labeling, FDA does not recommend comparing the incidence of antibody formation between products when different assays are used (page 2 in[14]).

DailyMed cull with the key phrase: 'comparison of the incidence of antibodies' seemingly within the context of immunogenicity, elucidated approximately 1500 labels (at 5:15 PST on 17 March 2010) with language explicitly stating that 'comparison of the incidence antibodies with the incidence of antibodies to other products may be misleading'. Sponsors of biologics may wish to proactively embrace such language should it reflect their supportive data as a means to facilitate interactions with the health agency (see Table 3).

Example: Pharmacogenomics

Given the complexities and relative newness of the general topic of personalized medicines, label life-cycle management, as an FDA-approved medicine, is evolving. In the case of pharmacogenomics affects on professional labeling, FDA Guidance was promulgated in early 2009 in the context of Clinical Pharmacology.[15] In particular, the guidance states:

> When there is genetic information that would be useful to prescribers and that is

Table 2: USPI sections containing the word-stem 'prophyla' deriving the terms 'prophylaxis' and 'prophylactic'

Sections affected (general types)	*Examples: product name*[a]
Indications and usage Dosage and administration	• Nitromist
Dosage and administration Warnings and precautions Clinical studies	• Uloric
Black box Dosage and administration Warnings and precautions Patient counseling information	• Campath
Indications and usage Dosage and administration Adverse reactions Clinical studies	• Cinryze
Indications and usage Dosage and administration Adverse reactions Use in special populations Clinical studies	• Depakote ER
Indications and usage Dosage and administration Adverse reactions Pediatric use Clinical studies	• Kogenate FS
Warnings and precautions	• Nasacort
Warnings and precautions Drug interactions Clinical studies	• Xigris
Indications and usage	• Zyflo CR
Dosage and administration Clinical studies	• Alphanate
Black box Indications and usage Dosage and administration Contraindications Warnings and precautions Adverse reactions Use in special populations Clinical studies	• Arixtra
Indications andusage Warnings and precautions	• Alvesco
Indications and usage Adverse reactions	• Von Willebrand Factor/ Coagulation factor VIII Complex

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more extensive than appropriate for the Pharmacokinetics or Pharmacodynamics subsection, a Pharmacogenomics subsection should be created to include the clinically relevant information on the effect of polymorphic variation in drug metabolizing enzymes, transporters, receptors, and other proteins on pharmacokinetics, pharmacodynamics, and/or clinical responses (both safety and efficacy).

This search was to understand how labels are implementing guidance. Using the key word 'pharmacogenomics', the DailyMed was culled using the google search engine as described above. The analysis found three pre-PLR and three post-PLR pharmacogenomics USPI records on 30 July 2009. Interestingly, as of 13 April 2010, the number of FDA-approved labels with a section header devoted to pharmacogenomics had evolved, with the addition of four post-PLR and an additional pre-PLR USPI records. It is noted that one USPI record (Selzentry) was not obtained from the search; this may be because of an issue concerning the veracity of the search engine. With respect to pharmacogenomics, analysis of Table 4 shows that pre-PLR labels focus primarily on references, whereas post-PLR records describe the new section opportunity and reference other sections of the label.

Example: Presentation of pH

Analysis of DailyMed may also be useful for those interested in scientometrics; that is, using the DailyMed repository as a tool to understanding socio-linguistic trends as a theoretical construct. For example, while presenting pH may seem trite, for sponsors developing language in the USPI, it is most helpful for them to know the types of presentations available to them. Sponsors may think that although the supportive data may provide a target pH or a range, they may not know that labels may contain ranges, targets and exact values for pH. FDA's notion of the presentation of a value such as pH in product labels is generally mentioned, as: 'If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated (21 CFR 201.57)'.

In such a context, the pH variable as a function of product description was probed

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Table 3: View into a comparison of incidence antibodies USPI language

Product name[a]	*Examples: USPI text*
Elspar (asparaginase)	'The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. Therefore, comparison of the incidence of antibodies to Elspar with the incidence of antibodies to other products may be misleading'
Ontak (denileukin difitox)	'An immune response to denileukin diftitox was assessed using two enzyme-linked immunoassays (ELISA). The first assay measured reactivity directed against intact denileukin diftitox calibrated against anti-diphtheria toxin, and the second assay measured reactivity against the IL-2 portion of the protein. An additional *in vitro* cell-based assay that measured the ability of antibodies in serum to protect a human IL-2R-expressing cell line from toxicity by denileukin diftitox was used to detect the presence of neutralizing antibodies, which inhibited functional activity. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to the intact fusion protein denileukin diftitox. These results are highly dependent on the sensitivity and the specificity of the assays. In addition, the observed incidence of the antibody positivity may be influenced by several factors, including sample handling, concomitant medication, and underlying disease. For these reasons, the comparison of the incidence of antibodies to denileukin diftitox with the incidence of antibodies to other products may be misleading'
Oncaspar (pegaspargase)	'The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. Therefore, comparison of the incidence of antibodies to Oncaspar® with the incidence of antibodies to other products may be misleading'
Elaprase (idursulfase)	'The data reflect the percentage of patients whose test results were positive for antibodies to idursulfase in specific assays, and are highly dependent on the sensitivity and specificity of these assays. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medication and underlying disease. For these reasons, comparison of the incidence of antibodies to idursulfase with the incidence of antibodies to other products may be misleading'
Erbitux	'The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Erbitux with the incidence of antibodies to other products may be misleading'

