Review Article

Theme: Emerging Role of Pharmacogenomics (PGx) and Big Data on Development of Biologics

Guest Editors: Shraddha Thakkar and Nisha Nanaware-Kharade

Pharmacogenomic Biomarkers: an FDA Perspective on Utilization in Biological Product Labeling

Robert N. Schuck^{1,2} and Joseph A. Grillo¹

Received 19 November 2015; accepted 15 February 2016; published online 24 February 2016

Abstract. Precision medicine promises to improve both the efficacy and safety of therapeutic products by better informing why some patients respond well to a drug, and some experience adverse reactions, while others do not. Pharmacogenomics is a key component of precision medicine and can be utilized to select optimal doses for patients, more precisely identify individuals who will respond to a treatment and avoid serious drug-related toxicities. Since pharmacogenomic biomarker information can help inform drug dosing, efficacy, and safety, pharmacogenomic data are critically reviewed by FDA staff to ensure effective use of pharmacogenomic strategies in drug development and appropriate incorporation into product labels. Pharmacogenomic information may be provided in drug or biological product labeling to inform health care providers about the impact of genotype on response to a drug through description of relevant genomic markers, functional effects of genomic variants, dosing recommendations based on genotype, and other applicable genomic information. The format and content of labeling for biologic drugs will generally follow that of small molecule drugs; however, there are notable differences in pharmacogenomic information that might be considered useful for biologic drugs in comparison to small molecule drugs. Furthermore, the rapid entry of biologic drugs for treatment of rare genetic diseases and molecularly defined subsets of common diseases will likely lead to increased use of pharmacogenomic information in biologic drug labels in the near future. In this review, we outline the general principles of therapeutic product labeling and discuss the utilization of pharmacogenomic information in biologic drug labels.

KEY WORDS: biomarkers; Pharmacogenomics; precision medicine.

INTRODUCTION

Precision medicine may broadly be defined as the tailoring of medical treatment to the individual characteristics of patients [1]. The potential to improve patient outcomes through precision medicine has led to much excitement among scientists, clinicians, and patients alike. From the Food and Drug Administration's (FDA) perspective, precision medicine promises to increase benefit and reduce risk of medical products [2]. This is accomplished by better informing why some individuals respond well to a drug and some experience adverse reactions, while others do not. In addition, precision medicine may be applied to drug development to improve the probability of a drug's success and reduce overall development costs. Given these potential

benefits, FDA has been proactive in implementing regulatory processes and policies to meet the challenges necessary to advance precision medicine research and implementation into patient care [2].

Pharmacogenomics is a key component of precision medicine that can be used to select an optimal dosage for patients, more precisely identify individuals who will respond to a treatment, and avoid serious drug-related toxicities. For example, when drugs are metabolized by polymorphic drug-metabolizing enzymes, utilization of pharmacogenomics aids in prospectively selecting a dosage that will be both safe and effective for each patient [3]. More recently, numerous "targeted" therapies, which benefit smaller, molecularly defined subsets of patients have been approved and are now being used clinically. These targeted drugs often require pharmacogenomic tests to identify the appropriate patient population for whom the drug is indicated [4]. Although the current landscape of molecularly targeted therapies is largely limited to oncology, targeted therapies in non-oncology fields are rapidly expanding [4]. In addition, pharmacogenomic tests can be applied clinically to identify patients that are more likely to experience drug-related adverse events and prevent

¹ Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA.

² To whom correspondence should be addressed. (e-mail: Robert.Schuck@fda.hhs.gov;)

use in these patients, where the benefit-risk profile of the drug is not favorable [5]. Therefore, pharmacogenomic information is specifically reviewed by FDA staff to ensure effective use of pharmacogenomic strategies in drug development and appropriate incorporation into product labels [6].

