



February 6, 2006

**SUBJECT:** Presence of Azithromycin monohydrate hemi-ethanolate (Form F) and Azithromycin sesquihydrate (Form G) in Teva Azithromycin 250, 500 and 600 mg Tablets Manufactured by Teva Pharmaceutical Ind. Ltd., Israel for Teva Pharmaceuticals USA

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### SUMMARY

Commercial samples of Azithromycin 250, 500 and 600 mg tablets manufactured by Teva Pharmaceutical Industries Inc, Israel were purchased in the United States and forwarded to Pfizer, Groton, CT for analysis to determine the form of azithromycin in the product. A combination of Fourier Transform Infrared Spectroscopy (FTIR), Powder X-Ray Diffraction (PXRD), and <sup>13</sup>C Solid State NMR (ssNMR) and headspace gas chromatographic (GC) analyses were performed on the samples. Results were compared to the data generated from reference materials of azithromycin Form G (azithromycin sesquihydrate), Form F (azithromycin monohydrate hemi-ethanolate) and Form A (azithromycin dihydrate). Results from FT-IR, PXRD, and ssNMR demonstrated the absence of Form A in all three tablet strengths. The PXRD results indicated that the samples contained azithromycin in a crystalline form within Family I, which is comprised of Forms F, G, H, J, M, N, O and P. The PXRD results also provided evidence for absence of Form Q and those in Family II, which is comprised of Forms C, D, E, and R.

Further analysis by ssNMR allowed differentiation between the Family I isomorphs. The ssNMR results obtained for the three tablet strengths demonstrated excellent agreement (48 of 50 peaks matched) with the ssNMR spectrum of our Form F reference material. Presence of an additional isomorph from Family I was indicated by the non-equivalence of carbonyl responses in the sample at 179.5 ppm and 178.6 ppm. Within Family I, Forms H, J, M, and N were eliminated from consideration by the absence of diagnostic ssNMR signals for these forms in the sample spectra. Two other isomorphs, Forms O and P, were concluded to be absent in the samples on the basis of headspace GC results. The headspace GC results for the tablet samples showed no detectable levels of the solvent components (n-butanol and n-pentanol) that characterize these forms. Headspace GC also demonstrated absence of detectable cyclohexane, tetrahydrofuran, methyl tert-butyl ether, n-propanol, and isopropanol in the samples. This added support to ssNMR and PXRD evidence demonstrating absence of Forms D, E, H, J, M, N and R.

By process of elimination, Form G is found to be the only isomorph in Family I that could account for the relative increase in carbonyl signal at 179.5 ppm in the samples. The levels of Form G and Form F were then calculated using responses for the characteristic carbonyl peaks at 179.5 ppm (characteristic for Forms G and F) and at 178.6 ppm (characteristic for Form F only). Based on ssNMR results, the relative content of the crystal forms was estimated as: 78% F and 22% G for the 250 mg tablet, 74% F and 26% G for the 500 mg tablet, and 72% F and 28% G for the 600 mg tablet. Analysis of ethanol content by headspace GC found levels ranging from 1.5-1.8% by weight relative to azithromycin content. By comparison to the theoretical content of 2.9% ethanol in azithromycin Form F, the levels of ethanol found in the samples indicate Form F must be present in substantially less than pure form. Based on results

of the IR, PXRD, and ssNMR, and headspace GC analyses, the Teva tablets are concluded to contain azithromycin monohydrate hemi-ethanolate and lesser, but significant amounts of azithromycin sesquihydrate.

## OBJECTIVES

Testing was performed on Azithromycin 250 mg, 500 mg and 600 mg tablets to determine the form of azithromycin present in the samples. A combination of ssNMR, FT-IR and PXRD spectroscopic techniques were used for the analysis. Additional testing by headspace gas chromatography was used to verify presence or absence of solvents associated with various known crystal forms of azithromycin.

## SAMPLE DESCRIPTION

The 250 mg and 600 mg tablets used in these analyses were obtained by Pfizer from the distributor (McKesson) and sent to the Special Testing & Analytical Development Laboratory at Pfizer GQAR, Groton, CT for testing. The 500 mg tablets were obtained from Walgreen's retail pharmacy (New York, NY) and forwarded to Pfizer GQAR Groton, CT for testing. All tablets were stored at all times at controlled room temperature. Photographs and other details for the 250 mg, 500 mg, and 600 mg tablet samples are presented in **Figures 1, 2 and 3**, respectively.

## ANALYTICAL RESULTS

### 1. Fourier Transform Infrared Spectroscopy (FTIR)

A Nicolet model Magna-IR 550 Fourier Infrared (FT-IR) spectrometer was used to analyze the azithromycin tablet samples in a potassium bromide pellet preparation. The spectra of the 250 mg, 500 mg, and 600 mg samples and the azithromycin dihydrate reference (lot # G37060-64140-980-1), are shown in **Figures 4, 5 and 6**, respectively. Diagnostic IR bands of  $3559\text{cm}^{-1}$ ,  $3495\text{cm}^{-1}$ ,  $1343\text{cm}^{-1}$ ,  $1282/1270\text{cm}^{-1}$  (doublet) and  $1083\text{cm}^{-1}$  that are unique to azithromycin dihydrate (Reference: Pfizer Standard Test Procedure I 3.94, effective date: 04/22/98) were not detected in spectra of the three tablet samples. These data indicate absence of azithromycin dihydrate in the samples (within estimated detection limit of 25% by weight relative to total azithromycin content).

### 2. Analysis by Powder X-Ray Diffraction (PXRD)

PXRD diffractograms were collected for the Azithromycin 250 mg, 500 mg, and 600 mg tablets using a Siemens D4 X-ray diffractometer. A portion of each tablet was gently ground to a fine powder in a mortar and pestle for the analysis. Resulting diffractograms were compared to those obtained previously for azithromycin dihydrate, azithromycin Form G, and azithromycin Form F reference samples.

The resulting diffractograms from the azithromycin 250 mg, 500 mg and 600 mg samples and azithromycin dihydrate reference are shown in **Figures 7, 8, and 9**, respectively. The most diagnostic peaks for azithromycin dihydrate in the region from 7 to 22 degrees in 2-theta were not present in a pattern indicative of Form A. These data provide evidence for the absence of detectable azithromycin dihydrate in the tablets. Estimated detection limit for azithromycin dihydrate by the PXRD technique is 5% by weight relative to total azithromycin content.

The PXRD results for the Teva samples indicate absence of Family II forms of azithromycin in the sample. Family II includes Form D (monohydrate/monocyclohexane solvate), Form E (azithromycin monohydrate/mono-tetrahydrofuran solvate), Form C (azithromycin monohydrate,

as described in US 6,977,243), and Form R (azithromycin hydrate/methyl tert-butyl ether solvate). The most diagnostic PXRD signals for the isomorphs in this family occur at 3.9, 10.1, 10.6 and 21.4 2-theta. All three spectra in **Figures 7, 8, and 9** were found to be missing the most easily discernible signals (i.e., those with highest intensity) at 3.9, 10.1 and 10.6 2-theta. One additional form, Form Q (azithromycin hydrate/hemi-tetrahydrofuran solvate) is also found to be absent in the three Teva tablets. This result is demonstrated by absence of diagnostic signals for Form Q at 6.8 and 8.4 2-theta in the sample spectra shown in **Figures 7, 8 and 9**.

Diffraction patterns of the 250 mg, 500 mg, and 600 mg tablets are shown with overlays of the Form F diffraction pattern in **Figures 10, 11, and 12**, respectively. These data indicate the presence of crystalline azithromycin in a form consistent with Form F and other isomorphs within Family I (F, G, P, H, J, M, N, and O). Each of the sample spectra are found to contain peaks that match both position and relative intensity of those found in the reference spectrum of Form F. Form F is one form in a family of eight azithromycin isomorphs (Family I) that have similar x-ray diffraction characteristics. In addition to Form F, other isomorphs in this family are Form G (azithromycin sesquihydrate), Form H (azithromycin monohydrate/hemi-propylene glycol solvate), Form J (azithromycin monohydrate/hemi-n-propanol solvate), Form M (azithromycin monohydrate/hemi-isopropanol solvate), Form N (azithromycin water/ethanol/isopropanol solvate), Form O (azithromycin hemi-hydrate/hemi-n-butanol solvate), and Form P (azithromycin hemi-hydrate/hemi-n-pentanol solvate). The PXRD spectra are essentially identical for each of the forms in this family and an example is illustrated in an overlay of diffraction patterns for Forms F and G in **Figure 13**. Therefore, additional analysis (e.g., ssNMR) is needed to distinguish which forms from among Family I are present in the samples.

### 3. Analysis by <sup>13</sup>C Solid State NMR (ssNMR)

The <sup>13</sup>C-ssNMR spectral analyses were conducted by the Pfizer Global Research and Development NMR Laboratory in Groton, CT, USA. Results of these experiments are summarized below. The results were obtained from an approximate 270 mg sample for each strength that had been gently ground to a powder. A one-dimensional <sup>13</sup>C-ssNMR spectrum was collected for each of the samples using a <sup>1</sup>H-<sup>13</sup>C carbon cross-polarization magic angle spinning (CPMAS) technique. Full details of the NMR analyses are reported in research reports cp62993\_IP06008a\_31JAN2006 and cp62993\_IP05055a.01FEB2006.

