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Comparison of Three Pharmaceutical Products Obtained from Mexico and the United States: A Case Study

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ABSTRACT In recent years, there has been much debate concerning the relative pros and cons of purchasing medications from foreign markets such as Mexico and Canada. The following study compares the content uniformity and weight variation for three medicinal products, acquired from pharmacies in both Mexico and the United States: amoxicillin capsules (500 mg), amoxicillin/clavulanic acid suspension (400 mg and 57 mg/5 mL, respectively), and furosemide tablets (40 mg). Twenty capsules/tablets were individually weighed and a designated aliquot was taken. Following dissolution in an appropriate solvent and sonication, a sample was taken and analyzed via high performance liquid chromatography (HPLC). The suspensions were prepared according to directions on the label. Five samples of the suspensions were then taken and analyzed via an appropriate HPLC method. The content uniformity for the amoxicillin capsules was found to be 15.4±2.4% and 99.4±9.3%, for Mexican and U.S. capsules, respectively. The percent relative standard deviation (% RSD) for weight variation was found to be 8.7% and 1.5% for capsules obtained from Mexico and the United States, respectively. Content uniformity analysis for the Mexican suspension product resulted in an average of 85.5±1.2% for amoxicillin and 98.6±1.9% for the clavulanic acid content, while the results for the U.S. suspension product were 104.4±3.1% and 117.8±3.6% for amoxicillin and clavulanic acid, respectively. Content uniformity for the furosemide tablets was found to be 90.3±4.8% and 95.6±2.1% for Mexican and U.S. tablets, respectively. The % RSD of weight variation for the Mexican tablets was 2.1%, while the % RSD for the U.S. tablets was found to be 1.0%. From the three products tested, content analysis revealed that the amount of active ingredients for two of the products acquired in Mexico were appreciably less than the concentrations for their U.S. counterparts.

KEYWORDS Content uniformity, Amoxicillin, Furosemide, Mexico, Foreign markets

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INTRODUCTION

In recent years there has been much debate concerning the purchase of medications from foreign markets such as Mexico and Canada. Studies by McKeithan and Shepherd (1996) and Calvillo and Lal (2003) have focused on demographics and types of medications being obtained. Both studies cite lower drug prices and easier accessibility as the main reasons why U.S. residents travel to Mexico to obtain medications. In fact, in a study performed by Casner and Guerra, 80% of the people they surveyed claimed to have purchased prescription-type medications at a pharmacy in Mexico without a physician's prescription (Casner & Guerra, 1992).

The U.S. Food and Drug Administration (FDA) warns potential buyers that the safety of these medicines cannot be guaranteed. Indeed, quality assurance concerns are at the top of their consumer education list (Food and Drug Administration, 2004). In fact, in May 2005, the FDA issued a warning to the public regarding the sale of possible counterfeit versions of the drugs Lipitor, Viagra, and an unapproved product promoted as a "generic Evista" to U.S. consumers at pharmacies in Mexican border towns (Food and Drug Administration, 2005).

In 1983, Lopez et al. performed a study in which dissolution rates of 15 different brands of metronidazole tablets obtained from Mexico were compared. The results of this study showed that four of the brands analyzed did not meet the standards for specific components and seven of the brands demonstrated higher dissolution times than those required by the United States Pharmacopeia (USP), thus indicating a need for monitoring the quality of these tablets. In another study in which amygdalin (Laetrile) products were obtained from a specific manufacturer in Mexico, several of the products analyzed were found to be sub-potent when compared with U.S. criteria for the manufacturing of pharmaceutical products (Davignon et al., 1978). In a similar fashion, Trujillo et al. (2003) reported the quality control results from studies of 27 herbal medicines manufactured in Mexico. They found that almost all of the products tested exceeded permissible limits when analyzed for microbial features, heavy metal content, and residues of pesticides.

While there is significant discussion on this issue, a large body of analytical data in the scientific literature has been somewhat lacking. The following study seeks to add to existing literature; it is a case report on the drug content and product variability of three medicinal products obtained from a pharmacy in Mexico and equivalently labeled products obtained from a pharmacy in the United States.

