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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

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STABILITY OF EXTEMPORANEOUSLY PREPARED ORAL LIQUID FORMULATIONS – Part VI

GOALS AND OBJECTIVES

Goal: To provide information from the peer-reviewed literature on stability studies of oral liquids.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss issues related to compounding with commercial products.
2. Assign a beyond-use date that can be used when compounding any of the compounded drug preparations discussed in this article.
3. Provide a method of compounding for any compounded preparation discussed in this article.
4. Describe two examples of problems that can occur when compounding with commercial products.

INTRODUCTION

Which is best? Compounding using commercial products or bulk drug substances? It is always best to use USP and NF grade substances in compounding, if available. If not, according to USP General Chapter <795>, one can use an appropriate ACS or FCC grade substance. The advantage in using these substances is the standards are generally about 98-102% of the label claim for potency.

In many cases, however, the only reasonable source of a drug for preparing an oral liquid for a child, elderly adult or for a patient that cannot swallow an oral solid, is a commercial drug product. Some concerns of which to be aware are the following:

1. Commercial products contain excipients that must be considered. For example, many products have cellulose derivatives and can result in a thick preparation that is difficult to pour; others may have excipients that cause a change in the pH of the preparation.
2. Commercial products have wide ranges in potency and still meet USP standards. For example, tablets and capsules generally are in the range of 90-110% of label. However, some products may be allowed 80-120% of label; some are even more broad. When calculating the quantity for the prescription, the dosage forms are considered as containing 100% of label. Generally, this is no problem. However, if a sample is analyzed for potency, it may be outside the USP standard for compounding of 90-110% of label; this out-of-specification result may occur through no fault of the compounder.

In summary, use bulk drug substances when compounding to be more accurate, as appropriate. In the formulations presented here, both bulk substances and commercial products are used. The concentrations of the active drugs in the various formulas in the studies reported in this paper are noted in Table 1.

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Table 1
Concentrations of the various drugs in the studies reported in this paper.

Drug	Concentration (mg/mL)
Codeine phosphate	3
Lisinopril	1
Naratriptan	0.5
Phenobarbital	10
Rifabutin	20
Sodium phenylbutyrate	200
Tacrolimus	0.5
Terbinafine	25
Valacyclovir	50
Valsartan	4

STABILITY OF EXTEMPORANEOUS FORMULATIONS

Codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2\ H_2O$, MW 406.35) is widely used as an analgesic and cough suppressant. It occurs as fine, white, needle-shaped crystals or as a white, crystalline odorless powder. It is freely soluble in water and slightly soluble in alcohol. It is affected by light and its solutions are acid to litmus.[1] For the preparation, codeine phosphate was dissolved in a small quantity of sterile water for irrigation and then diluted to volume with Ora-Sweet®. The preparation was placed in amber polyethylene terephthalate bottles and sealed with child-resistant caps as well as in amber oral polyethylene syringes with silicon elastomer tips and stored at 22-25° C for 98 days. The results of the study in Table 2 demonstrated that codeine phosphate in Ora-Sweet is stable for at least 98 days at room temperature protected from light. The pH of the syrup was initially 4.2 and remained unchanged throughout the study. There were no changes in color, clarity, or odor and no visible solids or microbial growth were observed.[2]

Table 2
Stability of 3 mg/mL codeine phosphate in Ora-Sweet stored at room temperature.

% Initial Concentration Remaining at 25° C		
	Containers	
Time (Days)	Oral Syringe	Plastic Bottle
0	3.04 (0.02)[a]	3.00 (0.02)[a]
7	100.4 (0.07)	---
14	101.4 (0.05)	99.8 (0.7)
28	99.6 (0.8)	99.5 (0.6)
42	100.1 (0.7)	100.9 (0.7)
56	99.7 (1.0)	100.2 (1.4)
70	100.8 (0.9)	100.9 (0.8)
98	100.0 (0.7)	99.7 (1.4)

[a] Mean (±S. D.) initial concentration (mg/mL)

Lisinopril ($C_{21}H_{31}N_3O_5 \cdot 2H_2O$, MW 441.52), an antihypertensive, occurs as a white, crystalline powder that melts at about 160° C with decomposition. It is soluble in water and practically insoluble in alcohol.[1] The tablets also contain calcium phosphate, mannitol, magnesium stearate, starch and iron oxide (10 and 20 mg tablets).