The resulting ssNMR spectra of the test samples were compared to the spectra of azithromycin Forms F, Form G and Form A in **Figure 14** (250 and 600 mg tablets) and **Figure 15** (500 mg tablets). Absence of azithromycin Form A in all three tablet strengths was demonstrated by absence of its characteristic peaks at 178.1, 104.1, 98.4, 84.6, 52.2, 26.9, 26.3, 19.5, 13.2, 11.3, and 7.2 ppm. These results are consistent with those obtained from FT-IR and PXRD analysis of the tablets.

PXRD analysis has already excluded presence of Family II isomorphs D, E, C, and R and Form Q. The ssNMR spectra of the tablets provides additional evidence for absence of Forms D and R. Form D is not present because its characteristic peaks at 178.1, 103.9, 84.2, 75.7, 67.8, 64.7, 49.2, 43.1, 40.6, 29.3, 10.6, 9.0, and 8.6 ppm are missing in the sample spectra. Absence of peaks in the sample spectra at 177.9, 104.6, 103.6, 95.3, 84.0, 79.4, 75.6, 64.5, 49.4, 42.9, 40.4, 29.4, 29.0, 21.4, 16.1, 10.3, 8.9, and 8.6 ppm supports absence of Form R.

A detailed analysis of the sample spectra and comparison to spectra of isomorphs within Family I suggests that the Teva tablets contain primarily azithromycin Form F with lesser, but significant amounts of azithromycin Form G. The most diagnostic indicators of Form F in the sample are its two carbonyl peaks at 179.5 ppm and 178.6 ppm and an ethanol peak at 58.0 ppm. The ssNMR spectra for Forms H, J, M, and N each contain two carbonyl signals near

those found in Form F, but each of these can be eliminated from consideration by the absence of signals corresponding to the solvents within each isomorph. Form J is excluded by the absence of detectable signals in the sample for crystal-bound n-propanol at 11.5 and 25.2 ppm. Forms M and N are excluded by absence of detectable signals for crystal-bound isopropanol at 26.0 ppm. Azithromycin Form H (monohydrate/hemi-propylene glycol solvate) is not present since its characteristic peaks at 103.2, 82.7, 66.9, 46.8, 33.3, 15.4 and 7.0 ppm are missing in the sample spectra.

**Table 1** lists the Form F peaks identified in US 6,977,243 patent along with corresponding peaks found in the 250 mg, 500 mg and 600 mg Teva tablets. Of 50 peaks listed in the patent, 48 were identified (within the  $\pm 0.2$  accuracy limits) in each of the tablet samples. Exceptions included a shoulder instead of a peak in the sample at 17.2 ppm and a peak in the 600 mg sample at 58.3 ppm that was shifted by 0.3 ppm from the reference. It is expected that some peaks will be affected when a pure reference material is mixed with other ingredients in preparing the tablets. Signal interferences from crystalline excipients and solid-solid interactions between the azithromycin and excipient materials leading to line width broadening can each contribute to these variations. Overall, the variations are minor and do not preclude a positive identification of Form F in the samples.

Presence of an additional azithromycin isomorph impurity with Form F is indicated by the non-equivalent responses in the samples at 179.5 ppm and 178.6 ppm. Azithromycin, when present as 100% Form F would show a spectrum with the two responses being roughly equal. Within Family I, only Forms G, O, and P were not excluded by PXRD or ssNMR data and remain as potential candidates that could account for this impurity. Separate analysis of the samples by headspace GC analysis (discussed in Section 4) demonstrated absence of n-butanol and n-pentanol and thus rules out the presence of Forms O and P in the Teva Azithromycin tablets.

By process of elimination, Form G was found to be the only isomorph in Family I that could account for the relative increase in carbonyl signal at 179.5 ppm in the samples. The calculation of the relative content of Form G in Form F was based on an assumption that the cross-polarization kinetics for forms F and G are equivalent. The levels of Form G and Form F were then calculated using responses for the characteristic carbonyl peaks at 179.5 ppm (characteristic for Forms G and F) and at 178.6 ppm (characteristic for Form F only). Using this approach, the amounts were calculated as:

	<b>Form F</b>	<b>Form G</b>
<b>250 mg tablet</b>	78%	22%
<b>500 mg tablet</b>	74%	26%
<b>600 mg tablet</b>	72%	28%

#### **4. Analysis by Headspace Gas Chromatography (GC).**

Headspace GC analyses were performed using a Tekmar 7000 Headspace Autosampler and Agilent 6890 Gas Chromatograph with flame ionization detection. Each tablet was dissolved in water (250 mg into 50 mL, 500 mg or 600 mg into 100 mL) and then 5 mL aliquots were placed into a 20 mL headspace vial containing 1 g of anhydrous sodium sulfate. Sealed vials were incubated at 85 C for 10 min and then 2 mL of headspace was injected into the chromatograph. Separation was performed using a 30 m x 0.32 mm i.d. RTX-624 (1.8  $\mu$ m film) capillary column. Oven temperature program was 40 C (5 min hold) – ramp 2 C/min to 90 C (0 min hold) – ramp 30 C/min to 225 C (2 min hold).

Retention times for various solvents on the chromatographic system were established by analyzing various aqueous solutions containing solvent reference materials. A summary of solvents and retention times is presented in the table below.

Solvent	Retention time
Ethanol	3.54
Isopropanol	4.33
Methyl tert-butyl ether	5.25
n-Propanol	6.52
Tetrahydrofuran	8.18
Cyclohexane	8.72
n-Butanol	12.21
n-Pentanol	19.80

Headspace GC profiles obtained for the 250 mg, 500 mg and 600 mg Teva Azithromycin tablets are presented in **Figure 16**. A major response for ethanol was detected in each of the tablet samples. None of the other seven solvents was detected in the samples. Based on a signal to noise analysis of responses from an external standard solution, limits of detection for n-propanol, isopropanol, 1-butanol, 1-pentanol, and tetrahydrofuran were each found to be 10 ppm (0.001%) or less. The limits of detection for cyclohexane and methyl tert-butyl ether were not specifically measured in this analysis, but would have lower detection limits as a result of relatively lower solubility in water (hence greater concentration in headspace) than the other solvents. The absence of detectable responses for the other seven solvents provides evidence that none of the Forms D, E, H, J, M, N, O, P, and R are present in the Teva Azithromycin tablets.

Ethanol content in the Teva tablets was estimated by comparison of the response in the sample to that from an external standard solution. Recovery of ethanol spiked into a 600 mg tablet was  $96 \pm 9\%$  (average  $\pm$  sd, n=3). Levels measured in the samples were: 1.5% ethanol in the 250 mg tablet, 1.5% ethanol in the 500 mg tablet, and 1.8% ethanol in the 600 mg tablet. The total ethanol content in the samples is significantly lower than the theoretical content of 2.9% ethanol in 100% azithromycin Form F. Assuming that all ethanol measured in the samples is present as azithromycin Form F, calculated amounts of Form F in the samples are 52% in the 250 mg and 500 mg tablets and 62% in the 600 mg tablets. These results support the ssNMR results indicating the azithromycin Form F is not present in a highly pure form.

## CONCLUSIONS

Based on results of the IR, PXRD, and ssNMR, and headspace GC analyses, the Teva tablets are concluded to contain primarily azithromycin monohydrate hemi-ethanolate (Form F) along with lesser, but significant amounts of azithromycin sesquihydrate (Form G).

## REFERENCES

1. Notebook B108526 pp. 9-10
2. Pfizer Standard Test Procedure I 3.94 (4/22/98) – Identification of azithromycin dihydrate by Infrared spectroscopy.
3. PGRD Report: CP62993\_IP5055\_13Dec2005, prepared by Ales Medek
4. PGRD Report: CP62993\_IP06008\_13Jan2006, prepared by Ales Medek
5. PGRD Report: CP62993\_IP06008a\_31Jan2006, prepared by Ales Medek
6. PGRD Report: CP62993\_IP05055a.01FEB2006, prepared by Ales Medek
7. United States Patent No. 6,977,243 (issued Dec. 20, 2005, Certificate of Correction issued Feb. 7, 2006)



A – Bottle (front)



B- Bottle (back)



C- Tablets

- **Manufacturer:** Manufactured in Israel by Teva Pharmaceutical Ind. Ltd. for Teva Pharmaceuticals USA.
- **Claimed active ingredient and strength:** Labelling states “Each tablet contains: azithromycin monohydrate equivalent to 250 mg azithromycin”.
- **Test sample details:** 250 mg tablet, Lot Number A42033 NDC 0093-7146-56, expiration date December 2007. Oval red tablets debossed with “93” on one side and “7416” on opposite side. Weight of one representative tablet recorded in laboratory as 436.6 mg.
- **Chain of custody information:** The samples were purchased by Pfizer from the distributor, McKesson, and sent to Pfizer GQAR, Eastern Point Road, Groton, CT 06340, USA for testing. The 250 mg bottle was received in the GQAR Groton laboratory with safety seal intact.

**Figure 1.** Teva Azithromycin 250 mg tablets – Photographs and details of samples received at Pfizer GQAR laboratory in Groton.