MATERIALS AND METHODS

Sealed bottles of amoxicillin capsules (500 mg),[a] the amoxicillin/clavulanic acid suspension, Augmentin (400 mg and 57 mg/5 mL, respectively),[b] and furosemide tablets (40 mg)[c] were obtained from a local pharmacy in Guaymas, Mexico. Equivalently labeled products[d,e,f] were also obtained from a U.S. pharmacy (Reed's Compounding Pharmacy, Tucson, AZ) in order to provide comparison points. Amoxicillin trihydrate, amoxicillin/potassium clavulanate (RPI Corp, Mt. Prospect, IL), and furosemide (Sigma Chemicals, St. Louis, MO) standards were acquired and used to prepare standard curves for each assay. All other chemicals and reagents were obtained from VWR International (Bristol, CT).

Sample analysis was performed utilizing reversed phase HPLC methods. The HPLC system consisted of a Waters 2690 Separations Module (Waters, Milford, MA) coupled with a Waters 996 Photodiode Array Detector. All target compounds were separated on an Apollo C18, 5 micron, 150×4.6 mm column (Alltech, Deerfield, IL), maintained at 30°C. Details of the individual assays are summarized below.

Amoxicillin Capsules and Suspension

The same HPLC assay was used for analysis of both the amoxicillin capsules and the amoxicillin/clavulanic acid suspension (The Official Compendia of

[a]Amoxicillin A; Laboratorios Kenedot, Tlaquepaque, Jal, Mexico; Lot No. 00546; Exp. Nov 05.
[b]Augmentin; SmithKline Beecham Mexico, Mexico D.F., Mexico; Lot No. 69263; Exp. Oct 04.
[c]Furosemide Gensemin; Genetica Laboratorios, Tecate, B.C., Mexico; Lot No. 31178; Exp. Nov 05.
[d]Amoxicillin; Ranbaxy Pharmaceuticals Inc., Princeton, NJ, USA; Lot No. 1255965; Exp. Oct 04.
[e]Augmentin; Lek Pharamceuticals Inc., Wilmington, NC, USA; Lot No. 2441901f; Exp. Jan 06.
[f]Furosemide Mylan tablet; Mylan Pharmaceuticals Inc., Morgantown, WV, USA; Lot No. 3L0343; Exp. Mar 07.

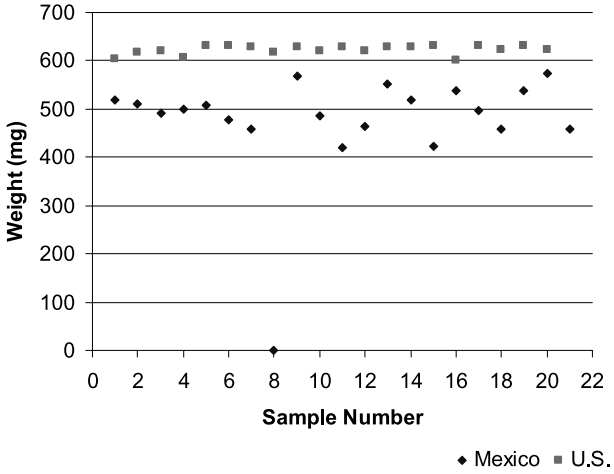

FIGURE 1 **Weight Variation Data for Amoxicillin Capsules. Avg. Weights: U.S. (n=20): 623.0±9.4 mg; Mex. (n=21): 497.9±43.4 mg.**

Standards, 2004a). The eluant consisted of a 50 mM potassium phosphate (KH_2PO_4) buffer (pH 5.0) and acetonitrile in a ratio of 96:4. An isocratic flow rate of 1.2 mL/min was employed. The injection volume was 10 μL. Ultraviolet detection was performed at 230 nm for the amoxicillin capsules and 220 nm for the suspension. Retention times were 2.4 and 3.2 min for the potassium clavulanate and the amoxicillin, respectively. Quantitation was accomplished through comparison of peak area to a standard curve, which was prepared on a daily basis, as needed.