For 200 mL, ten of the 20 mg lisinopril tablets were placed in 10 mL of purified water in a calibrated container and shaken for one minute. Bicitra (30 mL) was added and the container shaken again. Next, 160 mL of Ora-Sweet® SF was added and the product shaken well. The pH of the compounded preparations was within the targeted range of pH 4 to 5. Since the lisinopril tablets contain calcium phosphate that can result in an increase in pH in the vehicle, the Bicitra was added to keep the pH range below 5 to maintain the effectiveness of potassium sorbate, the preservative. The preparation is stable for at least four weeks when stored at or below 25° C under ambient light exposure.[3]

Table 3
Stability of 1 mg/mL lisinopril in Ora-Sweet and Bicitra stored at room temperature.

% Initial Concentration Remaining at 25° C	
Time (Days)	Concentration
0	100.0 (0.40)
7	99.7 (0.57)
14	100.0 (.078)
28	100.5 (0.21)
42	99.6 (0.14)

Naratriptan hydrochloride ($C_{17}H_{25}N_3O_2S \cdot HCl$, MW 371.93), used in the treatment of migraine headaches, occurs as a white to pale yellow solid that is readily soluble in water. The tablets also contain croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, triacetin and titanium dioxide, iron oxide yellow (2.5 mg tablet) and indigo carmine aluminum lake (FD&C Blue No. 2) (2.5 mg tablet).[4]

The 0.5 mg/mL oral suspension was prepared using 2.5 mg naratriptan hydrochloride tablets in a mortar and reducing them to a fine powder. The Ora-Plus® was added in small increments (half the volume of the preparation) with mixing to form a smooth, uniform mixture. The Ora-Sweet or Ora-Sweet SF was added to volume after transferring the mixture to a calibrated plastic bottle. The preparation was stored at room temperature for up to 7 days and refrigerated temperature for 90 days.

Table 4
Stability of naratriptan hydrochloride 0.5 mg/mL stored at room and refrigerated temperatures.

% Initial Concentration Remaining				
Day	23° C Ora-Sweet /Ora-Plus	23° C Ora-Sweet SF /Ora-Plus	4° C Ora-Sweet /Ora-Plus	4° C Ora-Sweet SF /Ora-Plus
0 (µg/mL)*	19.1 (0.6)	19.1 (0.4)	18.9 (0.5)	18.8 (0.4)
7	100.0 (1.0)	99.0 (3.2)	102.1 (1.6)	98.9 (.5)
14	--	--	98.4 (1.1)	99.5 (2.7)
21	--	--	97.9 (1.1)	99.5 (2.7)
30	--	--	100.5 (1.1)	101.6 (3.1)
60	--	--	97.9 (1.0)	100.0 (4.8)
90	--	--	95.8 (2.8)	100.5 (2.6)

* Nominal concentration. Diluted 25 fold with mobile phase for analysis

The results of the study in Table 4 showed that naratriptan prepared from tablets in equal-parts of Ora-Plus with Ora-Sweet and Ora-Plus with Ora-Sweet SF are stable for at least 7 days at 23° C and 90 days at 4° C.[5]

Phenobarbital ($C_{12}H_{12}N_2O_3$, MW 232.24), used in treating seizures, occurs as white, odorless, glistening, small crystals or as a white, crystalline powder that may exhibit polymorphism. It is very slightly soluble in water and is soluble in alcohol. Its saturated solution has a pH of about 5 and the powder is stable in air.[1]

Table 5
Stability of phenobarbital 10 mg/mL in Ora-Plus with Ora-Sweet or Ora-Sweet SF in amber plastic bottles stored at room temperature.