A – Bottle (front)



B- Bottle (back)



C- tablets

- **Manufacturer:** Teva Pharmaceutical Industries, 5 Basel St., PO Box 3190, Petah Tikva 49131, Israel.
- **Claimed active and strength:** azithromycin 500 mg.
- **Test sample details:** 20 x 500 mg tablets, Prescription No. 0427075-06, NDC 00093-7169-56, expiration date December 8, 2006. Oval red tablets debossed with “93” on one side and “7469” on opposite side. Weight of one representative tablet recorded in laboratory as 882.3 mg.
- **Chain of custody information:** The prescription was filled on Dec. 9, 2005 for a Pfizer colleague at Walgreens Pharmacy (145 Fourth Ave., New York, NY) and then forwarded from Pfizer New York office to Pfizer GQAR, Eastern Point Road, Groton, CT 06340, USA for testing.

**Figure 2.** Teva Azithromycin 500 mg tablets - Photographs and details of samples received at Pfizer GQAR laboratory in Groton.



A – Bottle (front)



B- Bottle (back)



C- Tablets

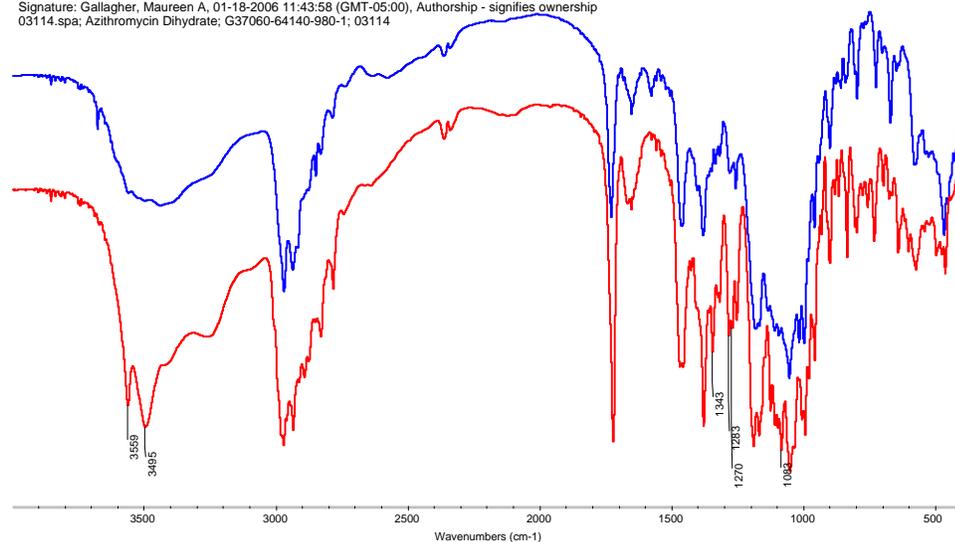
- **Manufacturer:** Manufactured in Israel by Teva Pharmaceutical Ind. Ltd. for Teva Pharmaceuticals USA.
- **Claimed active ingredient and strength:** Labelling states “Each tablet contains: azithromycin monohydrate equivalent to 600 mg azithromycin”.
- **Test sample details:** 600 mg tablets, Lot Number A43004 NDC 0093-7147-56; expiration date March 2007. White round/elongated tablets debossed with “93” on one side and “7417” on opposite side. Weight of one representative tablet recorded in laboratory as 1080.2 mg.
- **Chain of custody information:** The samples were purchased by Pfizer from the distributor, McKesson, and sent to Pfizer GQAR, Eastern Point Road, Groton, CT 06340, USA for testing. The 600 mg bottle was received in the laboratory with safety seal intact.

**Figure 3.** Teva Azithromycin 600 mg tablets - Photographs and details of samples received at Pfizer GQAR laboratory in Groton.

**A**

Azithromycin 250mg Lot A42033 (IP06008) by KBR Wed Jan 18 11:29:23 2006 (GMT-05:00)  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114

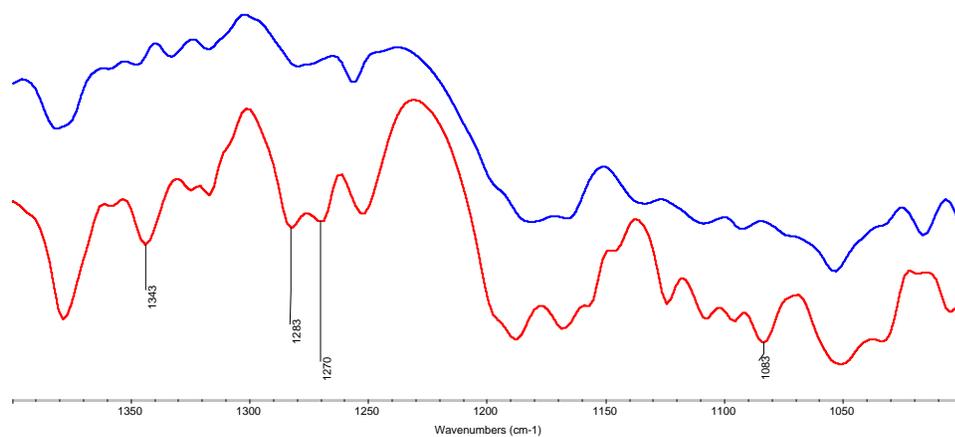
Signature: Gallagher, Maureen A, 01-18-2006 11:43:58 (GMT-05:00), Authorship - signifies ownership  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114



**B**

Azithromycin 250mg Lot A42033 (IP06008) by KBR Wed Jan 18 11:29:23 2006 (GMT-05:00)  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114

Signature: Gallagher, Maureen A, 01-18-2006 11:43:58 (GMT-05:00), Authorship - signifies ownership  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114

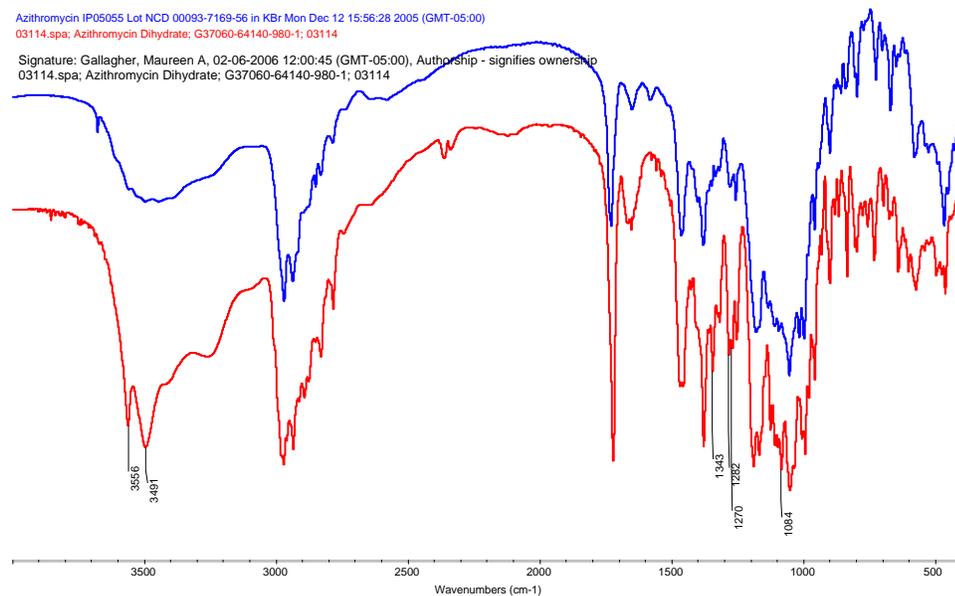


**Figure 4.** FTIR spectra of Teva Azithromycin 250 mg tablet (upper trace, blue) and azithromycin dihydrate lot G37060-64140-980-1 (lower trace, red) shown: (A) full scale from  $4000\text{ cm}^{-1}$  –  $400\text{ cm}^{-1}$  and (B) expanded scale from  $1400\text{ cm}^{-1}$  -  $400\text{ cm}^{-1}$  range. The analysis indicated that azithromycin dihydrate was not detected in the sample.

**A**

Azithromycin IP05055 Lot NCD 00093-7169-56 in KBr Mon Dec 12 15:56:28 2005 (GMT-05:00)  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114