Regulations for labeling of prescription drugs and biological products require that prescription drug labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug, and that labeling must be informative and accurate [7]. Pharmacogenomic information may be useful in labeling to inform health care providers about the impact (or lack of impact) of genotype on phenotype through description of relevant genomic markers, functional effects of genomic variants, dosing recommendations based on genotype, or other applicable genomic information [8].

GENERAL LABELING PRINCIPLES FOR PRESCRIPTION DRUGS AND BIOLOGICAL PRODUCTS

The initial drug labeling distributed at the time of drug approval contains information derived from studies that are submitted in support of the application (New Drug Application (NDA) or Biologics License Application (BLA)) to market the drug. Data are critically reviewed by FDA staff, and a summary of the essential scientific information needed for the safe and effective use of the drug is agreed upon by the FDA and the submitting pharmaceutical company (applicant) for inclusion in labeling. The information and clinical data that are ultimately included in the drug labeling come from both adequate and well-controlled trials designed to demonstrate safety and efficacy of the therapeutic product and from additional studies that help inform the most appropriate use of the product. These studies may include clinical pharmacology studies such as dose ranging studies, pharmacokinetic/pharmacodynamic studies, drug-drug interaction studies, organ impairment studies (e.g., studies evaluating the impact of hepatic impairment or renal impairment on drug pharmacokinetics), pharmacogenomics studies, and many other clinical and non-clinical studies.

Regulations require that labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading [7]. Therefore, updates may be made to drug labels following approval based on data accrued in the post-market setting. Post-marketing labeling changes may come about by multiple mechanisms. The FDA or the application holder may request to change labeling based on updated safety or efficacy data. Alternatively, under Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may compel changes to previously approved labeling when new safety information becomes available for the drug. New safety information may come from clinical trials, adverse event reports, peer-reviewed biomedical literature, and other appropriate scientific data [9]. As with the original NDA/BLA application, a multidisciplinary team at FDA evaluates potential new safety information in order to determine if it should be incorporated into a drug's labeling. Many factors are considered when deciding whether or not to revise the labeling of an approved therapeutic product (as well as the final updated language); these include the reliability of the data,

magnitude of risk, seriousness of event, and others [10]. Prior to making a labeling change, a consensus must be reached among the FDA review team followed by agreement with the application holder [10].

LABELING PRINCIPLES—PHARMACOGENOMICS

Pharmacogenomic information is included in labeling for the same purpose as other types of information and data—to help provide information to the health care provider that aids in safe and effective use of the product. Therefore, pharmacogenomic information about the impact, or lack thereof, of genotype on phenotype should be included in labeling if it is clinically meaningful and informs prescribing decisions by health care providers [8]. General information that may be useful to health care providers in assessing the clinical relevance of the pharmacogenomic effect, such as frequencies of the relevant alleles, genotypes, phenotypes, and other genomic markers, is frequently included in labeling as well. The labeling may also indicate whether or not a genomic test is available and whether testing should be considered, is recommended, or is necessary [8]. For example, the inclusion of pharmacogenomic information in labeling is useful to optimize dosing for drugs that exhibit variable pharmacokinetics secondary to polymorphic drug metabolism, activation, or transport, and to optimize patient selection for drugs that may have poor efficacy or poor tolerability in certain genetic subgroups [11].

Pharmacogenomic information that may be useful to inform dosing often includes the effect of genotype on pharmacokinetic parameters and/or pharmacodynamic endpoints. In addition, a description of the functional effects of genomic variants (or lack thereof) in drug-metabolizing enzymes or transporters on important pharmacokinetic parameters is often appropriate when the drug is a known substrate of a polymorphic drug-metabolizing enzyme or transporter, and data are available. Inclusion of this information is analogous to describing the impact of other intrinsic (e.g., organ impairment, sex, age) or extrinsic (e.g., drug-drug interactions) factors on pharmacokinetic or pharmacodynamic parameters in order to help inform the optimal dose in individual patients. In addition, pharmacogenomic information may also provide insight into dose optimization for complex scenarios where a polymorphism affects the magnitude of a known intrinsic or extrinsic factor on drug exposure. Therefore, specific dosing recommendations based on genotype may be included in labeling, depending on the data supporting the magnitude of impact of genotype on phenotype and whether or not the effect of dose adjustment has been evaluated.