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with the DailyMed USPI repository. Executing this search on 14 August 2010 finds the following: 4530 pre-PLR records and 344 post-PLR records were retrieved with a keyword of 'pH.' Owing to the large number of records, the first 20 of pre- and post-PLR records were extracted to facilitate realization of the number of typologies (see Tables 5a and 5b). To understand the scope of these classifications, various searches were then performed to 'prune' the dataset, each searching using one of the types from the first two entries. The general thought is that searching with each type would remove more than one record from the total dataset, thereby after a sufficient number of such runs are performed, the final dataset should be comprised of a limited set of records. Although this approach may not be exhaustive, it does provide a method to gain a granular view of the search space (see Figure 1). The 'pruning' approach accounts for 50 per cent (173 records out of 344) and 33 per cent (1506 records out of 4540) of the total variance accountable within the data.

CONCLUSION

To the author's knowledge, this is a first article investigating prescribing information through the analysis of the publicly available data

Table 4: Pre- and post-PLR formatted USPI records: Proposed typologies of pharmacogenomics (see text for search criterion; data culled on 29 July 2009)

Typology	*Examples: product name*[a] *and USPI text*
Reference Only (pre-PLR)	• IMURAN (azathioprine) tablet ○ Section clinical pharmacology: 'Adapted from Pharmacogenomics 2002; 3:89–98; and Cancer Res 2001; 61:5810–5816'. ○ Section References: 'McLeod HL, Siva C. The thiopurine S-methyltransferase gene locus – implications for clinical pharmacogenomics. Pharmacogenomics. 2002;3:89–98'.
Separate section Potential typologies: ('being tested'; 'no relevant effect')	• Tasigna (nilotinib) capsule for oral use ○ Section 12.5 pharmacogenomics: 'Tasigna can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment. In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. However, the largest increases in bilirubin were observed in the (TA)7/(TA)7 genotype (UGT1A1*28) patients (See Warnings and Precautions (5.5))'

[a]Product names may be registered trademarks owned by their respective manufacturers.

Table 5a: Post-PLR formatted USPI records: Proposed typologies of pH within the description section of the USPI (first 20 records displayed as a function of typology)

Typology	*Examples: product name*[a] *and USPI text*
'pH of X.X–Y.Y'; 'pH is from X.X to Y.Y'	• Ak-fluor (Fluorescein Sodium) injection for intravenous use ○ pH of 8.3–9.8
'pH approximately of'	• Nevanac (nepafenac) suspension for ophthalmic use ○ pH approximately of 7.4
'adjust pH'	• CETRAXAL (ciprofloxacin) solution/drops; Oraverse (Phentolamine mesylate) injection, solution for submucosal use; RiaSTAP (fibrinogen human) injection, powder, lyophilized, for solution ○ Adjust the pH
'pH X and above'; 'pH X or greater'	• APRISO (mesalamine) capsule, extended release ○ At pH 6 and above
'pH X'	• Elspar (Asparaginase) powder, for solution; Oncaspar (pegaspargase) injection, solution for intramuscular and intravenous use ○ At pH 7.3
'pH of the'	• Chirhostim (Secretin human) injection, powder, lyophilized, for solution for intravenous use ○ The pH of the reconstituted solution has a range of 3 to 6.5
'independent of pH'	• Carisoprodol tablet ○ solubility is practically independent of pH
'pH range of X to Y'	• Ontak (denileukin diftitox) solution ○ The solution has a pH range of 6.9 to 7.2
Hybrid	• Combigan (brimonidine tartrate and timolol maleate) solution ○ a pH during its shelf life of 6.5–7.3 ○ at pH 7.2 ○ to adjust pH

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repository – DailyMed – with a publicly available web search tool, google. A key finding from this work is that the methodology may provide a view into FDA thinking, as reflected by linguistic similarities (typologies) of label language across USPI. This general result is of particular interest when FDA guidance is non-existent, general, evolving and/or emergent, and presents an opportunity for sponsors to develop labeling language through precedent analysis of labels, on the basis of data availability and interpretation, and therefore potentially facilitate USPI development. Further, it is a hope of this manuscript to yield

