

## 5-Month 40-Formulation Investigation

POTENTIAL CAUSE OF DEGRADATION?		RESULTS
<b>Water</b>	– Drying agent	<b>NO</b>
<b>Metals</b>		<b>NO</b>
<b>Polymers</b>	– Different polymer classes	<b>NO</b>
<b>Solvents</b>		<b>NO</b>
<b>Oxygen</b>	– Patches surrounded by O <sub>2</sub> , N <sub>2</sub> , or room air – Antioxidants	<b>YES</b>

# Manufacturing Process for Generic's ANDA Products

## Opportunities for Exposure to Oxygen and Other Free-Radicals

### STEP 1:

MIXING ACTIVE  
CASTING SOLUTION

- Add Duro-Tak® 905A Adhesive and Active Base to 15 gallon mixer. Mix for 2 to 4 hours.

### STEP 2:

COATING OF  
BACKING FILM LAYER

### STEP 3:

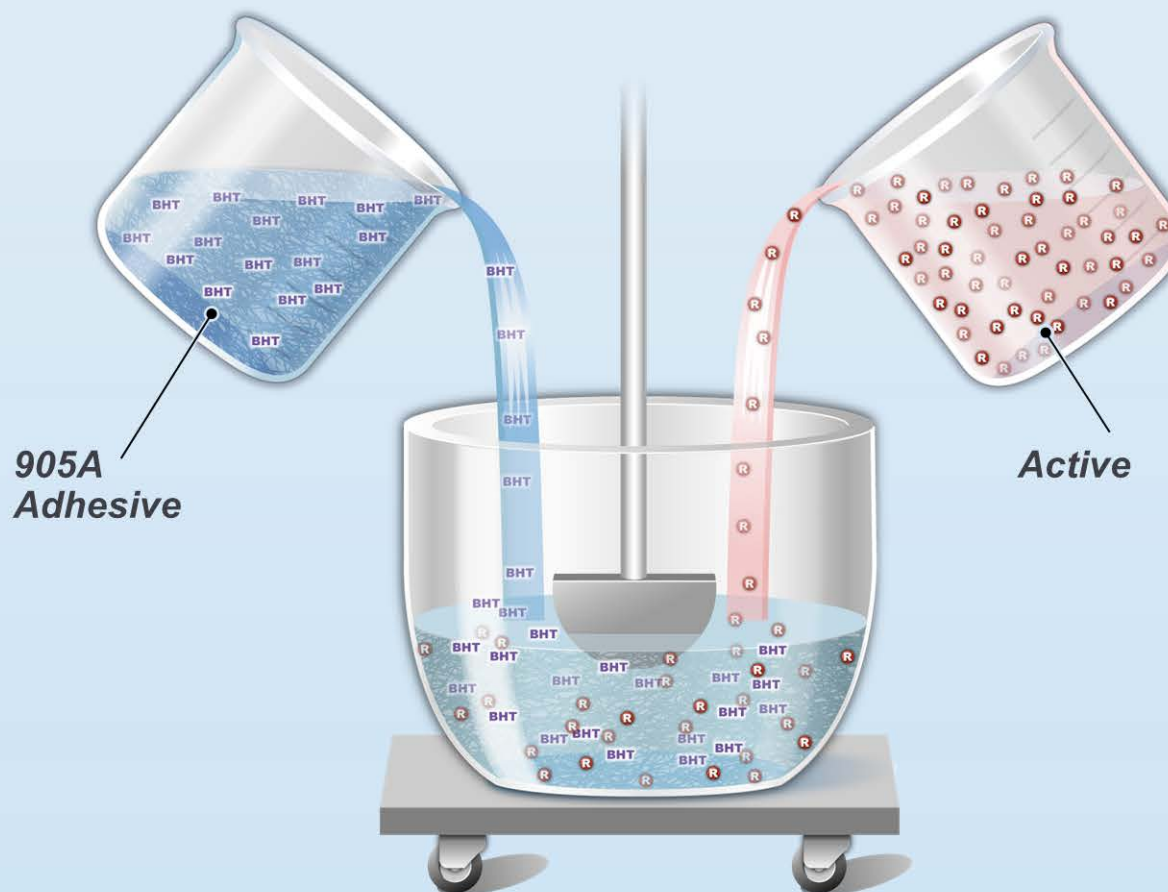
COATING/LAMINATING  
OF PROTECTIVE  
RELEASE LINER