As stated previously, in addition to aiding in prospective identification of the optimal dose for individual patients, pharmacogenomic information may help more precisely identify which patients will benefit from a therapeutic product and which patients are at higher risk for serious adverse events. Drugs with polymorphic drug targets may exhibit different efficacy profiles across genotypes, and in these cases, pharmacogenomic information may help health care providers identify a more appropriate therapy or therapeutic class of drug for patients based on likelihood of response. The development and approval of numerous targeted therapies in

recent years, which may offer substantial benefits over existing therapies, but only in molecularly defined subsets of patients, has greatly increased the prevalence of using pharmacogenomics in labeling to identify the appropriate patient population for a drug [4, 11]. Moreover, focus on preventing drug-related toxicities in susceptible patients has led to inclusion of pharmacogenomic information related to drug safety and adverse events in numerous drug labels.

Data supporting the inclusion of pharmacogenomic information in labeling is derived from the same sources as other information included in the label—from studies submitted with the original NDA or BLA or from post-market data from clinical trials, adverse event reports, peer-reviewed biomedical literature, and other appropriate sources. Inclusion of pharmacogenomic information to guide dosing relies on data sources similar to other intrinsic or extrinsic factors. These may include dedicated gene-drug interaction studies or a clear association between genotype and pharmacokinetics or pharmacodynamics demonstrated by other means. For targeted therapies that are approved for a molecularly defined group of patients, the data supporting inclusion of the biomarker information in labeling, and the context in which biomarker information is included in labeling (e.g., the section and whether or not testing is compulsory), is generally dependent on the design and outcomes of the pivotal clinical trials. For more discussion regarding the use of molecular biomarkers in clinical trials, and the potential impact on labeling, we refer the reader to the FDA Draft Guidance for Industry—Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products [12]. A brief description of the evidence (i.e., the pharmacogenomic studies) supporting the impact of genotype on phenotype, or a reference to the appropriate published literature, may be provided in labeling if it informs prescribing decisions. As with all other information, many factors are considered when deciding whether or not to include pharmacogenomic information in initial drug labeling, or to update existing labeling. Great care is taken by the applicant and regulators when proposing the use of pharmacogenomic data to inform patient selection, since inclusion of this information may ultimately limit the patient population who has access to the drug [2].

BIOLOGICAL PRODUCT LABELING

As with small molecule drugs, the labeling requirements for biological products (e.g., monoclonal antibodies, therapeutic proteins, and enzyme replacement therapies) for human use are described under 21 C.F.R. § 201.56. Therefore, the format and content of labeling for biologic drugs will generally follow that of small molecule drugs. Similarly, most of the principles for including pharmacogenomic information in labeling of small molecule drugs will also apply to biologic drugs. There are, however, some notable differences in pharmacogenomic information that might be considered useful for biologics in comparison to small molecules.

Approximately half of pharmacogenomic information that is included in drug labeling describes the impact of polymorphic drug-metabolizing enzymes (or lack thereof) on the drug's pharmacokinetic properties. Biologic drugs are administered parenterally, and oral administration is not possible because gastrointestinal degradation and other factors limit bioavailability.

Following administration, biologic drugs are metabolized to peptides and amino acids. Mechanisms of elimination include proteolysis by the liver and the reticuloendothelial system, target-mediated elimination, and nonspecific endocytosis; these processes are not impacted by known genetic polymorphisms [13]. Since biologic drugs are not administered orally and are not substrates for membrane transporters or polymorphic drug-metabolizing enzymes, there are not known pharmacogenomic liabilities that lead to variable bioavailability or metabolism. Consequently, pharmacogenomic information has not demonstrated utility to describe variable pharmacokinetics and alternative dosing secondary to these factors for any currently marketed biologic drugs. However, genetic predisposition to immunogenicity and formation of antidrug antibodies may impact the pharmacokinetic profile of some biologic drugs. Moreover, efforts are underway to reformulate biologic drugs for non-invasive routes of administration [14], and pharmacogenomic biomarkers may ultimately be identified that impact the pharmacokinetic properties of these reformulated products.