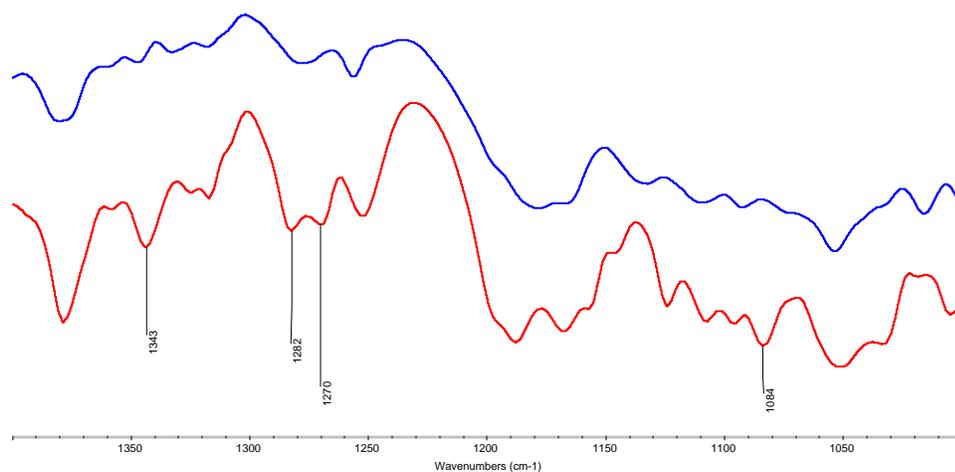
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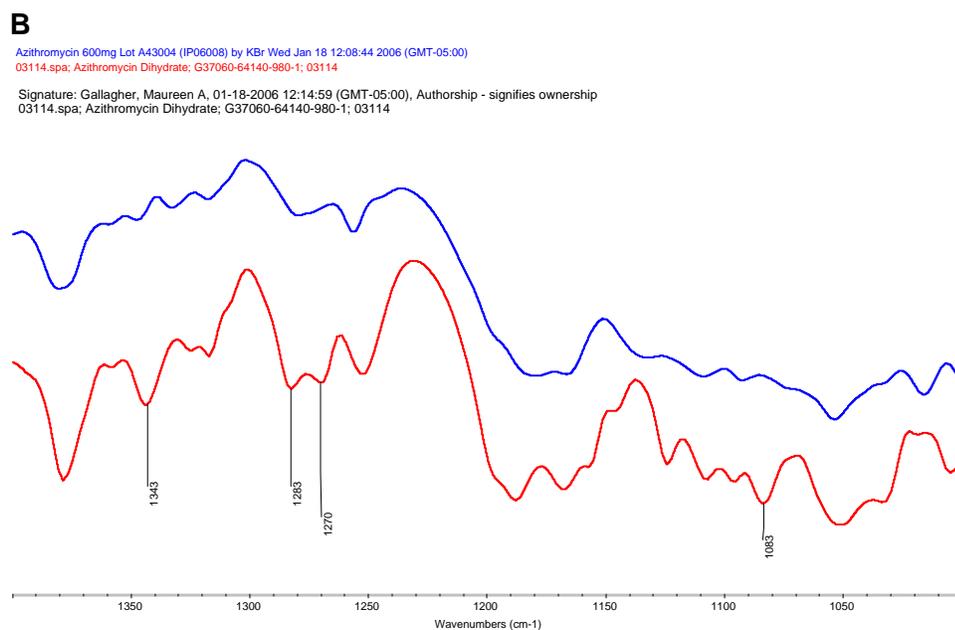
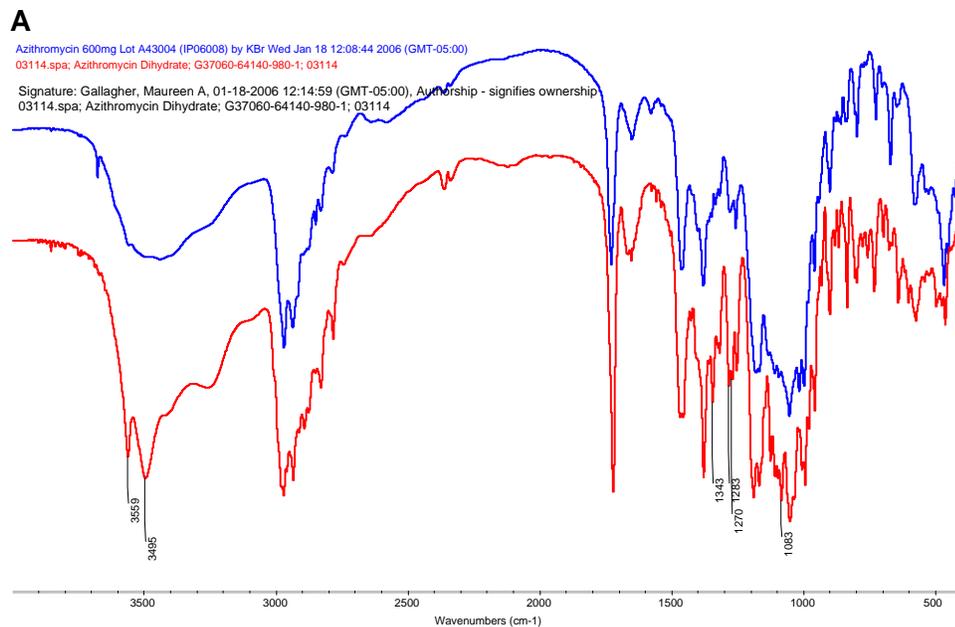
**B**

Azithromycin IP05055 Lot NCD 00093-7169-56 in KBr Mon Dec 12 15:56:28 2005 (GMT-05:00)  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114

Signature: Gallagher, Maureen A, 02-06-2006 12:00:45 (GMT-05:00), Authorship - signifies ownership  
03114.spa; Azithromycin Dihydrate; G37060-64140-980-1; 03114

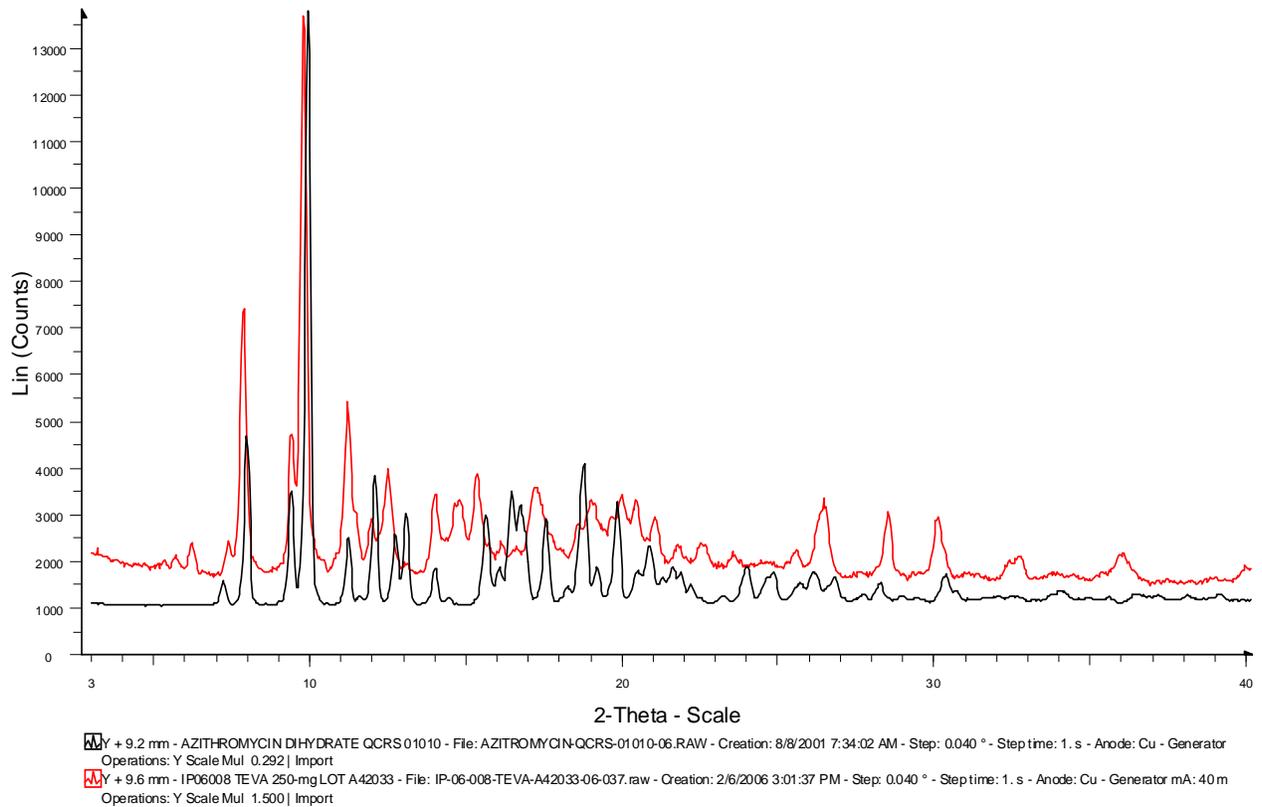


**Figure 5.** FTIR spectra of Teva Azithromycin 500 mg tablet (upper trace, blue) and azithromycin dihydrate lot G37060-64140-980-1 (lower trace, red) shown: (A) full scale from  $4000\text{ cm}^{-1}$  –  $400\text{ cm}^{-1}$  and (B) expanded scale from  $1400\text{ cm}^{-1}$  -  $400\text{ cm}^{-1}$  range. The analysis indicated that azithromycin dihydrate was not detected in the sample.