### STEP 4:

PRODUCTION OF  
905A/900A  
ADHESIVE BILAYER

### STEP 5:

DIE CUTTING AND  
POUCHING



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## Opportunities for Exposure to Oxygen and Other Free-Radicals

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► Transfer casting solution through a 40µm filter.

### STEP 2:

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### STEP 3:

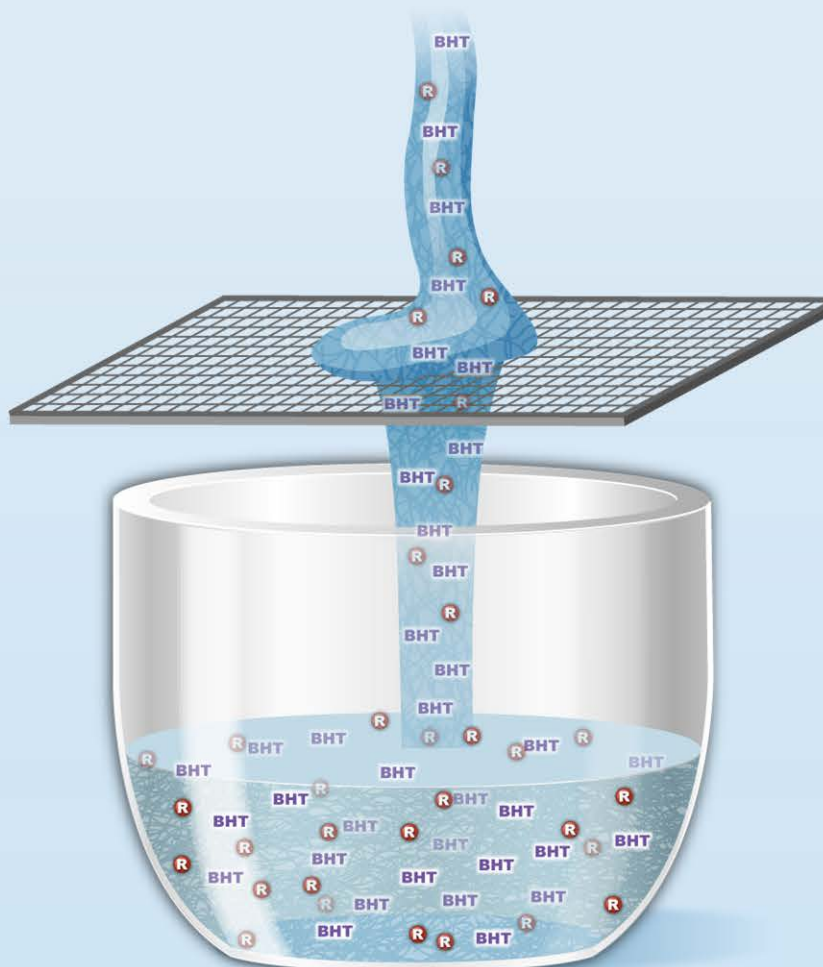
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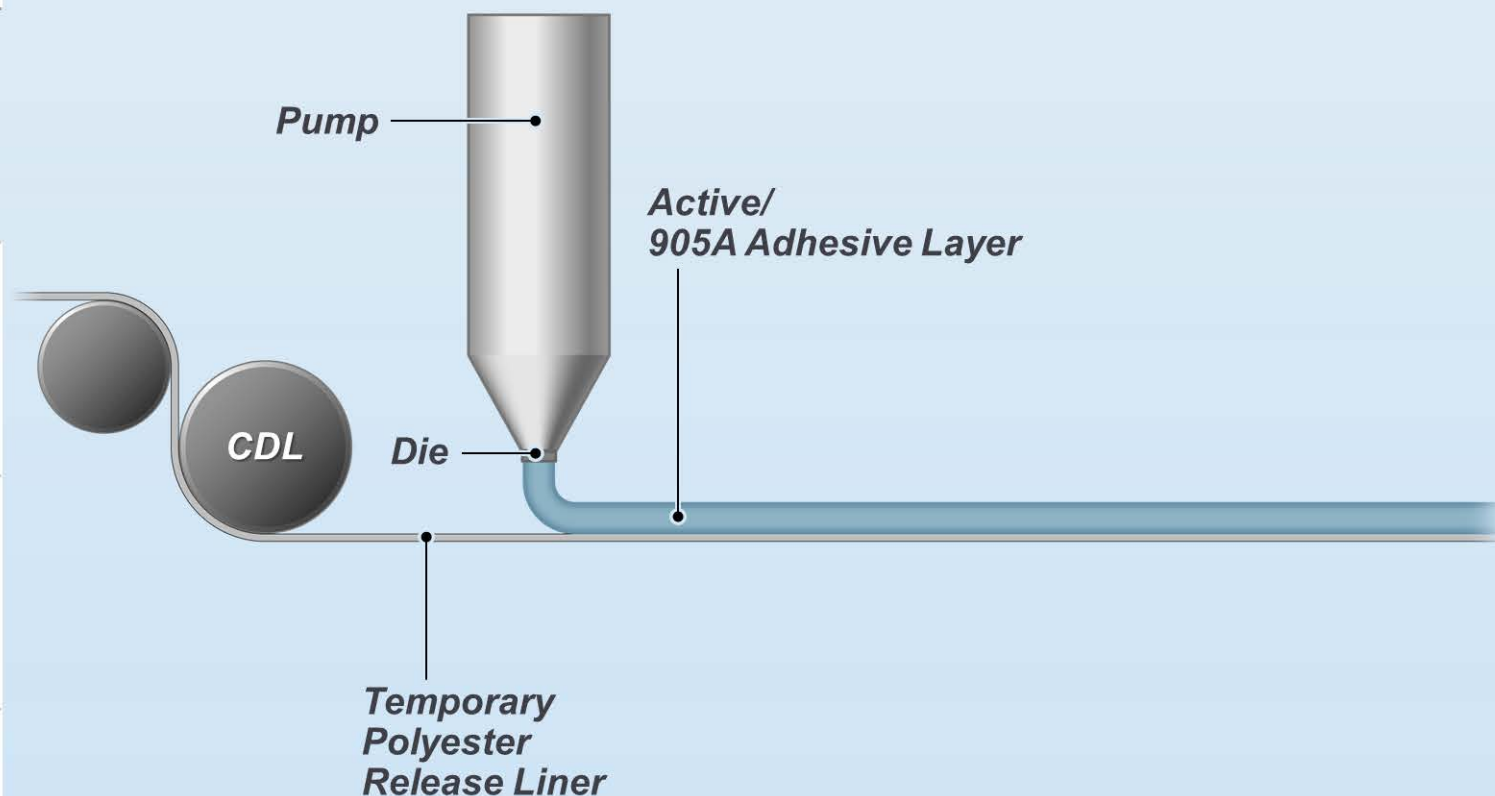
### STEP 4:

PRODUCTION OF  
905A/900A  
ADHESIVE BILAYER

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POUCHING

- ▶ As the polyester release liner is drawn past the extrusion die, it is coated with a thin, uniform film of the Active/905A Adhesive Matrix.