Since the pharmacokinetic properties of biologic drugs are not impacted by known pharmacogenomic factors, the pharmacogenomic information in biologic drug labeling generally describes the impact of pharmacogenomics on the drug's safety or efficacy profile. Of the currently marketed biologic drugs with pharmacogenomic information in the product labeling, the majority of pharmacogenomic information describes the impact of a molecular alteration in the drug target or biological pathway on efficacy (Table 1). For these targeted therapies, the pharmacogenomic information helps identify the patient population in which the drug has demonstrated safety and efficacy. Therefore, in most cases, the information is described in the Indications and Usage section of labeling, and there is a corresponding FDA-approved *in vitro* companion diagnostic device that is cross-labeled with the biologic drug. Pharmacogenomic information may also appear in the Clinical Studies section of labeling to describe the patient population that was evaluated in clinical trials, the Clinical Pharmacology section to provide additional information on the molecular alteration, or other appropriate sections of labeling.

Another frequent purpose for inclusion of pharmacogenomic information in labeling of biologic drugs is to describe potential safety issues. For example, the most frequent pharmacogenomic biomarker related to drug safety that is included in labeling of biologic drugs is glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetic disorder that can lead to hemolysis when affected individuals take certain drugs. Many small molecule drugs also have pharmacogenomic information related to G6PD deficiency included in labeling. Pharmacogenomic information related to safety issues will frequently be described in the Warnings and Precautions or Contraindications sections of labeling or other appropriate sections depending on the information described.

FUTURE BIOLOGICAL PRODUCT LABELING

Current Pharmacogenomic Investigations

The pharmacogenomics field is advancing rapidly, and pharmacogenomic discoveries are now frequently included in product labeling and incorporated into patient care. Many areas of pharmacogenomic research are highly relevant to biologic drugs in addition to small molecule drugs. For

Table I. Pharmacogenomic Biomarkers in FDA Drug Labels

Biologic	Therapeutic area	Biomarker	Information type	Labeling location
Ado-trastuzumab emtansine	Oncology	ERBB2	Target/pathway	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cetuximab	Oncology	1) EGFR 2) KRAS	Target/pathway	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Denileukin diftitox	Oncology	IL2RA	Target/pathway	Indications and Usage, Warnings and Precautions, Clinical Studies
Obinutuzumab	Oncology	MS4A1	Target/pathway	Clinical Studies
Panitumumab	Oncology	1) EGFR 2) KRAS	Target/pathway	1) Clinical Pharmacology, Clinical Studies 2) Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Pegloticase	Rheumatology	G6PD	Safety	Contraindications, Patient Counseling Information
Pertuzumab	Oncology	ERBB2	Target/pathway	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Rasburicase	Oncology	1) G6PD 2) CYB5R1-4	Safety	1) Boxed Warning, Contraindications, Warnings and Precautions 2) Warnings and Precautions
Rituximab	Oncology	MS4A1	Target/pathway	Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Tositumomab	Oncology	MS4A1	Target/pathway	Indications and Usage, Clinical Pharmacology
Trastuzumab	Oncology	ERBB2	Target/pathway	Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies

Source: FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>) Accessed November, 2015

FDA Food and Drug Administration, *ERBB2* erb-b2 receptor tyrosine kinase 2 (HER2), *EGFR* epidermal growth factor receptor, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *IL2RA* interleukin 2 receptor alpha, *MS4A1*, membrane spanning 4-domains A1 (CD20), *G6PD* glucose-6-phosphate dehydrogenase, *CYB5R1-4* cytochrome b5 reductase

example, research on genetic variation in the drug target and upstream or downstream pathways that may identify individuals likely or unlikely to respond to a given drug continues to be an active area of research [15, 16].