After the weight of an individual capsule was recorded, a 240 mg portion was taken from that capsule and dissolved in 200 mL of 50 mM KH_2PO_4 buffer. The solution was sonicated for 10 min, after which time an aliquot was taken and filtered for analysis by the HPLC method, as previously described. A total of 20 capsules were analyzed in this manner for both the medicine acquired in Mexico and the medicine acquired in the United States. In addition, the contents of 20 capsules from each medicine were pooled into a single sample. Three separate 240 mg aliquots were then taken from this pooled sample and analyzed in the same manner as the individual capsules.

A dissolution assay was also performed for the amoxicillin capsules. For this assay, a 240 mg aliquot was taken from an individual capsule. This aliquot was placed in 200 mL of 50 mM KH_2PO_4 buffer, and the resulting solution was sonicated. A 1.0 mL sample was withdrawn at 5, 10, 15, 30, and 60 min. These samples were filtered and analyzed by HPLC, as described earlier. This assay was performed for three capsules from each medicine.

The amoxicillin/clavulanic acid suspension was prepared by adding an appropriate amount of water, as determined by preparation directions, to the entire contents of the bottles. A 1.0 mL aliquot was removed and an appropriate dilution was performed. The sample was then filtered and analyzed. Five samples were taken from each bottle.

Furosemide

The eluant for the furosemide assay consisted of water, tetrahydrofuran, and glacial acetic acid (70:30:1)

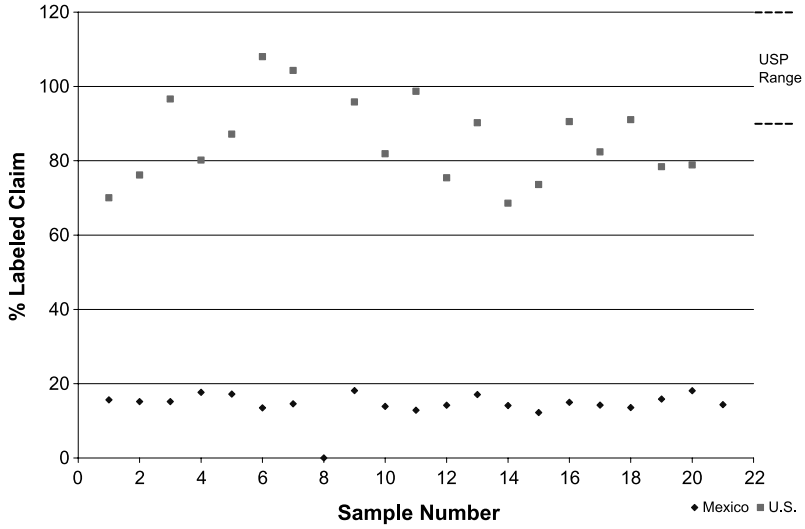

FIGURE 2 **Content Uniformity for Amoxicillin Capsules: 10 min. Sonication. Label Claim: 500 mg Amoxicillin/capsule; U.S. (n=20): 342.8–540. 1 mg/capsule±55.6 mg (avg. 85.8% Labeled claim), Pooled Samples: 71.0% Labeled Claim; Mex. (n=21): 61.1–90.7 mg/capsule±8.5 mg (avg. 15.1% Labeled Claim), Pooled Samples: 15.2% Labeled Claim.**

