HRT Heavy™ & Phytobase™

Beyond Use Date Study

Updated as of January 2026

Fagron is on a mission to develop the most extensively studied creams for transdermal and vaginal hormones on the market. The revisions to USP <795> (official November 1st, 2023) indicate a changing regulatory climate and a trend towards increasingly high standards for the extension of beyond use dates (BUDs). Given the increased scrutiny and the additional requirements for establishing extended BUDs, additional testing is required to help pharmacies provide the best formulations with scientifically robust data to support an extended BUD for patient convenience. In this study we validate the suitability of two vehicles, Phytobase™ and HRT Heavy™ for compounded hormone replacement therapy by demonstrating stability and antimicrobial effectiveness per USP <51> of the vehicles with various common combinations of hormones. For a summary of results, see below.

New Guideline Compliant HRT BUD Studies in Phytobase™

Currently, the below preparations in Phytobase™ already receive extended dating per guidelines official in November 2023. You can view the entire publication in IJPC March/April 2021.[3]

Active Ingredient Bracketed Range	Studied BUD	Container Closure Composition*
Estriol 0.5-20 mg/g	180 days	Polypropylene (Topi-Click)
Estradiol 0.5-20 mg/g	180 days	Polypropylene (Topi-Click)
Estrone 1-10 mg/g	180 days	Polypropylene (Topi-Click)
Progesterone 1-200 mg/g	180 days	Polypropylene (Topi-Click)
Testosterone 1-200 mg/g	180 days	Polypropylene (Topi-Click)
Low: Estriol 0.5 mg, Estradiol 0.5 mg, Progesterone 5 mg/g High: Estriol 10mg, Estradiol 20 mg, Progesterone 200 mg/g	180 days	Polypropylene (Topi-Click)

*The same BUD may be applied to preparations in another polypropylene based container such as UnoDose

Updates to Previous HRT Heavy™ Studies and New Combination Studies in Phytobase™ and HRT Heavy™

The previous HRT Heavy™ studies did not meet requirements for BUD extension per the November guideline update as they did not have associated antimicrobial effectiveness testing (AET) per USP <51>. In this study we add AET to validate those previous HRT Heavy studies as well as add on a variety of new combinations bracketed at high and low concentrations for both HRT Heavy™ and Phytobase™. Stability indicating testing for combination products in HRT Heavy™ and Phytobase™ added on in this new study was completed by an independent, third-party, FDA registered, and cGMP compliant laboratory and AET was completed by a combination of the same laboratory and internal testing by Fagron Solutions.

Combinations with a checkmark at the given timepoint have completed both HPLC stability indicating testing to that timepoint as well as AET per USP <51> in the noted container closure. While AET was performed at the 90- and 180-day timepoints, only HPLC stability indicating testing was performed at the 120-day timepoint. Completed stability testing at the 120-day timepoint is noted with a green dot. The 180-day results are published in the July/August 2024 edition of the International Journal of Pharmaceutical Compounding. The below Table 1 and Table 2 are a summary of the results with information regarding container closure, Table 3 lists values obtained for each time point from previous HRT Heavy studies, and Table 4 and Table 5 list values reported as percentage of label strength for the current beyond use date study in HRT Heavy™ and Phytobase™ respectively. Table 6 summarizes the AET per USP <51> for category 2 products (non-sterile aqueous topical products) passed by all individual API and combination products tested at both the 90- day and 180-day timepoints.