Other active areas of pharmacogenomic research are specific to biologic therapies. For example, the pharmacogenomic basis for immunogenicity has been extensively investigated resulting in progress both in understanding the relationship between genetic variability and immunogenicity [15] and in developing precision medicine-based strategies to circumvent immunogenicity in the clinical setting [17]. Moreover, studies have demonstrated that immune reactions triggered by binding of the Fc region of monoclonal antibodies to cell surface Fcγ receptors on immune effector cells is a key component of the tumor cell killing activity of some biologic anticancer agents (e.g., trastuzumab, rituximab) [18]. Some recent clinical studies indicate that genetic polymorphisms in the Fcγ receptor may also impact response to other anticancer agents as well as biologic therapies for other diseases [19, 20]. Information from these research endeavors has the potential to be incorporated in labeling updates or in product labels for new biologics if the level of evidence eventually supports the clinical utility of the pharmacogenomic information.

Rare Diseases

In recent years, drugs for rare “orphan” diseases have been approved in record numbers, with many of these drugs being

biologics [21]. Moreover, phenotypically homogeneous diseases are now being divided into genomic disease subsets, and precision medicines are being designed and evaluated in these subsets, which are often exceedingly small [22]. Review of applications for rare diseases, where very small numbers of patients with a disease or disease subset are evaluated in clinical trials, presents many challenges that are unique from more prevalent diseases, and FDA has exercised flexibility in these circumstances [23]. One of these challenges is labeling for small genomic subsets, where very small numbers of patients have been studied to evaluate the drug or biologic product's safety and efficacy, and additional genomic subsets may exist that have not been represented in clinical trials at all. As genomic technologies continue to advance and therapeutic products are developed for smaller and smaller disease subsets, FDA will continue to promote effective utilization of pharmacogenomic information in drug labeling to identify the patient population(s) for which the drug has demonstrated safety and efficacy.

SUMMARY AND PERSPECTIVE

Precision medicine strategies and pharmacogenomics are becoming more prevalent in research, drug development, and clinical practice. Therefore, including appropriate pharmacogenomic information and accurately describing it in labeling is critical. The purpose of including pharmacogenomic information in labeling is to provide information to the health care

provider that aids in safe and effective use of the product, similar to other kinds of information (e.g., recommendations for dosing, drug-drug interactions, and description of the product's clinical pharmacology), and FDA relies on similar principles when determining whether or not pharmacogenomic information should be included in a new or updated product labeling.

Biologics differ from small molecule drugs in their unique clinical pharmacology properties. Unlike small molecule drugs, biologics are not subject to the same pharmacogenomic liabilities in drug disposition as small molecule drugs. Therefore, in contrast to small molecule drugs where most pharmacogenomic information is related to the clinical pharmacology properties of the drug, in current examples of labeling from biologic drugs, most pharmacogenomic information informs the patient population that the drug is indicated for, or potential safety issues.

Biologic drugs are rapidly being developed and marketed for myriad indications, including molecular subsets of diseases. Moreover, research on potentially important pharmacogenomic liabilities with biologic drugs is ongoing and information from these studies may eventually warrant inclusion in labeling. Therefore, the importance of appropriate inclusion of pharmacogenomic information in labeling of biologic drugs will grow in the coming years. As biologic drugs continue to enter the market and pharmacogenomic strategies become more commonly utilized in drug development and clinical practice, FDA will continue to employ regulatory processes and policies to guide appropriate inclusion of important pharmacogenomic information in labeling in a clear and consistent fashion.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