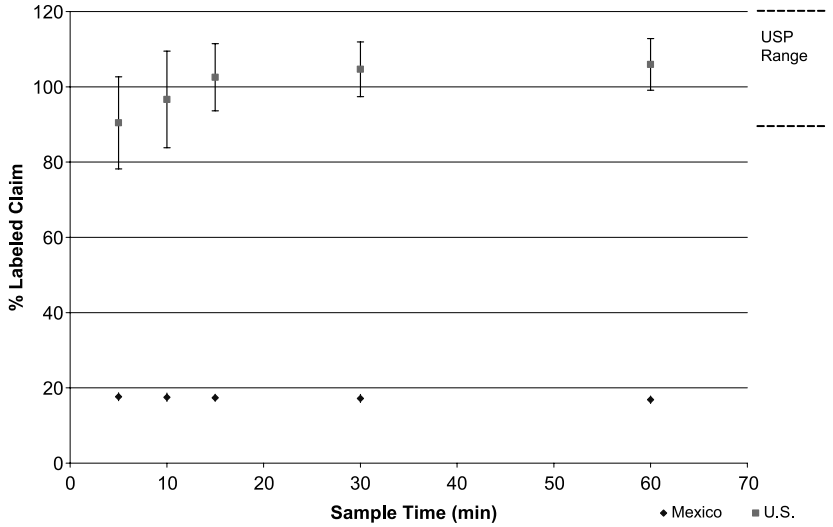

FIGURE 3 **Results for Dissolution Studies. Data Points Represent the Average ($n=3$) for Each Sample Time. Error Bars Represent Standard Deviations.**

at an isocratic flow rate of 1.0 mL/min (The Official Compendia of Standards, 2004b). The injection volume was 20 μL. Although the furosemide response was quantitated at 254 nm, ultraviolet detection was also monitored at 272 nm. The retention time for the furosemide peak was 15.8 min. Quantitation was accomplished through comparison of peak area to a standard curve, which was prepared on a daily basis.

After recording the weight, an individual tablet was crushed and the resulting powder was then added to 50 mL of diluent solution (22 mL of glacial acetic acid brought up to 1000 mL volume with 50:50 ACN:H_2O). Following sonication, the resulting solution was filtered and analyzed. A total of twenty tablets were analyzed in this manner for both the medicine acquired in Mexico and the medicine acquired in the United States. In addition, 20 tablets from each medicine were pooled. Three separate 40 mg aliquots were then taken from the pooled samples. These aliquots were prepared and analyzed in the same manner as the individual tablets.

RESULTS AND DISCUSSION

Amoxicillin Capsules

Weight variation data for the amoxicillin capsules is depicted in Fig. 1. The average weight for the U.S.

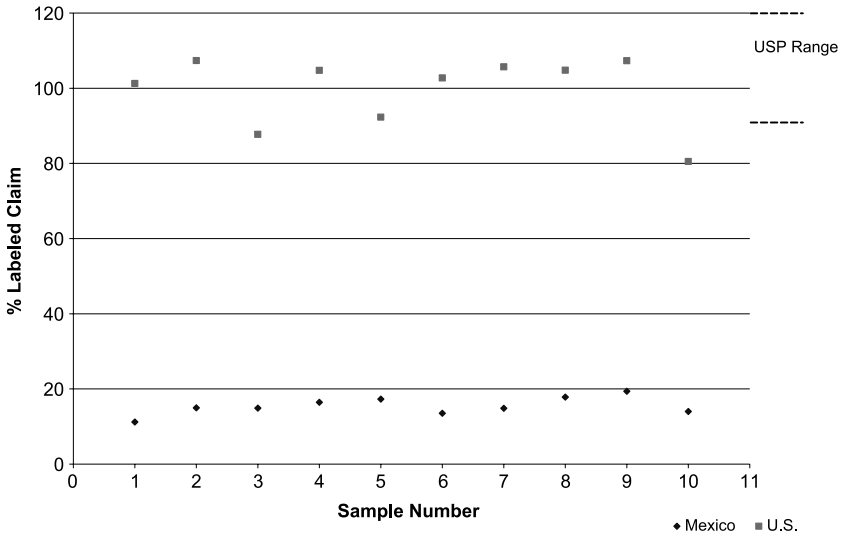

FIGURE 4 **Content Uniformity for Amoxicillin Capsules: 30 min. Sonication ($n=10$). Label Claim: 500 mg Amoxicillin/Capsule; U.S.: 402.5–536.9 mg/Capsule ± 46.6 mg (avg. 99.4% Labeled Claim); Mex.: 55.9–96.9 mg/Capsule ± 11.2 mg (avg. 15.4% Labeled Claim).**