	% Initial Concentration Remaining at 25° C	
Day	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus
0	10.03 (0.06)[a]	9.97 (0.20)[a]
14	99.20 (0.89)	100.51 (0.85)
30	99.45 (1.26)	99.78 (1.19)
60	98.36 (2.07)	99.02 (1.11)
115	98.10 (1.26)	99.54 (1.50)

[a] Mean (±S.D.) initial concentration (mg/mL)

The phenobarbital 10 mg/mL suspension was made by crushing ten 60 mg phenobarbital tablets in a glass mortar followed by the addition of 30 mL of Ora-Plus with mixing. Finally, either Ora-Sweet or Ora-Sweet SF was added with mixing to a final volume of 60 mL. The suspensions were placed in two ounce amber plastic bottles and stored at room temperature. The results showed at least 98% of the initial concentration remained throughout the 115 day study period, as shown in Table 5.[6]

Rifabutin ($C_{46}H_{62}N_4O_{11}$, MW 847.02), an antimycobacterial, occurs as a red-violet powder that is very slightly soluble in water and sparingly soluble in alcohol.[1]

Table 6
Stability of rifabutin 20 mg/mL in Ora-Plus with Ora-Sweet (1:1) stored at room and refrigerated temperatures.

	% Initial Concentration Remaining	
Week	25° C Ora-Sweet /Ora-Plus	4° C Ora-Sweet /Ora-Plus
0	20.6 (0.4)[a]	20.6 (0.4)[a]
1	97.7 (0.7)	99.1 (0.1)
2	100.4 (2.8)	101.6 (1.5)
4	101.8 (2.1)	103.1 (1.6)
8	98.4 (2.2)	100.9 (1.2)
12	99.2 (2.2)	101.1 (1.2)

[a] Mean (±S.D.) initial concentration (mg/mL)

Rifabutin 20 mg/mL oral liquid was prepared by using the rifabutin capsules. The capsules were emptied into a mortar and Ora-Plus with Ora-Sweet (1:1) was added in portions to volume. The liquid was placed in polyethylene terephthalate G prescription bottles sealed with child-resistant caps and stored at 4, 25, 30 and 40° C. Samples were obtained periodically for 12 weeks. The results showed rifabutin 20 mg/mL was stable for at least 12 weeks at all temperatures used in the study, as shown in Table 6.[7]

Sodium phenylbutyrate ($C_{10}H_{11}NaO_2$, MW 186.18) is a prodrug for sodium phenylacetate that is used for hyperammonemia in patients with enzymatic deficiencies in the urea cycle. It is also under investigation for treatment of some sickle-cell disorders.[8]

Sodium phenylbuturate 200 mg/mL suspension was prepared using sodium phenylbutyrate powder. The powder was levigated with a small quantity of the diluent (Ora-Plus with Ora-Sweet or Ora-Plus with Ora-Sweet SF; 1:1) to form a smooth suspension. The liquid was transferred to a calibrated amber plastic prescription bottle and additional diluent was used to rinse the mortar and add to the calibrated volume until the final volume was reached. The preparations were stored at room temperature and sampled periodically for up to 90 days. The results showed that sodium phenylbutyrate 200 mg/mL oral liquid is stable in both vehicles for at least 90 days at room temperature, as shown in Table 7.[9]

Table 7
Stability of sodium phenylbutyrate 200 mg/mL in two vehicles at room temperature.

	% Initial Concentration Remaining at 25° C	
Day	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus
0	200.16 (0.15)[a]	199.64 (1.16)[a]
7	98.70 (0.94	95.44 (2.50)
14	99.52 (1.03)	98.28 (1.06)
28	99.47 (0.79)	98.06 (0.95)
60	99.71 (0.99)	99.70 (0.80)
90	97.17 (2.00)	97.44 (1.34)

[a] Mean (±S.D.) initial concentration (mg/mL)

Tacrolimus ($C_{44}H_{69}NO_{12}\cdot H_2O$, MW 822.03) appears as white crystals or as a crystalline powder that is practically insoluble in water and freely soluble in ethanol. It has a melting point of 127-129° C.[4] Tacrolimus is a potent macrolide immunosuppressant derived from Streptomyces tsukubaensis and has activity similar to cyclosporin. It is used to prevent or reverse transplant rejection and is also applied topically in the management of moderate to severe atopic eczema.[8] The capsules also contain lactose, hydroxypropyl methylcellulose, croscarmellose sodium, magnesium stearate, gelatin, titanium dioxide and ferric oxide.