Discussion

All 12 new combination formulations both high and low (24 total preparations) tested within range at the 90-day mark. All 17 bracketed high and low formulations (34 total preparations) demonstrated antimicrobial effectiveness per USP <51> for the entire duration of the study and passed testing at both the 90-day and 180-day timepoints. In HRT Heavy, the estriol/estradiol (biest) combination was originally limited to 120 days due to estriol testing just below acceptable range (89% of label strength) at the 180-day mark, however, a re-evaluation with our independent lab resulted in acceptable stability at all retested timepoints allowing for a BUD of up to 180 days as of 2025. The estriol/estradiol/progesterone/testosterone/DHEA combination is limited to 90 days due to the high concentration testing high out of range at the 120-day mark and has not been retested. The reason for this has not been fully elucidated, however, we posit that it may be related to the relative total API load as compared to the cream base. The high concentration product contains 31% weight by weight as active pharmaceutical ingredient. Though our container closure of choice (Topi-Click) does offer a tight seal, it may be that the high overall API to cream base ratio exacerbated minimal water loss over the course of the study contributing to higher-than-expected API concentrations. We posited that this water loss may be exacerbated by how the product was stored and used throughout the test. During the test, the product was kept sealed in the Topi-Click devices, however, material was only removed for testing and not used on a daily basis as we would commonly see for regular patient use of HRT products. This means that cream at the top of the container remained there for long periods of time without being used until the product was opened at the 90-, 120-, and 180-day timepoints, potentially contributing to that slight water loss we saw with the highest API load product. Future studies may consider a lower overall concentration or a procedure that mimics regular usage in which some material is removed from the top on a regular basis. It should also be noted at the 120 -day timepoint our lab did note that some of the Topi-Click containers had not been capped correctly after testing at the 90 -day timepoint, this may also have contributed to some water loss or inconsistent results noted with biest in HRT Heavy in the initial test. In Phytobase, the biest/progesterone/testosterone low combination had estriol test low (89%) at the 180-day timepoint, and estradiol/testosterone high combination had both active ingredients test slightly above range at the 180-day timepoint, perhaps due to similar factors that influenced the high combination product HRT Heavy, though the reason for this was not entirely clear as similar combinations remained acceptably within range for the entire duration of the study. A re-evaluation of the biest/progesterone/testosterone low combination with our independent lab resulted in acceptable stability at all retested timepoints allowing for a BUD of up to 180 days as of 2025. Overall, all formulations in HRT Heavy were found to be stable for a minimum of 90 days, and all formulations in Phytobase were

found to be stable for a minimum of 120 days. Most preparations in both vehicles tested within range for the full 180-day duration of the study.

Results

This study found a wide range of compatibility of hormones in both HRT Heavy™ and Phytobase™, demonstrating the suitability of these vehicles both from a stability and an antimicrobial effectiveness perspective for a wide range of compounded hormone combinations and preparations.

Summary of Results

Table 1. HRT Heavy Bracketed Stability Study Summary

Active Ingredient Bracketed Range[1]	90 days	120 days	180 days	Container Closure Composition[3]
Estriol 0.5-100 mg/g	✓	N/A[2]	✓	Polypropylene/Polyethylene (Unguator)
Estradiol 0.5-100 mg/g	✓	N/A[2]	✓	Polypropylene/Polyethylene (Unguator)
Progesterone 10-400 mg/g	✓	N/A[2]	✓	Polypropylene/Polyethylene (Unguator)
Testosterone 0.5-300 mg/g[4]	✓	N/A[2]	✓	Polypropylene/Polyethylene (Unguator)
Dehydroepiandrosterone (DHEA) 1-50mg/g	✓	N/A[2]	✓	Polypropylene/Polyethylene (Unguator)
Low: Estriol 0.1mg, Estradiol 0.1mg/g High: Estriol 20mg, Estradiol 20mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg/g High: Estriol 20mg, Estradiol 20mg, Testosterone 20mg, Progesterone 200mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg/g High: Estriol 20mg, Estradiol 20mg, Testosterone 20mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg, DHEA 1mg/g High: Estriol 20mg, Estradiol 20mg, Testosterone 20mg, Progesterone 200mg, DHEA 50mg/g	✓	Limited to 90-day BUD	Limited to 90-day BUD	Polypropylene (Topi-Click)

Low: Estradiol 0.1mg, Testosterone 0.1mg/g High: Estradiol 20mg, Testosterone 20mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg/g High: Estradiol 20mg, Testosterone 20mg, Progesterone 200mg/g	✓	●	✓	Polypropylene (Topi-Click)