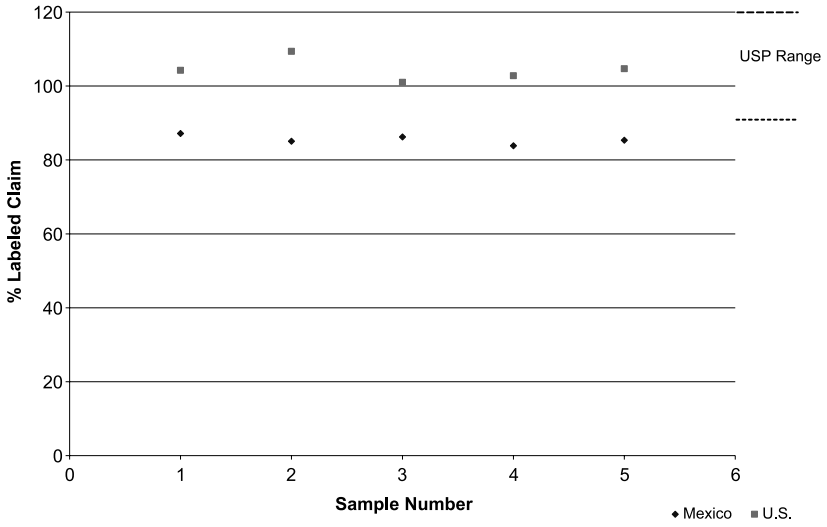

FIGURE 5 **Content Uniformity for Amoxicillin in Suspension Product (*n*=5). Label Claim: 400 mg per 5 mL Suspension. U.S.: 404–437.5 mg/5 mL Suspension ± 12.5 mg (avg. 104.4% Labeled claim); Mex.: 335.4–348.6 mg/5 mL Suspension ± 5.0 mg (avg. 85.52% Labeled Claim).**

capsules was 623.0±9.4 mg, as compared to an average of 497.9±43.4 mg for the Mexican capsules. It can also be seen from Fig. 1 that the weights for the Mexican capsules were appreciably lower than the weights for the U.S. capsules. The percent relative standard deviation (% RSD) for weight variation data was calculated to be 1.5% and 8.7% for U.S. and Mexican capsules, respectively. As a point of interest, one of the capsules obtained from Mexico contained no product whatsoever (this value was not included in the average value).

The label claim, for both the U.S. and the Mexican medications, was 500 mg amoxicillin per capsule. The USP range for amoxicillin capsules is stated between 90 and 120% of the label claim. As seen in Fig. 2, the amoxicillin content, for both the U.S. and Mexican capsules (85.8% and 15.1%, respectively) was below the USP range. This observance necessitated additional testing. Thus, 10 additional capsules from each bottle were evaluated by whole capsule content analysis, wherein the entire contents of a capsule was added to 500 mL of 50 mM KH_2PO_4 buffer. The following results were obtained from this second assay: the average amoxicillin content for the capsules from Mexico was 14.8% of the labeled amount and 88.4% of the labeled amount for the U.S. capsules. These findings confirmed earlier results obtained from the first assay, in which only a 240 mg aliquot from