Tacrolimus 0.5 mg/mL oral liquid was prepared using the tacrolimus capsules which were opened and emptied into a glass mortar. The vehicle used was an equal mixture of Ora-Plus and Simple Syrup, NF. A small quantity of the vehicle was added to form a paste then a liquid. The mixture was transferred to either a calibrated amber plastic or glass prescription bottle and additional vehicle was used to rinse the mortar before being added to the remainder of the preparation. This was repeated until the final volume

was achieved. The preparation was stored at room temperature for 56 days with periodic sampling. The results, as shown in Table 8, reveal that tacrolimus 0.5 mg/mL in a mixture of Ora-Plus and Simple Syrup, NF (1:1) is stable in either glass or plastic for at least 56 days at room temperature. There was no detectable change in color or odor and no appreciable change from the initial pH value of 4.6 (+/- 0.1) in any of the suspensions.[10]

Table 8
Stability of tacrolimus 0.5 mg/mL in a 1:1 mixture of Ora-Plus and Simple Syrup, NF stored at room temperature in both glass and plastic containers.

	% Initial Concentration Remaining	
Day	**Glass**	**Plastic**
0	0.5033 (0.0073)[a]	0.4971 (0.0049)[a]
7	102.2 (1.3)	101.3 (1.1)
15	99.3 (2.5)	100.2 (0.7)
30	100.7 (1.6)	98.9 (1.6)
45	100.0 (1.1)	99.1 (1.9)
56	98.3 (1.3)	100.7 (1.3)

[a] Mean (±S.D.) initial concentration (mg/mL)

An additional study involving tacrolimus was conducted at 1 mg/mL in a 1:1 mixture of Ora-Plus and Ora-Sweet in amber plastic containers at room temperature where the results demonstrated stability for about 4 months (132 days). [11]

Terbinafine hydrochloride ($C_{21}H_{25}N$•HCl, MW 327.90), an allylamine derivative with a broad spectrum of antifungal activity, occurs as a white to off-white fine crystalline powder that is slightly soluble in water and soluble in alcohol and melts at 195-198° C.[1,8] The tablets also contain colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

Table 9
Stability of terbinafine hydrochloride 25 mg/mL stored at room and refrigerated temperatures.

	% Initial Concentration Remaining	
	25° C	**4° C**
Day	**Ora-Sweet /Ora-Plus**	**Ora-Sweet /Ora-Plus**
0	27.7 (1.5)[a]	26.5 (0.9)[a]
7	95.2 (0.8)	98.7 (3.3)
14	97.8 (1.4)	95.3 (2.1)
28	95.5 (3.1)	96.4 (2.3)
42	93.7 (1.9)	96.6 (1.3)
56	79.0 (4.0)	87.4 (3.7)
70	71.8 (4.0)	76.3 (1.9)
91	72.6 (2.3)	77.6 (2.1)

[a] Mean (±S.D.) initial concentration (mg/mL)

Terbinafine hydrochloride 25 mg/mL was prepared using the terbinafine tablets. The tablets were crushed to a fine powder in a mortar and a small quantity of the vehicle (Ora-Plus and Ora-Sweet; 1:1) was used for make a smooth paste. Additional volumes of the vehicle were added and the preparation transferred to a graduate where it was brought to final volume. The suspension was packaged in amber polyethylene prescription bottles and stored at both room and refrigerated temperatures. Samples were withdrawn for up to 91 days. The results in Table 9 show that terbinafine hydrochloride 25 mg/mL is stable for up to 42 days in polyethylene prescription bottles at both room and refrigerated temperatures. The pH of the suspension decreased only very slightly over 91 days, from an initial pH 5.6 to 5.5. [12]

Valacyclovir hydrochloride ($C_{13}H_{20}N_6O_4$•HCl, MW 360.80) is a white to off-white powder that is soluble in water to the extent of 174 mg/mL. It is a prodrug of the antiviral acyclovir used in the treatment of herpes zoster and herpes simplex infections of the skin and mucous membranes, including genital herpes.[8] The caplets also contain carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide.[4]

Table 10
Stability of valacyclovir 50 mg/mL oral liquids at refrigerated temperatures.