Table 5b: Pre-PLR formatted USPI records: Proposed typologies of pH within the description section of the USPI (first 20 records displayed as a function of typology)

Typology	*Examples: product name*[a] *and USPI text*
'pH: X.X (Y.Y–Z.Z)'	• Acetic acid irrigant ○ pH: 3.1 (2.8–3.4)
'at pH X'	• Entocortec (Budesonide) capsule ○ at pH 5
'pH of X.X (YY–ZZ)'	• Sodium bicarbonate (sodium bicarbonate) injection, solution ○ pH of 8.0 (7.5–8.5)
Hybrid	• Cardioplegic (calcium chloride dihydrate, magnesium chloride hexahydrate, potassium chloride and sodium ch=loride) injection, solution; Plegisol (calcium chloride, magnesium chloride, potassium chloride, and sodium chloride) injection, solution ○ To adjust pH ○ for pH adjustment ○ pH 3.8 (3.5–3.9) ○ the approximate pH of 7.8 ○ due to the varying pH's ○ pH 7.8 (approx.) ○ after adjusting pH

[a]Product names may be registered trademarks owned by their respective manufacturers.

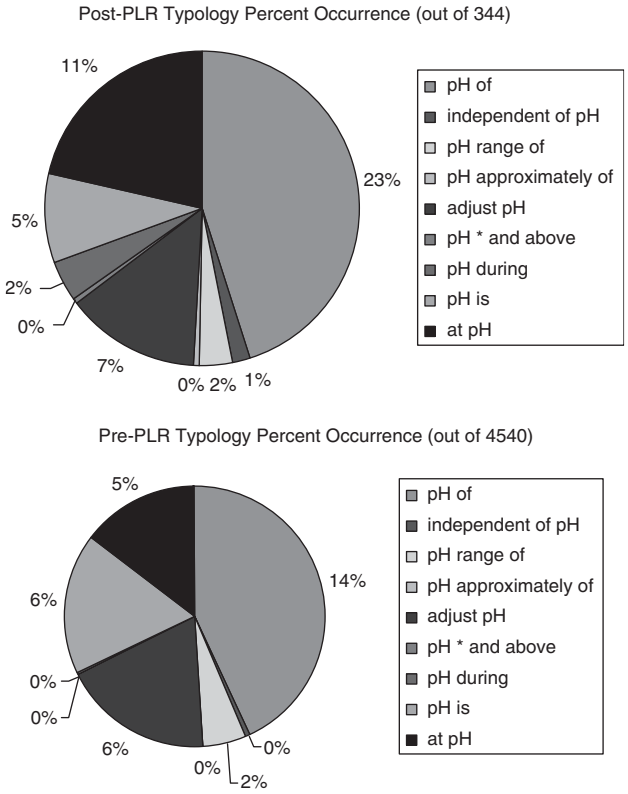

Figure 1: Set analysis of proposed typologies of pH within pre- and post-PLR USPI records.

an opportunity to create and integrated USPI metrics for potential scientometric and/or econometric modeling (for example[16]).

However, there are several key issues that need to be contemplated by practitioners using this method.

Foremost, DailyMed is a new and evolving data repository. As mentioned above, it has grown tremendously, effectively doubling in size over the recent year. Thus, practitioners need to realize that for precedent analysis, one may not be searching all of the potentially interesting labels. Of equivalent concern are the limitations of the search criteria for the public on the DailyMed site and the dependence on an external search engine. As of 1 July 2010 (15:30 PST), the current search opportunities on the DailyMed site include: Search by Drug Name or NDC Code. Further, in some instances labels quickly evolve, and it would behoove the practitioner to confirm the version of a particular label on DailyMed with either the drugs@fda.gov and/or the product-specific website, as available. The use of google as a search engine to explore DailyMed may be considered problematic as it is not clear when and how the google algorithm is updated and, if such updates, affects its abilities for searching SPL content. Clearly, programmatically developing a specific analysis tool would be beneficial, should the DailyMed search opportunities (such as a general keyword search or ideally a Boolean type searching capabilities embraced by current search engines) not be further developed.

Additional work is required to extend these preliminary results. Interesting research questions may include:

- searching for USPI language trends (for example, across products for a given indication for use, or by FDA review division);
- metrics (for example, number of USPI label updates by modality or class/clinical context);
- analysis (eg, simulation) to determine if a trend elucidated in a subset of USPI is extendable to the greater set;
- analysis to determine the stability and 'goodness' of the search tool.

In summary, if users approach the DailyMed search algorithm as described herein with the judicious use of caution, they may be rewarded with rapid and rich insight into the socio-linguistic dynamics of labeling language that may expedite label language development and subsequently facilitate health agency dialog.

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