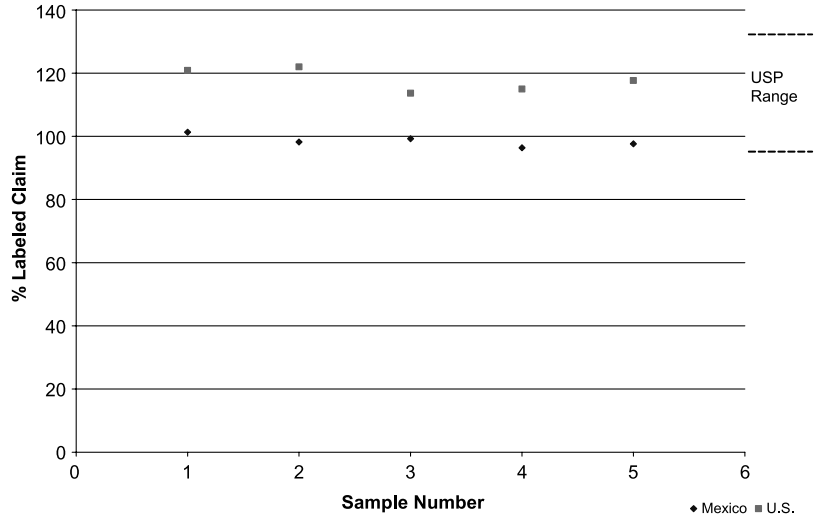

FIGURE 6 **Content Uniformity for Clavulanic Acid in Suspension Product (*n*=5). Label Claim: 57 mg per 5 mL Suspension. U.S.: 64.8–69 mg/5 mL Suspension ± 2.0 mg (avg. 117.8% Labeled Claim); Mex.: 54.9–57.8 mg/5 mL Suspension ± 1.1 mg (avg. 98.6% Labeled Claim).**

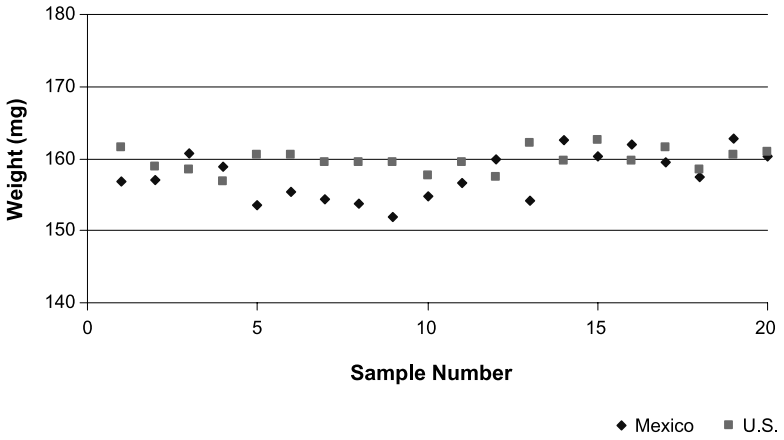

FIGURE 7 **Weight Variation Data for Furosemide Tablets (n=20). Avg. Weights: U.S.: 159.8±1.6 mg; Mex.: 157.6±3.3 mg.**

each capsule was tested. Therefore, it was determined that the initially observed results were not due to sampling distribution errors. In addition, the results from the pooled samples (71.0% and 15.2% for the United States and Mexican, respectively) also support the earlier data.

Hassan et al. (1996) performed a study which found that certain excipients often used in solid dosage forms could interfere with the dissolution rates of amoxicillin trihydrate. In addition, dosage forms which contain gelatin (an ingredient used to form both hard and soft capsules) can also exhibit changes in dissolution profiles (Singh et al., 2002). Based on these observations, dissolution studies were performed; the results of which are shown in Fig. 3.

From Fig. 3, it can be seen that while increasing sonication time, prior to pulling a sample for analysis, had little to no effect for the capsules obtained from Mexico (avg: 15.4%); there was a slight increase for the capsules obtained from the U.S. pharmacy. Based on these findings, an additional 10 capsules were assayed, following 30 min of sonication. In doing so, the average percent of amoxicillin recovered from each capsule was increased from 85.8% (10 min sonication) to 99.4%, well within the acceptable range designated by USP specifications (Fig. 4).