[1] Studies in HRT Heavy did not use any additional solvent
[2] Stability indicating testing as been completed to 180 days in previous studies, only AET is needed to make these studies compliant with new guidelines
[3] The same BUD may be applied to preparations in another polypropylene based container such as UnoDose
[4] Testosterone 300 mg/g added on after the fact, stability indicating testing at 0, 90, 120, and 180 days as well as AET per USP <51> at 90 and 180 days passed
✓ At these timepoints, both stability indicating testing and antimicrobial effectiveness testing per USP <51> was performed
● At these timepoints, only stability indicating testing was performed

Table 2. Phytobase Bracketed Stability Study Summary

Active Ingredient Bracketed Range[1]	90 days	120 days	180 days	Container Closure Composition[3]
Estriol 0.5-20 mg/g[3]	●	●	✓	Polypropylene (Topi-Click)
Estradiol 0.5-20 mg/g[3]	●	●	✓	Polypropylene (Topi-Click)
Estrone 1-10 mg/g[3]	●	●	✓	Polypropylene (Topi-Click)
Progesterone 1-200 mg/g[3]	●	●	✓	Polypropylene (Topi-Click)
Testosterone 1-200 mg/g[3]	●	●	✓	Polypropylene (Topi-Click)
Dehydroepiandrosterone 0.1-10%[4]	✓	●	Results Expected May 2026	Polypropylene (Topi-Click
Low: Estradiol 0.1mg, Progesterone 1mg/g High: Estradiol 10mg, Progesterone 300mg/g	✓	●	Results Expected May 2026	Polypropylene (Topi-Click
Low: Estriol 0.1mg, Estradiol 0.1mg/g High: Estriol 20mg, Estradiol 20mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg/g High: Estriol 20mg, Estradiol 20mg, Testosterone 20mg, Progesterone 200mg/g	✓	●	Limited to 120-day BUD	Polypropylene (Topi-Click)
Low: Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg/g High: Estriol 20mg, Estradiol 20mg, Testosterone 20mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estradiol 0.1mg, Testosterone 0.1mg/g High: Estradiol 20mg, Testosterone 20mg/g	✓	●	Limited to 120-day BUD	Polypropylene (Topi-Click)

Low: Progesterone 1mg, Testosterone 0.1mg/g High: Progesterone 200mg, Testosterone 20mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg/g High: Estradiol 20mg, Testosterone 20mg, Progesterone 200mg/g	✓	●	✓	Polypropylene (Topi-Click)
Low: Estriol 0.5mg, Estradiol 0.5mg, Progesterone 5mg/g3 High: Estriol 10mg, Estradiol 20mg, Progesterone 200mg/g3	●	●	✓	Polypropylene (Topi-Click)

[1] Studies in Phytobase used 5-10% weight by weight ethoxy diglycol as solvent
[2] The same BUD may be applied to preparations in another polypropelyne base container such as UnoDose
[3] Completed as part of the previous Phybase study published in 2021, see reference [3] for more details
✓ At these timepoints, both stability indicating testing and antimicrobial effectiveness testing per USP <51> was performed
● At these timepoints, only stability indicating testing was performed

Data

Table 3. HRT Heavy Single API High and Low Bracketed Results

API	Elapsed Time (days)	Low Concentration (%)	High Concentration (%)
Estriol (0.5-100mg/g)	0	100.0	100.0
	30	90.2	102.7
	90	92.6	98.5
	120	93.0	95.6
	170	101.7	100.9
	180	108.9	99.8
Estradiol (0.5-100 mg/g)	0	100.0	100.0
	30	103.5	100.9
	90	105.6	100.3
	120	102.3	104.4
	170	98.0	101.4
	180	98.8	101.9
Progesterone (10-400 mg/g)	0	100.0	100.0
	30	100.4	96.9
	90	98.0	100.4
	120	98.4	101.0
	170	98.2	99.7
	180	106.7	100.2
Testosterone (0.5-200 mg/g)	0	100.0	100.0
	30	102.0	102.1
	90	95.7	102.5
	120	90.2	108
	170	92.5	100.9
	180	93.7	103.2
Dehydroepiandrosterone (DHEA) (1-50 mg/g)	0	100.0	100.0
	30	94.0	100.8
	90	95.9	98.8
	120	97.7	98.7
	17	96.3	101.0
	180	92.0	97.9