	% Initial Concentration Remaining	
	4° C	
Day	**Ora-Sweet /Ora-Plus**	**Ora-Sweet SF /Ora-Plus**
0	51.6 (0.2)[a]	52.4 (0.2)[a]
2	97.0 (3.1)	99.5 (4.3)
7	94.5 (2.1)	96.8 (2.4)
14	92.6 (0.5)	94.7 (1.9)
21	91.6 (2.4)	90.1 (3.8)
28	87.7 (1.1)	87.4 (0.6)

[a] Mean (±S.D.) initial concentration (mg/mL)

The valacyclovir hydrochloride 50 mg/mL oral liquid was prepared using the caplets and a porcelain mortar; the caplets were first crushed to a fine powder. Then 40 mL of Ora-Plus was added, 5 mL at a time with mixing between additions. The product was transferred to an amber glass bottle. The mortar and pestle were thoroughly rinsed with 10 mL of Ora-Plus and added to the final container (5 rinses). Then either Ora-Sweet or Ora-Sweet SF was added to bring the total volume to 180 mL. The bottles were stored at refrigerated temperature. Table 10 shows both preparations stable in the refrigerator for 14 days. The standard deviations are too great to extend the storage period to 21 days. The pH values remained unchanged as did the physical observations.[13]

Valsartan ($C_{24}H_{29}N_5O_3$, MW 435.52) is a white to practically white fine powder that is slightly soluble in water, soluble in alcohol and melts at 116-117° C. It is an angiotensin II receptor antagonist with actions similar to those of losartan and is used in the management

of hypertension.[8] The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000 and titanium dioxide.[4]

Valsartan 4 mg/mL suspension was prepared by adding 80 mL of Ora-Plus to an amber glass bottle containing eight Diovan 80 mg tablets and shaken for 2 minutes. The resulting suspension was allowed to stand for 1 hour after which it was shaken again for a minimum of 1 additional minute. After shaking, 80 mL of Ora-Sweet SF was added with shaking for at least 10 seconds. When stored at room temperature, the suspension is good for 30 days and when stored at refrigerated temperature, is good for 75 days.[14]

CORRECTION: Secundum Artem Volume 14, Number 3 vehicle of losartan potassium should read "a volumetric mix of Ora-Plus and **Ora-Sweet SF**..."

REFERENCES

1. Anon. Pharmacists Pharmacopeia. Rockville MD, U.S. Pharmacopeial Convention, Inc., 2005, pp 679, 693, 697, 701, 707.
2. Dentinger PJ and Swenson CF. Stability of codeine phosphate in an extemporaneously compounded syrup. Am J Health-Syst Pharm. 2007;64:2569-73.
3. Thompson KC, Zhao Z, Mazakas JM, Beasley CA, Reed RA, Moser CL. Characterization of an extemporaneous liquid formulation of lisinopril. Am J Health-Syst Pharm. 2003;60:69-74.
4. Anon. Physicians' Desk Reference 2008, 62nd Ed. Thomson Healthcare Inc. Montvale, NJ, 2007, pp 602-608, 1320-1324, 1601-1604, 2248-2249.
5. Zhang YP, Trissel LA, Fox JL. Naratriptan hydrochloride in extemporaneously compounded oral suspensions. Int J Pharm Comp 4(1) Jan/Feb 2000, pp 69-71.
6. Cober MP and Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. Am J Health-Syst Pharm. 2007;64:644-6.
7. Haslam JL, Egodage KL, ChenY, Rajewski RA, Stella V. Stability of rifabutin in two extemporaneously compounded oral liquids. Am J Health-Syst Pharm. 1999;56:333-6.
8. Sweetman SC, Ed., MARTINDALE The Complete Drug Reference, 33rd Ed., 2002, London, Pharmaceutical-Press. pp 394, 569-571, 643, 988-999, 1666, 2203-2207.
9. Caruthers RL and Johnson CE. Stability of extemporaneously prepared sodium phenylbuturate oral suspensions. Am J Health-Syst Pharm. 2007;64:1513-15.
10. Jacobson PA, Johnson CE, West NJ, Foster JA. Stability of tacrolimus in an extemporaneously compounded oral liquid. Am J Health-Syst Pharm. 1997;54:178-80.
11. Elefante KA, Muindi J, West K, Dunford L, Abel S, Paplham P, Brown K, Hahn T, Padmanabhan S, Batti walla M, McCarthy Jr PL. Long-term stability of a patient-convenient 1 mg/mL suspension of tacrolimus for accurate maintenance of stable therapeutic levels. Bone Marrow Transplantation (2006) 37, 781-784.
12. Abdel-Rahman SM and Nahata MC. Stability of terbinafine hydrochloride in an extemporaneously prepared oral suspension at 25 and 4° C. Am J Health-Syst Pharm. 1999;56:243-5.
13. Fish DN, Vidaurri VA, Deeter RG. Stability of valacyclovir hydrochloride in extemporaneously prepared oral liquids. Am J Health-Syst Pharm. 1999;56:1957-60.
14. Anon. Package Insert. Diovan. Novartis Pharmaceuticals Corp. East Hanover, NJ. 2007.