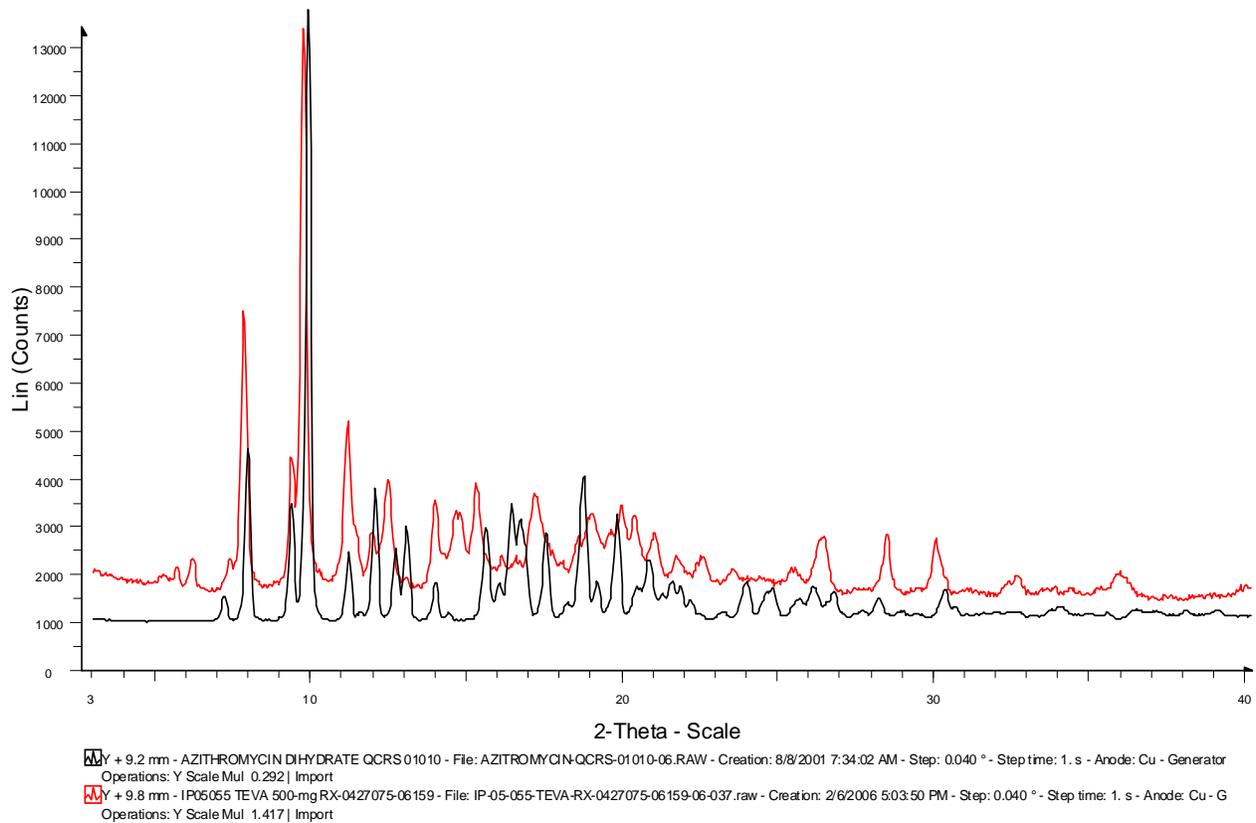
**Figure 6.** FTIR spectra of Teva Azithromycin 600 mg tablet (upper trace, blue) and azithromycin dihydrate lot G37060-64140-980-1 (lower trace, red) shown: (A) full scale from 4000  $\text{cm}^{-1}$  – 400  $\text{cm}^{-1}$  and (B) expanded scale from 1400  $\text{cm}^{-1}$  - 400  $\text{cm}^{-1}$  range. The analysis indicated that azithromycin dihydrate was not detected in the sample.

IP06008 TEVA 250-mg LOT A42033 vs. AZITHROMYCIN DIHYDRATE REF.



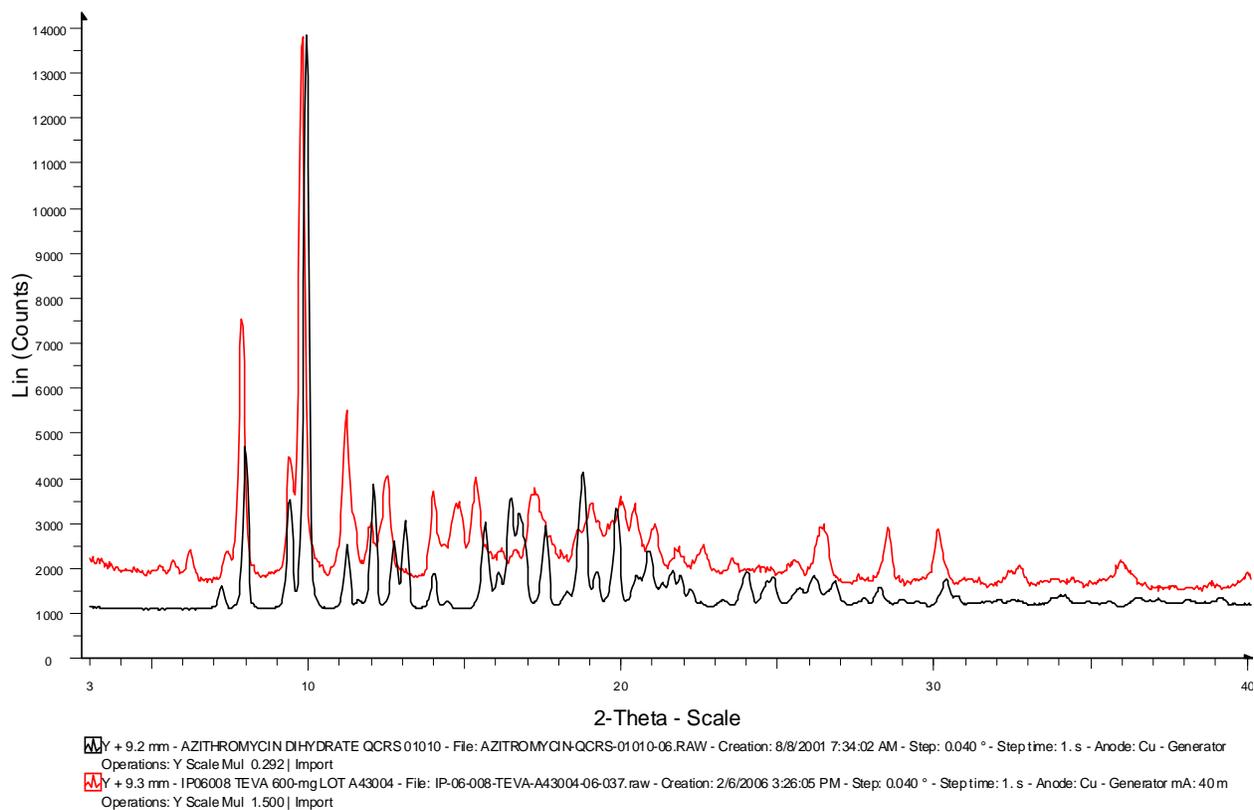
**Figure 7.** Overlay of diffractograms for Teva Azithromycin 250 mg tablet and azithromycin dihydrate reference (QCRS lot 03114-QCS-12). The absence of several diagnostic peaks for azithromycin dihydrate in the sample over range of 7 to 22 degrees in 2-theta indicated that azithromycin dihydrate was not detected.

IP05055 TEVA 500-mg TAB vs. AZITHROMYCIN DIHYDRATE REF.



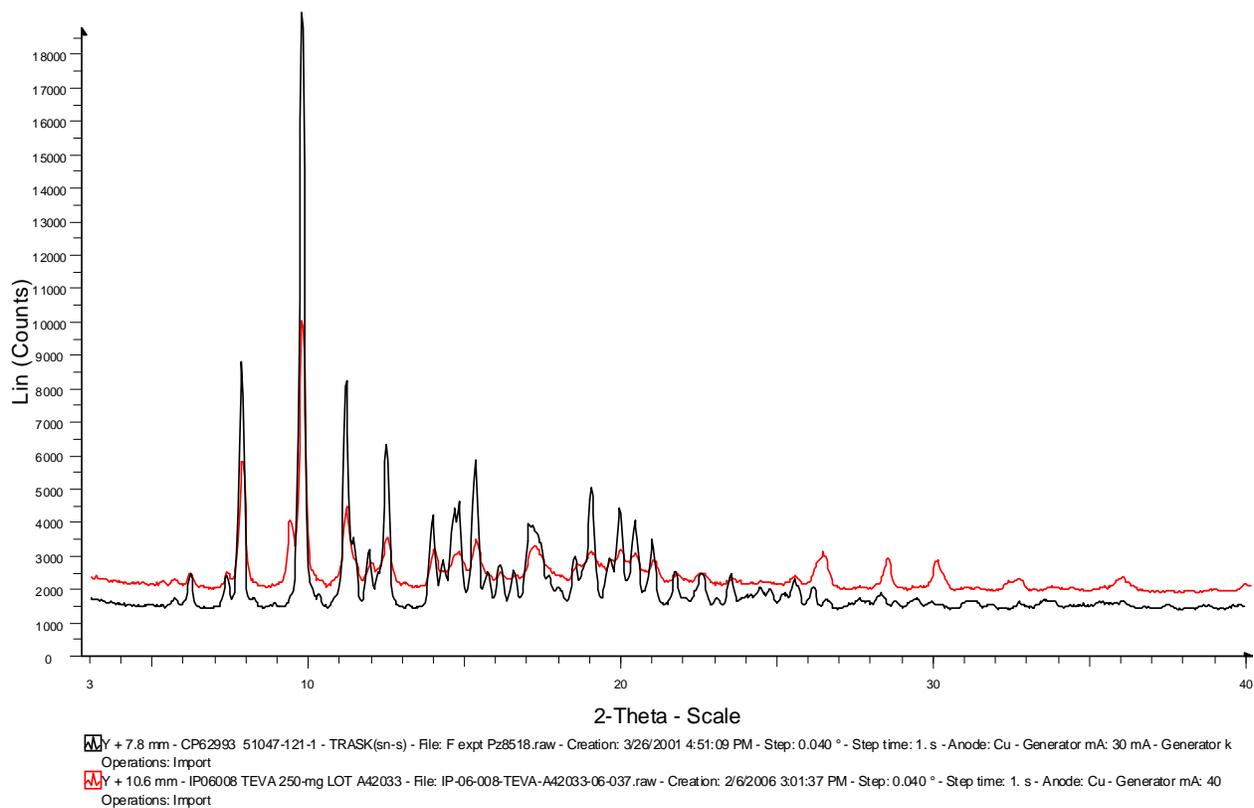
**Figure 8.** Overlay of diffractograms for Teva Azithromycin 500 mg tablet and azithromycin dihydrate reference (QCRS lot 01010-QCS-10). The absence of several diagnostic peaks for azithromycin dihydrate in the sample over range of 7 to 22 degrees in 2-theta indicated that azithromycin dihydrate was not detected.