Table 4. HRT Heavy Combination Product High and Low Bracketed Results

Combination (High and Low)	Estriol (%)	Estradiol (%)	Progesterone (%)	Testosterone (%)	DHEA (%)
Estriol 0.1 mg, Estradiol 0.1 mg/g					
T=0	102	102			
T=90	98	100			
T=120	94	95			
T=180*	93	90			
Estriol 20 mg, Estradiol 20 mg/g					
T=0	101	101			
T=90	100.5	103			
T=120	102.5	104			
T=180	107	108			
Estriol 0.1 mg, Estradiol 0.1 mg, Progesterone 1 mg, Testosterone 0.1 mg/g					
T=0	96	101	99.3	104	
T=90	98	92	102.6	99	
T=120	101	97	106.7	101	
T=180	97	99	103.6	97	
Estriol 20mg, Estradiol 20mg, Progesterone 200 mg, Testosterone 20 mg/g					
T=0	101.5	102	97.6	102	
T=90	102.5	104.5	103.1	103.5	
T=120	104.5	105.5	105.7	104	
T=180	107.5	108.5	106.6	106.5	
Estriol 0.1 mg, Estradiol 0.1 mg, Testosterone 0.1 mg/g					
T=0	102	98		109	
T=90	96	102		101	
T=120	95	97		101	
T=180	99	100		98	
Estriol 20mg, Estradiol 20mg, Testosterone 20mg/g					
T=0	100.5	101		100.5	
T=90	101	102		100.5	
T=120	103	103		102	
T=180	108.5	108.5		107.5	
Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg, DHEA 1mg/g					
T=0	101	97	95.5	105	96.7
T=90	98	103	105.5	103	103.7
T=120	97	99	101.4	107	96.9
T=180	88	96	101.2	95	97.3
Estriol 20mg, Estradiol 20mg, Testosterone 20mg, Progesterone 200mg, DHEA 50mg/g					
T=0	100.5	101	101.2	100.5	98.4
T=90	106	108	106.2	107	106.4
T=120	113	115	114.3	113	114.2
Estradiol 0.1mg, Testosterone 0.1mg/g					
T=0		96		103	
T=90		98		95	
T=120		99		100	
T=180		99		94	
Estradiol 20mg, Testosterone 20 mg/g					
T=0		101		100.5	
T=90		101.5		101.5	

T=120		107.5		106	
T=180		107.5		105.5	
Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg/g					
T=0		96	96.3	106	
T=90		99	103.8	99	
T=120		97	101	104	
T=180		101	107.1	98	
Estradiol 20mg, Testosterone 20mg, Progesterone 200mg/g					
T=0		102	108.6	103	
T=90		102	102.9	101.5	
T=120		102.5	105.2	101.5	
T=180		109.5	109	108	
Testosterone 300mg/g					
T=0				102.2	
T=90				101.9	
T=120				102.8	
T=180				101.5	

*Retested

Table 5. Phytobase Combination Product High and Low Bracketed Results

Combination (High and Low)	Estriol (%)	Estradiol (%)	Progesterone (%)	Testosterone (%)	DHEA (%)
Dehydroepiandrosterone 1mg/g					
T=0					90
T=90					101
T=120					94.6
T=180					
Dehydroepiandrosterone 100mg/g					
T=0					99
T=90					98.6
T=120					
T=180					
Estradiol 0.1mg, Progesterone 1mg/g					
T=0		95	103.6		
T=90		99	113.4*		
T=120		94	106		
T=180					
Estradiol 10mg, Progesterone 300mg/g					
T=0		97	99		
T=90		111.3*	106.2		
T=120		103.3	106.4		
T=180					
Estriol 0.1mg, Estradiol 0.1mg/g					
T=0	98	93			
T=90	94	90			
T=120	93	91			
T=180	100	100			
Estriol 20mg, Estradiol 20mg/g					
T=0	101.5	102.5			