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Please circle the most appropriate answer for each of the following questions. There is only ONE correct answer per question.

1. Which of the active ingredients in lisinopril tablets necessitates the use of Bicitra in the formulation?

   A. calcium phosphate
   B. iron oxide
   C. magnesium stearate
   D. mannitol
   E. starch

2. According to the data given, which drug is stable for the longest period of time?

   A. codeine phosphate
   B. lisinopril
   C. naratriptan hydrochloride
   D. phenobarbital
   E. sodium phenylbutyrate

3. According to the data provided, which drug decomposed to the greatest extent more rapidly and at room temperature as compared to refrigerated temperature?

   A. naratriptan hydrochloride
   B. phenobarbital
   C. rifabutin
   D. tacrolimus
   E. valacyclovir

4. All but which of the following preparations exhibited essentially no loss of drug during the study period?

   A. codeine phosphate
   B. lisinopril
   C. phenobarbital
   D. rifabutin
   E. valacyclovir

5. Which of the following preparations would be the deepest red in color?

   A. codeine phosphate
   B. phenobarbital
   C. rifabutin
   D. terbinafine
   E. valacyclovir

6. Which of the following are not really water soluble?

   A. codeine phosphate
   B. lisinopril
   C. naratriptan hydrochloride
   D. tacrolimus
   E. valacyclovir

7. What is the potency allowed for compounding according to the USP standard in USP General Chapter <795> Pharmacy Compounding-Nonsterile Preparations?

   A. 98-102%
   B. 95-105%
   C. 90-110%
   D. 80-120%
   E. 90-120%

8. Glass bottle were used in which of the following drug studies?

   A. codeine phosphate
   B. naratriptan hydrochloide
   C. phenobarbital
   D. tacrolimus
   E. terbinafine

9. For valacyclovir, why is the beyond-use date limited to 14 days?

   A. the vehicle does not contain a preservative
   B. the pH values changed to much
   C. the mean was too low at 21 days
   D. the standard deviation was too small at 21 days
   E. the standard deviation was too large at 21 days

10. For which of the following drugs was the oral preparation developed by the manufacturer and instructions placed in the package insert?

    A. codeine phosphate
    B. phenobarbital
    C. sodium phenylbutyrate
    D. valacyclovir
    E. valsartan

11. My practice setting is:
    A. Community-based C. Hospital-based
    B. Managed care-based D. Consultant and other

12. The quality of the information presented in this article was:
    A. Excellent B. Good C. Fair D. Poor

13. The test questions correspond well with the information presented.
    A. Yes B. No

14. Approximately how long did it take you to read the Secundum Artem article AND respond to the test questions?

    _____

15. What topics would you like to see in future issues of Secundum Artem?

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