Amoxicillin Suspension

Figures 5 and 6 display the results for the amoxicillin and clavulanic acid content, respectively, obtained from the analyses of the amoxicillin suspensions. The defined USP range for this product is between 90 and 120% of label claim for amoxicillin,

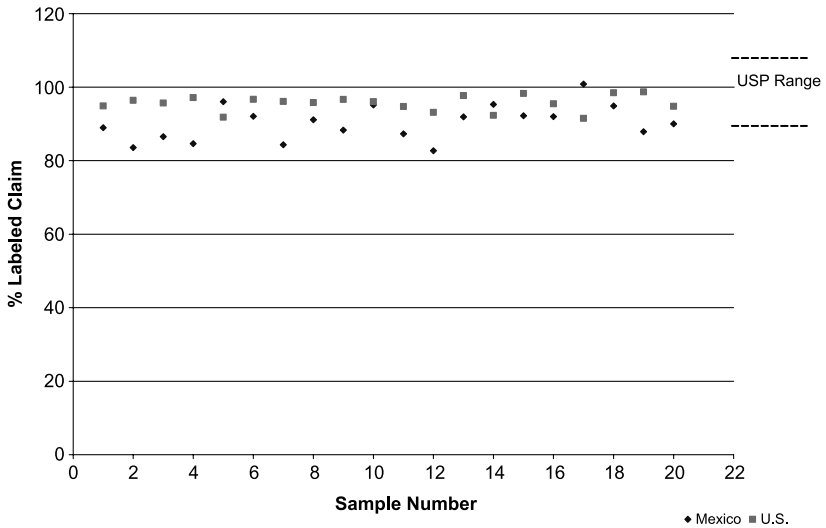

FIGURE 8 **Content Uniformity for Furosemide Tablets. Label Claim: 40 mg Furosemide per Tablet. U.S.: 36.6–39.5 mg/Tablet±0.8 mg (avg. 95.6% Labeled Claim), Pooled Samples: 97.2% Labeled Claim; Mex.: 35.2–35.6 mg/Tablet±2.0 mg (avg. 90.3% Labeled Claim), Pooled Samples: 95.0% Labeled Claim.**

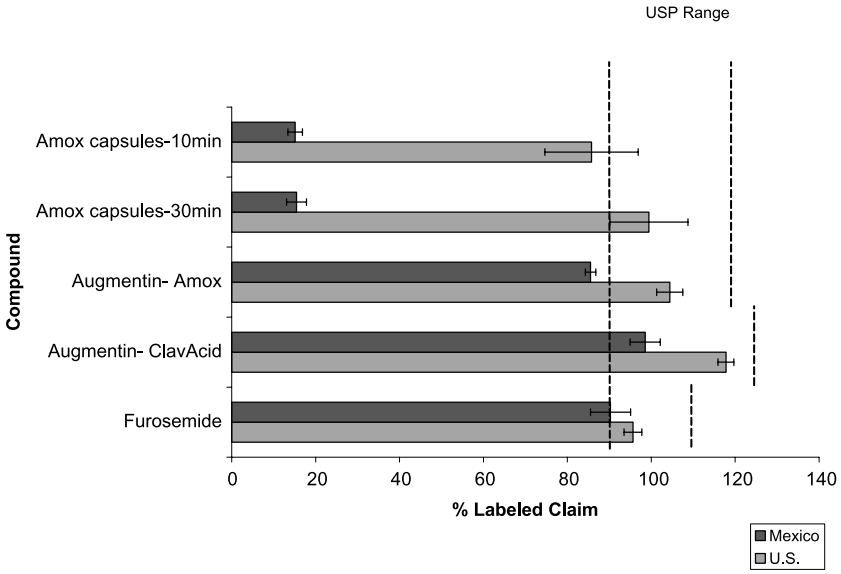

FIGURE 9 **Content Uniformity Summary for All Products.**

and 90 and 125% of label claim for clavulanic acid. In this case, the label claim, for both products, was 400 mg amoxicillin and 57 mg clavulanic acid per 5 mL of suspension. Both the amoxicillin and clavulanic acid content were within the USP range for the U.S. product (104.4% and 117.8%, respectively). However, only the clavulanic acid content (98.6%) was in agreement with USP specifications for the Mexican product. As seen with the capsules, the amoxicillin content for the Mexican product (85.58%) was under the acceptable USP range.