T=90	98.5	99.5			
T=120	102.5	102.5			
T=180	103.5	105			
Estriol 0.1mg, Estradiol 0.1mg, Progesterone 1mg, Testosterone 0.1mg/g					
T=0	97	98	91.9	96	
T=90	101	97	96.5	99	
T=120	103	100	97.3	99	
T=180	98	99	103.1	106	
Progesterone 200mg, Testosterone 20mg/g					
T=0	98.5	99.5	101.7	100	
T=90	106.5	108	110	109.5	
T=120	103	100	97.3	99	
T=180	105	106.5	108.8	106	
Estriol 0.1mg, Estradiol 0.1mg, Testosterone 0.1mg/g					
T=0	101	99		100	
T=90	98	104		100	
T=120	91	104		110	
T=180	99	103		101	
Estriol 20mg, Estradiol 20mg, Testosterone 20mg/g					
T=0	95	100		99	
T=90	105.5	101.5		101.5	
T=120	107	102		106.5	
T=180	99.5	107.5		103	
Estradiol 0.1mg, Testosterone 0.1mg/g					
T=0		101		102	
T=90		98		102	
T=120		102		105	
T=180		103		107	
Estradiol 20mg, Testosterone 20mg/g					
T=0		101		101	
T=90		105		105.5	
T=120		107.5		107	
T=180		112.5		113	
Estradiol 0.1mg, Testosterone 0.1mg, Progesterone 1mg/g					
T=0		97	98.1	100	
T=90		101	109.4	104	
T=120		90	98.7	97	
T=180		90	98.9	96	
Estradiol 20mg, Testosterone 20mg, Progesterone 200mg/g					
T=0		101.5	99.6	101.5	
T=90		105.5	100.5	105.5	
T=120		107.5	107.4	107	
T=180		105	104.6	104.5	
Progesterone 0.1mg, Testosterone 0.1mg/g					
T=0			99.6	95	
T=90			105.4	96	
T=120			101.6	102	
T=180			106.4	107	
Progesterone 200mg, Testosterone 20mg/g					

T=0			99.5	101.5	
T=90			100.8	105.5	
T=120			104.8	103.5	
T=180			104.1	103.5	

*Retested, out of spec results were due to capping issues during storage and resultant issues with water loss. The 120-day timepoint testing result is the result of four pooled tests performed with the appropriate protocol

Table 6. Antimicrobal Effectiveness Testing per USP <51> Performed on All Formulations

Organism	Time	Results	Acceptable Limit
Candida albicans	14 days	Pass	No increase in the number of CFU initially inoculated
Candida albicans	28 days	Pass	No increase in the number of CFU initially inoculated
Aspergillus brasiliensis	14 days	Pass	No increase in the number of CFU initially inoculated
Aspergillus brasiliensis	28 days	Pass	No increase in the number of CFU initially inoculated
Escherichia coli	14 days	Pass	NLT 2 log reduction in the number of CFU initially inoculated
Escherichia coli	28 days	Pass	No increase from the 14 days count
Pseudomonas aeruginosa	14 days	Pass	NLT 2 log reduction in the number of CFU initially inoculated
Pseudomonas aeruginosa	28 days	Pass	No increase from the 14 days count
Staphylococcus aureus	14 days	Pass	NLT 2 log reduction in the number of CFU initially inoculated
Staphylococcus aureus	28 days	Pass	No increase from the 14 days count

Antimicrobial effectiveness testing per USP <51> is intended to test the viability of the preservative system of a preparation. The process involves inoculation with the above listed organisms and then monitoring for 28 days after inoculation to see if the preservative system can adequately prevent microbial growth and replication. In our study, we did the first round of AET at day 90 (inoculation occurred at the 90 day timepoint, and then the preparation was monitored for 28 days in accordance with USP <51>), then we did a second round of AET at day 180 (inoculation occurred at the 180 day timepoint, and then the preparation was monitored for 28 days in accordance with USP <51>).

Conclusion

This study found a wide range of compatibility of hormones in both HRT Heavy™ and Phytobase™, demonstrating the suitability of these vehicles both from a stability and an antimicrobial effectiveness perspective for a wide range of compounded hormone combinations and preparations.

References

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