IP06008 600-mg TAB LOT A43004 vs. AZITHROMYCIN DIHYDRATE REF.



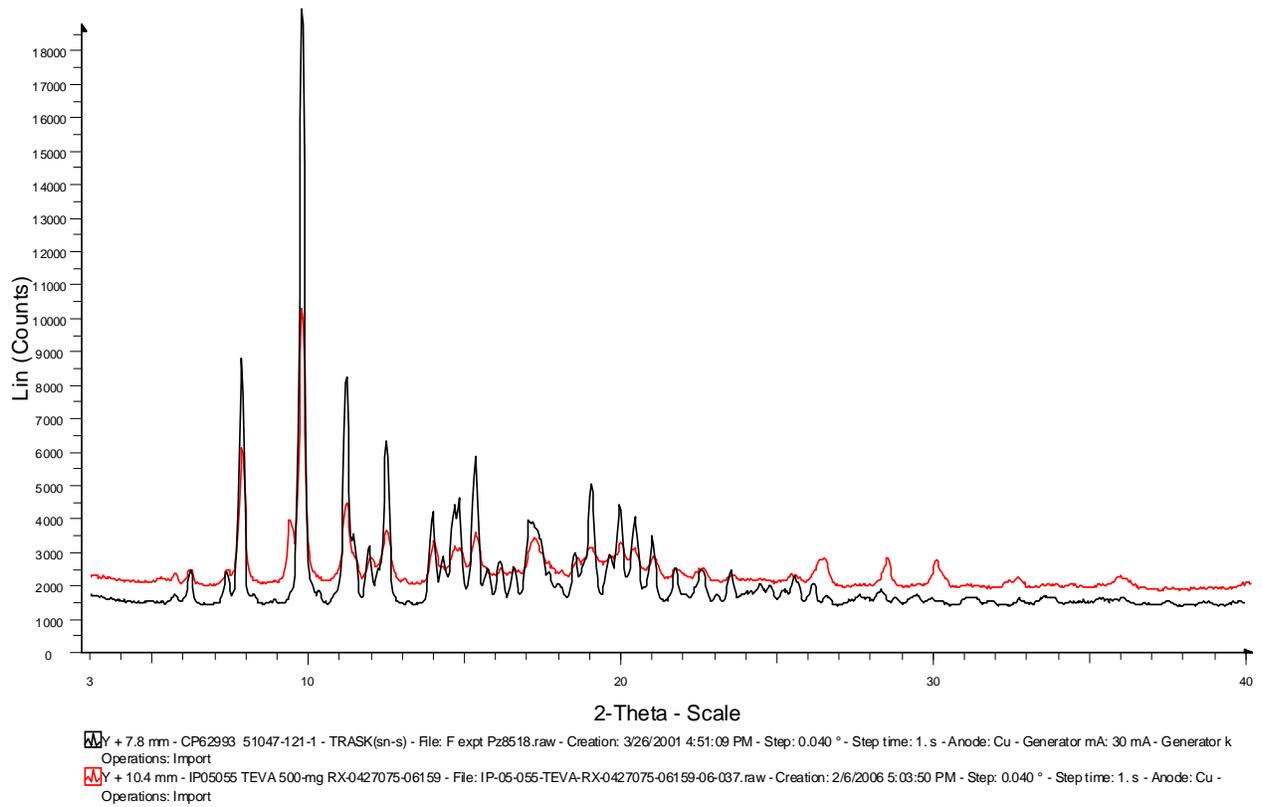
**Figure 9.** Overlay of diffractograms for Teva Azithromycin 600 mg tablet and azithromycin dihydrate reference (Form A, QCRS lot 03114-QCS-12). The absence of several diagnostic peaks for azithromycin dihydrate in the sample over range of 7 to 22 degrees in 2-theta indicated that azithromycin dihydrate was not detected.

# IP06008 250-mg TAB LOT A42033 vs. AZITHROMYCIN FORM F



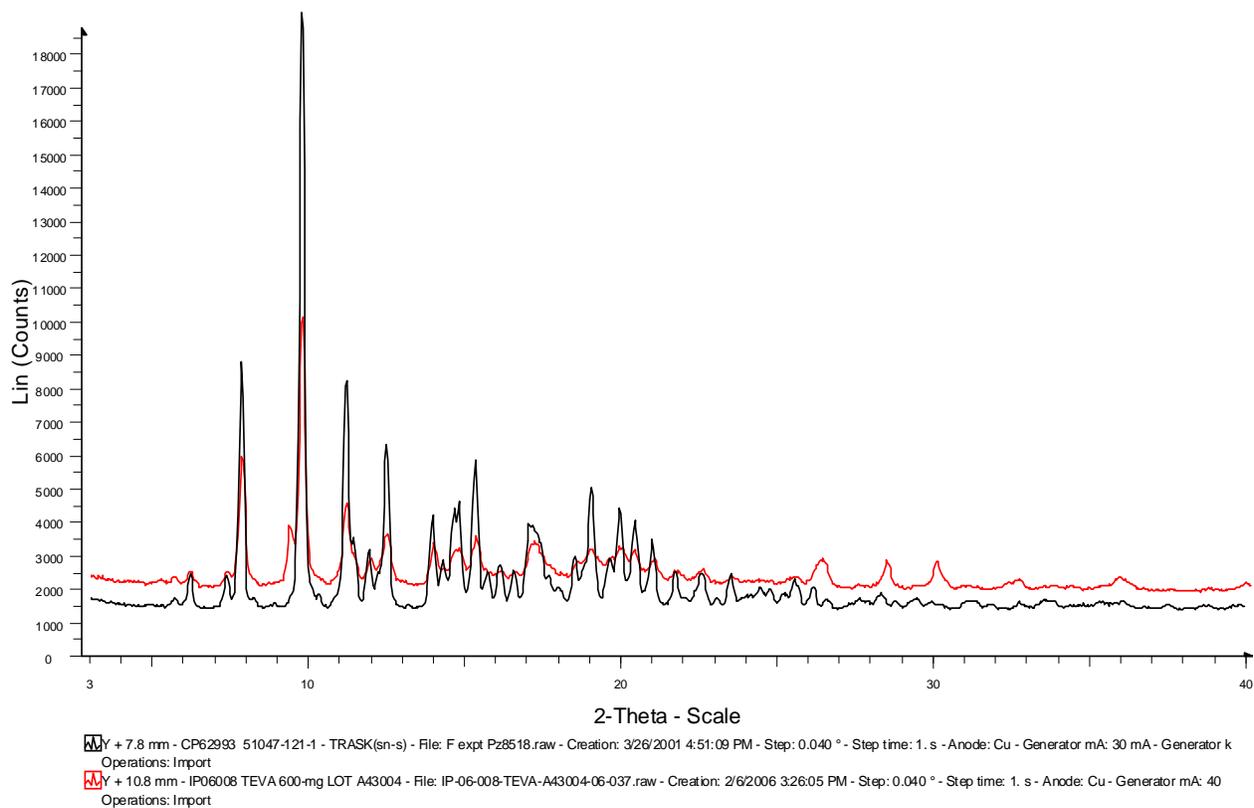
**Figure 10.** Overlay of diffractograms for Teva Azithromycin 250 mg tablet and azithromycin Form F.