Furosemide

Weight variation data for the furosemide tablets is shown in Fig. 7. From this figure, it can be seen that both the tablets from the United States (average weight: 159.8±1.6 mg) and the tablets from Mexico (average weight: 157.6±3.3 mg) had only slight variation in weight resulting in a 1.0% and 2.1% RSD for United States and Mexican tablets, respectively. The content uniformity data (Fig. 8) shows that both the Mexican and the U.S. medications were within the USP range of 90 to 110% of the labeled claim, which was 40 mg of furosemide per tablet. For 20 tablets, the average for the U.S. medication was 95.6%, while the average for the Mexican medication was 90.3%. The pooled samples, which were also taken, concur with the individual samples (97.2% and 95.0%, respectively).

CONCLUSIONS

As demonstrated by Fig. 9, which summarizes the content uniformity, all of the medicines obtained from the pharmacy in Mexico were found to contain lower amounts of active ingredients than their U.S. counterparts. However, the furosemide tablets and the clavulanic acid in the Augmentin suspension were still within the acceptable range designated by the USP; only the amoxicillin content for both the suspension and the capsules were outside the designated USP range. While no broad conclusions can be made regarding the overall quality of medications obtained from Mexico, due to the limited sample size utilized, the findings of this study offer compelling preliminary evidence that further investigation and direct quality comparisons for medications obtained in Mexico are warranted.

REFERENCES

Calvillo, J. P., & Lal, L. (2003). Pilot study of a survey of U.S. residents purchasing medications in Mexico: demographics, reasons, and types of medications purchased. *Clinical Therapeutics*, *25*(2), 561–577.

Casner, P. R., & Guerra, L. G. (1992). Purchasing prescription medication in Mexico without a prescription: the experience at the border. *Western Journal of Medicine*, *156*(5), 512–516.

Davignon, J. P., Trissel, L. A., Kleinman, L. M., & Cradock, J. C. (1978). Pharmaceutical assessment of amygdalin (Laetrile) products. *Cancer Treatment Reports*, *62*(1), 99–104.

Food and Drug Administration Consumer education: buying medicine from outside the United States. www.fda.gov/cder/consumerinfo/buy_outside_US_text.html (accessed Sept. 2004).

Food and Drug Administration. FDA warns consumers about counterfeit

drugs purchased in Mexico. www.fda.gov/bbs/topics/ANSWERS/2005/ANS01 (accessed June 2005).
Hassan, M. A., Kaloustian, J., Prinderre, P., Ramsis, H., Khaled, K. A., El-faham, T. H., Tous, S. S., Maury, L., & Joachim, J. (1996). Physicochemical study on the interactions between amoxicillin trihydrate and some excipients used in solid dosage forms. *Pharmazie*, *51*(6), 400–403.
Lopez, A. A., Garcia, C. R., Lapiedra, C. B., Dorantes, A. G., Jung, H. C., & Espejo, O. G. (1983). Comparative dissolution of solid pharmaceutical forms found on the Mexican drug market. I. Metronidazole. *Revista de la Sociedad Química de México*, *27*(4), 164.
McKeithan, E. K., & Shepherd, M. D. (1996). Pharmaceutical products declared by U.S. residents on returning to the United States from Mexico. *Clinical Therapeutics*, *18*(6), 1242–1251.
(2004a). *The Official Compendia of Standards, USP 27/NSF 22*. Rockville, MD: United States Pharmacopeial Convention, Inc., 138–143. Official Monographs.
(2004b). *The Official Compendia of Standards, USP 27/NSF 22*. Rockville, MD: United States Pharmacopeial Convention, Inc., 845–846. Official Monographs.
Singh, S., Rao, K. V. R., Venugopal, K., & Manikandan, R. (2002). Alteration in dissolution characteristics of gelatin-containing products: a review of the problem, test methods, and solutions. *Pharmaceutical Technology*, April. www.pharmtech.com (accessed Sept. 2004).
Trujillo, V. A., Herrera, P. Ma.D., Zamudio, A. R., Espinoza, R. M., & Luna, G. A. (2003). Herbal medicines and quality control. *Revista Mexicana de Ciencias Farmacéuticas*, *34*(1), 22–27.