REFERENCES

1. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. The National Academies Collection: Reports funded by national institutes of health. Washington (DC) 2011.
2. U.S. Food and Drug Administration: Paving the way for personalized medicine. Accessed from <http://www.Fda.Gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.Pdf>. 2013.
3. Walko CM, McLeod H. Pharmacogenomic progress in individualized dosing of key drugs for cancer patients. *Nat Clin Pract Oncol*. 2009;6(3):153–62.
4. Agarwal A, Ressler D, Snyder G. The current and future state of companion diagnostics. *Curr Pharmgenomics Pers Med*. 2015;8:99–110.
5. Pacanowski MA, Zineh I. Pharmacogenomic strategies in drug safety. *Drug Discov Today Ther Strategy*. 2012;9(2–3):e67–74.
6. Zineh I, Woodcock J. The clinical pharmacogeneticist: an emerging regulatory scientist at the us food and drug administration. *Hum Genomics*. 2010;4(4):221–5.
7. Food and drugs, 21 c.F.R. § 201.56 (2010).
8. U.S. Food and Drug Administration: Guidance for industry—clinical pharmacogenomics: premarket evaluation in early-phase clinical studies and recommendations for labeling. Accessed from <http://www.Fda.Gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm337169.Pdf>. 2013.
9. U.S. Food and Drug Administration: Guidance for industry—safety labeling changes—implementation of section 505(o)(4) of the fd&c act. Accessed from <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>. 2013.
10. Zineh I, Pacanowski MA. Pharmacogenomics in the assessment of therapeutic risks versus benefits: inside the United States Food and Drug Administration. *Pharmacotherapy*. 2011;31(8):729–35.
11. Pacanowski MA, Leptak C, Zineh I. Next-generation medicines: past regulatory experience and considerations for the future. *Clin Pharmacol Ther*. 2014;95(3):247–9.
12. U.S. Food and Drug Administration: Draft guidance for industry—enrichment strategies for clinical trials to support approval of human drugs and biological products. Accessed from <http://www.Fda.Gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.Pdf>. 2012.
13. Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet*. 2010;49(8):493–507.
14. Shi S. Biologics: an update and challenge of their pharmacokinetics. *Curr Drug Metab*. 2014;15(3):271–90.
15. Pandey GS, Sauna ZE. Pharmacogenetics and the immunogenicity of protein therapeutics. *J Interferon Cytokine Res*. 2014;34(12):931–7.
16. Grimstein C, Bai JP. Individualizing therapy of monoclonal antibodies and fusion proteins: emerging potential in the age of personalized medicine. *Ther Deliv*. 2011;2(3):369–81.
17. Simhadri VL, Banerjee AS, Simon J, Kimchi-Sarfaty C, Sauna ZE. Personalized approaches to the treatment of hemophilia A and B. *Perinat Med*. 2015;12(4):403–15.
18. Carter P. Improving the efficacy of antibody-based cancer therapies. *Nat Rev Cancer*. 2001;1(2):118–29.
19. Mellor JD, Brown MP, Irving HR, Zalcberg JR, Dobrovic A. A critical review of the role of fc gamma receptor polymorphisms in the response to monoclonal antibodies in cancer. *J Hematol Oncol*. 2013;6:1.
20. Louis E, El Ghoul Z, Vermeire S, Dall'Ozzo S, Rutgeerts P, Paintaud G, *et al*. Association between polymorphism in IGG FC receptor IIIA coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther*. 2004;19(5):511–9.
21. U.S. Food and Drug Administration: Annual novel new drugs summary. Accessed from <http://www.Fda.Gov/downloads/drugs/developmentapprovalprocess/druginnovation/ucm430299.Pdf>. 2014.
22. Maher PD, Haffner M. Orphan drug designation and pharmacogenomics: options and opportunities. *BioDrugs*. 2006;20(2):71–9.
23. Sasinowski FJ, Panico EB, Valentine JE. Quantum of effectiveness evidence in FDA's approval of orphan drugs: update, July 2010 to June 2014. *Ther Innov Regul Sci*. 2015;49:680–97.