IP05055 500-mg Rx 0427075-06159 vs. AZITHROMYCIN FORM F



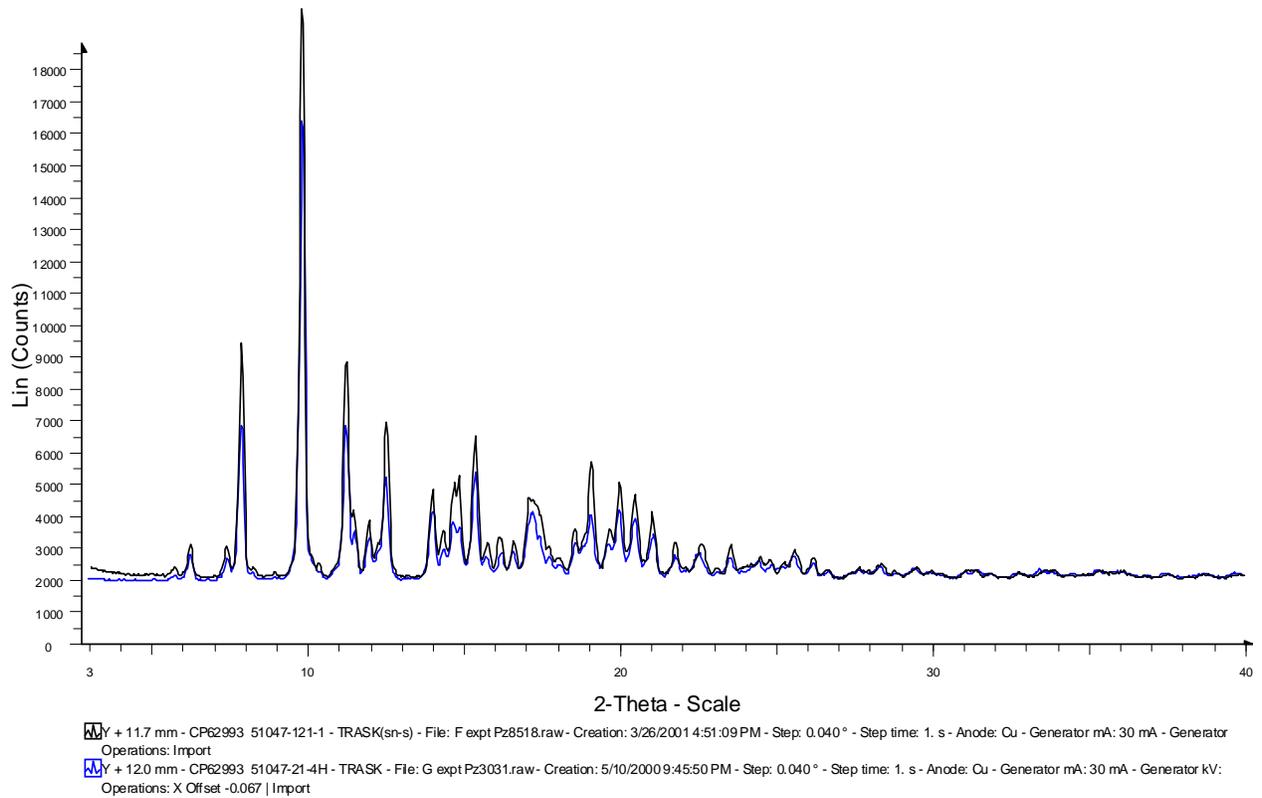
**Figure 11.** Overlay of diffractograms for Teva Azithromycin 500 mg tablet and azithromycin Form F.

# IP06008 600-mg TAB LOT A43004 vs. AZITHROMYCIN FORM F

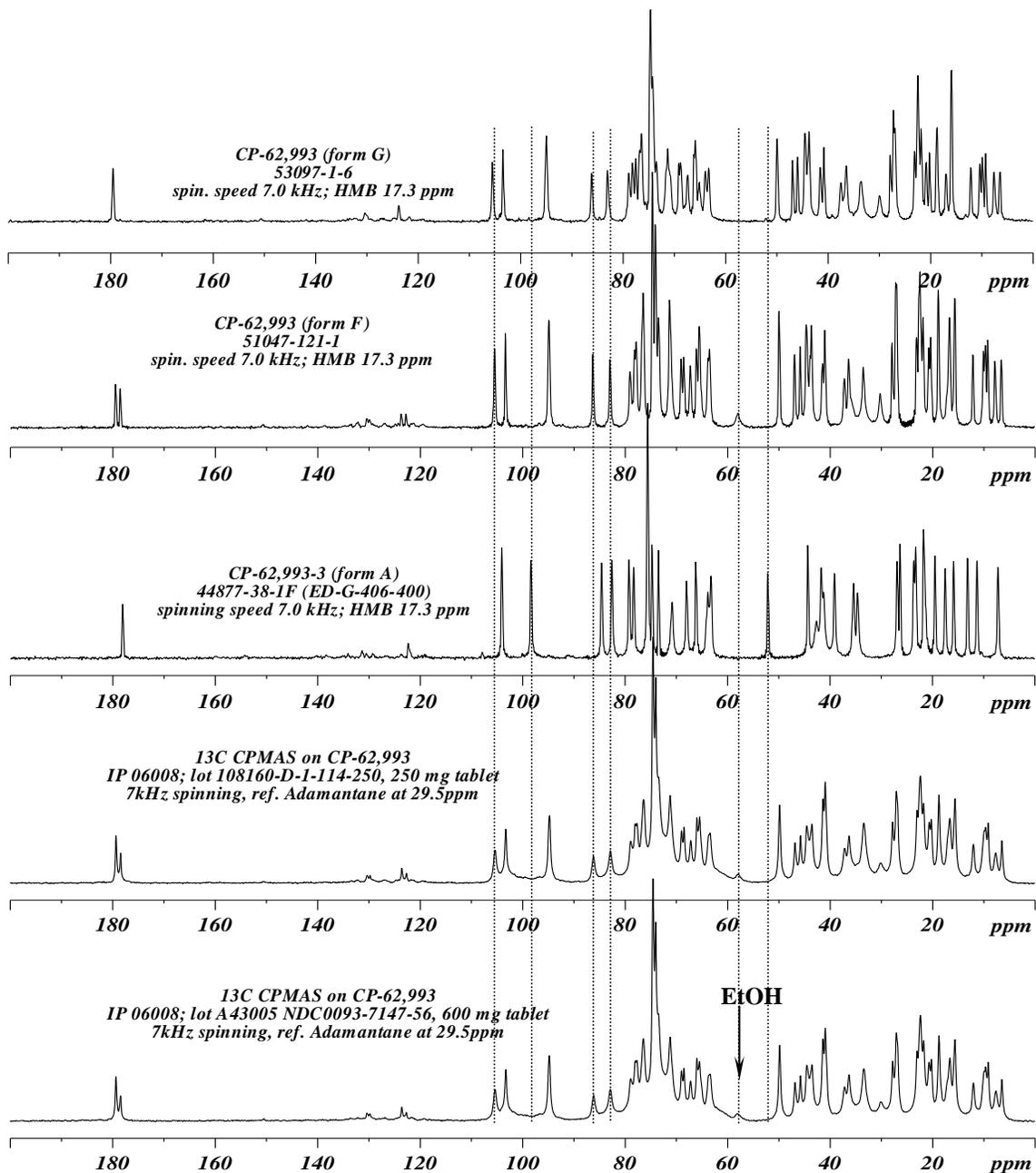


**Figure 12.** Overlay of diffractograms for Teva Azithromycin 600 mg tablet and azithromycin Form F.

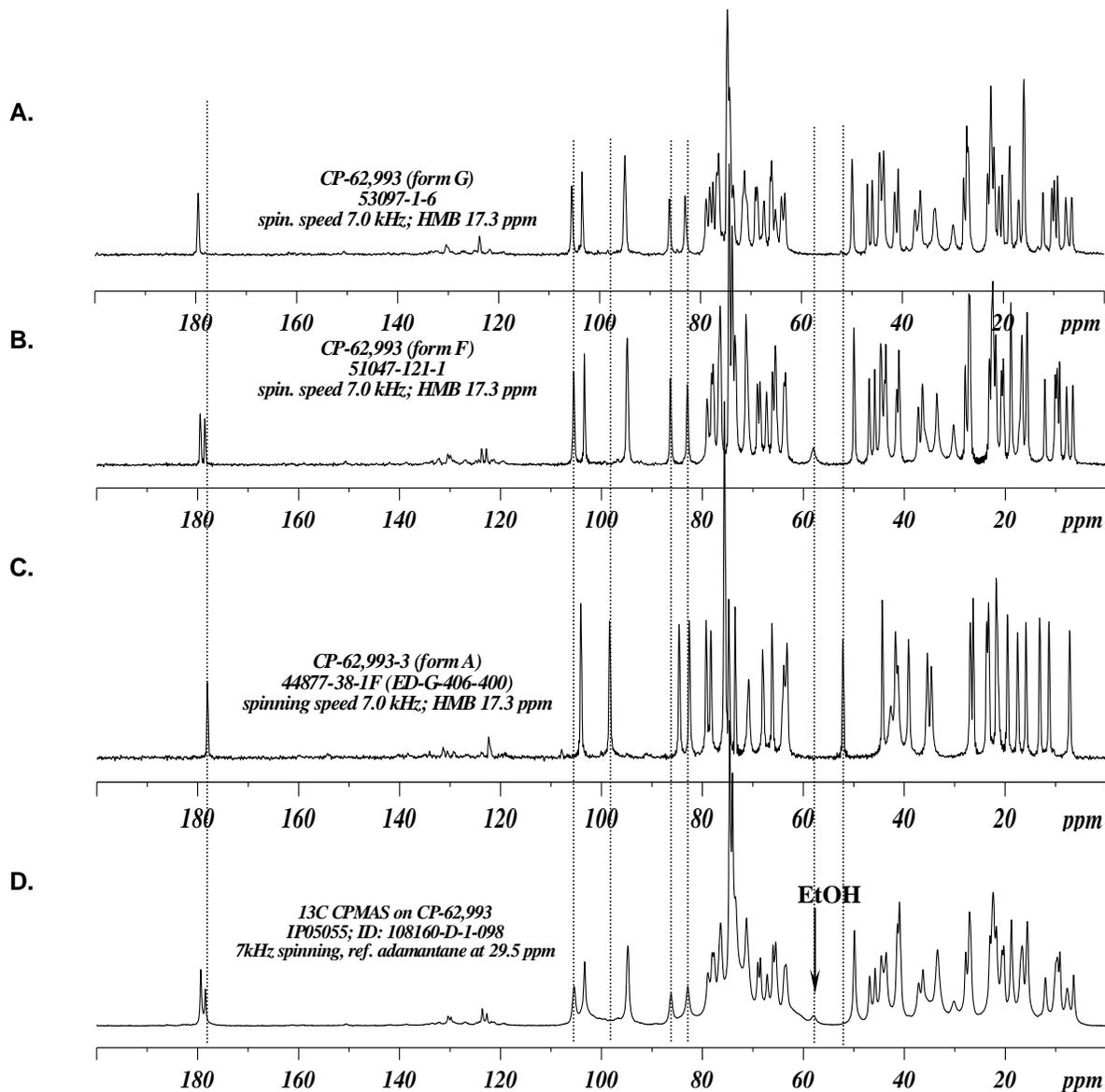
## AZITHROMYCIN FORM F vs. FORM G



**Figure 13.** Diffractograms of azithromycin Form F (ethanolate, upper trace) and Form G (sesquihydrate, lower trace) reference materials. The PXRD technique is sufficient to differentiate forms in Family I from Form Q and those in Family II (i.e., Forms D, E, C and R). Diffractograms for Family I isomorphs I (i.e., Forms F, G, H, J, M, N, O, and P) are essentially identical and further analysis is required to differentiate between these forms.

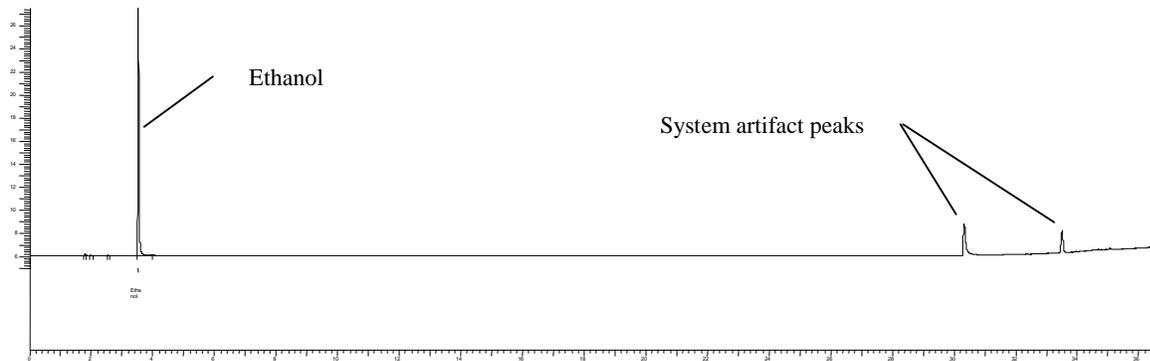


**Figure 14.**  $^{13}\text{C}$  CPMAS NMR spectra of the 250 mg and 600 mg tablets compared to carbon spectra of azithromycin Form G reference standard (CP-62,993, lot 53097-1-6), azithromycin Form F reference standard (CP-62,993, lot 51047-121-1), and azithromycin form A reference standard (CP-62,993, lot 44877-38-1F). The ssNMR data indicate that the samples contain azithromycin Form F and Form G, but no Form A.

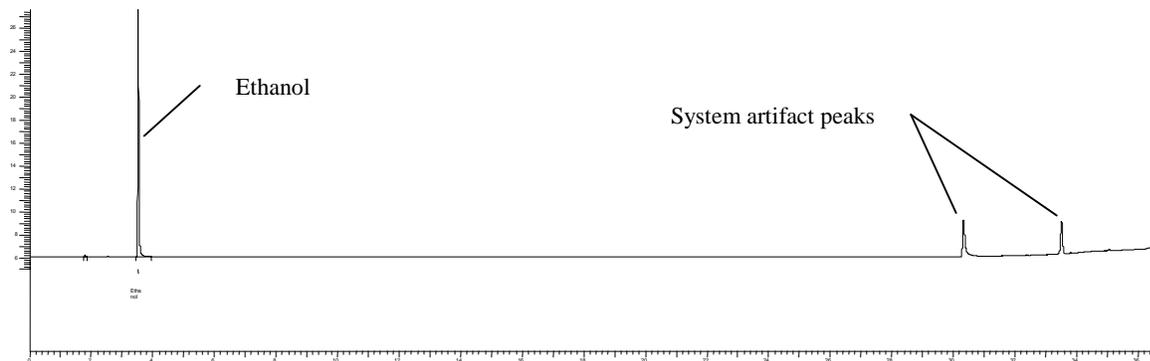


**Figure 15.**  $^{13}\text{C}$  CPMAS NMR spectra of the 500 mg tablet (**D**) compared to carbon spectra of azithromycin Form G reference standard (CP-62,993, lot 53097-1-6) (**A**), azithromycin Form F reference standard (CP-62,993, lot 51047-121-1) (**B**), and azithromycin Form A reference standard (CP-62,993, lot 44877-38-1F) (**C**). The ssNMR data indicate that the sample contains azithromycin Form F and Form G, but no Form A.

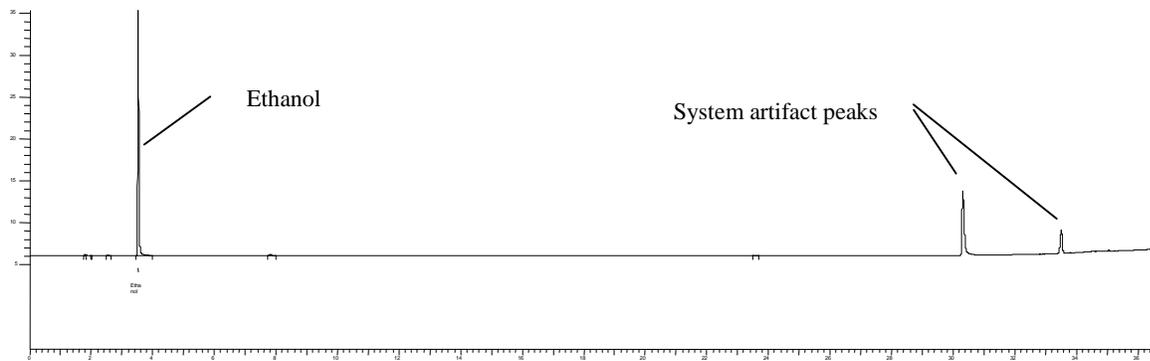
Teva 250mg IP06008



Teva 500mg IP05055



Teva 600mg IP06008



**Figure 16.** Headspace GC profiles for Teva Azithromycin tablets: (A) 250 mg tablet, (B) 500 mg tablet, and (C) 600 mg tablet. System artifact peaks eluting after 30 minutes are from high boiling solvent contamination from previous (unrelated) testing. Overall, the system artifact peaks are minor and did not impact the conclusions from the headspace GC analyses.

**Table 1.** Carbon chemical shifts of the active ingredient (azithromycin) in ppm units for United States Patent No. 6,977,243 azithromycin Form F (accurate to  $\pm 0.2$  ppm) and Teva Azithromycin samples. Of 50 peaks listed in the patent, 48 were identified (within the  $\pm 0.2$  accuracy limits) in each of the tablet samples. Exceptions (noted in footnotes below) were minor and do not preclude a positive identification of Form F in the samples. The peak positions were extracted from results shown in **Figures 14 and 15.**

250 mg sample	500 mg sample	600mg sample	Chemical Shifts for Form F from Patent
179.5	179.5	179.5	179.5
178.6	178.6	178.6	178.6
105.5	105.5	105.5	105.5
103.4	103.4	103.4	103.4
94.9	94.9	94.9	94.9
86.3	86.3	86.3	86.4
83.0	83.0	83.0	83.0
79.0	79.0	79.0	79.1
78.1	78.2	78.1	78.1
77.8	77.8	77.8	77.9
76.5	76.5	76.6	76.5
74.7	74.7	74.7	74.7
74.1	74.1	74.2	74.1
73.6	73.5	73.6	73.5
71.3	71.4	71.3	71.4
69.1	69.1	69.1	69.1
68.6	68.6	68.6	68.6
67.3	67.3	67.3	67.3
66.1	66.1	66.1	66.1
65.6	65.6	65.6	65.6
63.6	63.6	63.6	63.6
58.2	58.1	58.3 (b)	58.0
50.0	50.0	50.0	50.0
47.0	47.0	47.0	47.0
45.9	45.9	45.9	45.9
44.7	44.7	44.6	44.7
43.7	43.7	43.7	43.7
41.5	41.5	41.5	41.5
41.1	41.1	41.1	41.1
37.3	37.3	37.3	37.3
36.4	36.4	36.4	36.4
33.5	33.5	33.5	33.6
30.2	30.3	30.2	30.3
27.9	28.0	27.9	28.0
27.2	27.2	27.2	27.1
23.2	23.2	23.2	23.2
22.5	22.5	22.5	22.6
21.9	21.9	21.9	21.9
20.8	20.8	20.8	20.8
20.4	20.4	20.4	20.4
18.9	18.9	18.9	18.9
16.8	16.8	16.8	16.8
a	a	a	17.2
15.8	15.7	15.8	15.7
12.2	12.2	12.2	12.2
10.0	10.0	10.0	10.1
9.8	9.8	9.8	9.8
9.3	9.3	9.3	9.3
7.8	7.8	7.8	7.9
6.6	6.6	6.6	6.6

(a) Present as a shoulder with no defined maximum near 17.2 ppm.

(b) Peak position in sample differs from position listed in patent by more than 0.2 ppm.