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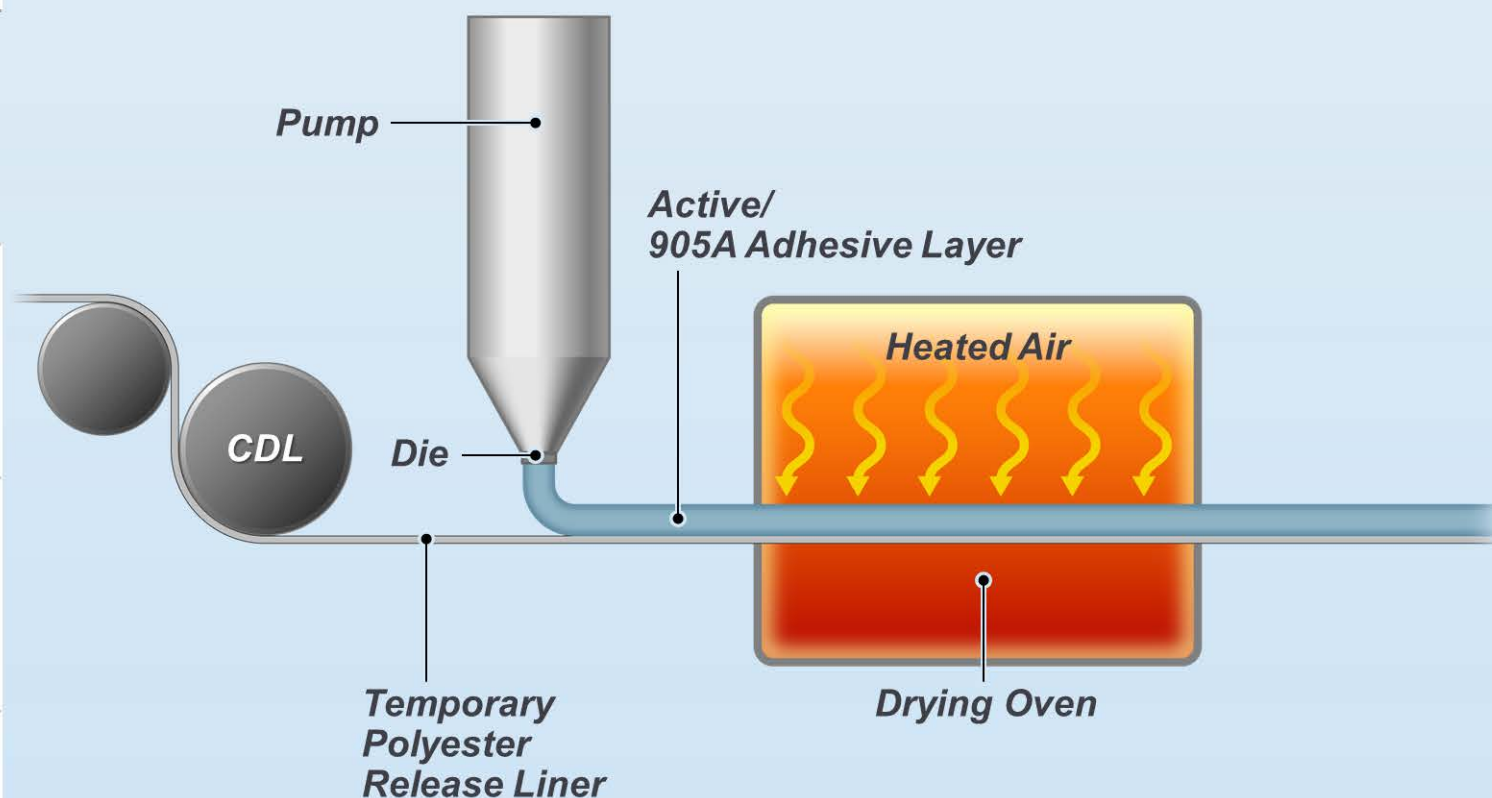
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- ▶ The coated polyester release liner is then passed through the drying oven, where filtered and heated air reduces the level of solvents in the casting solution.



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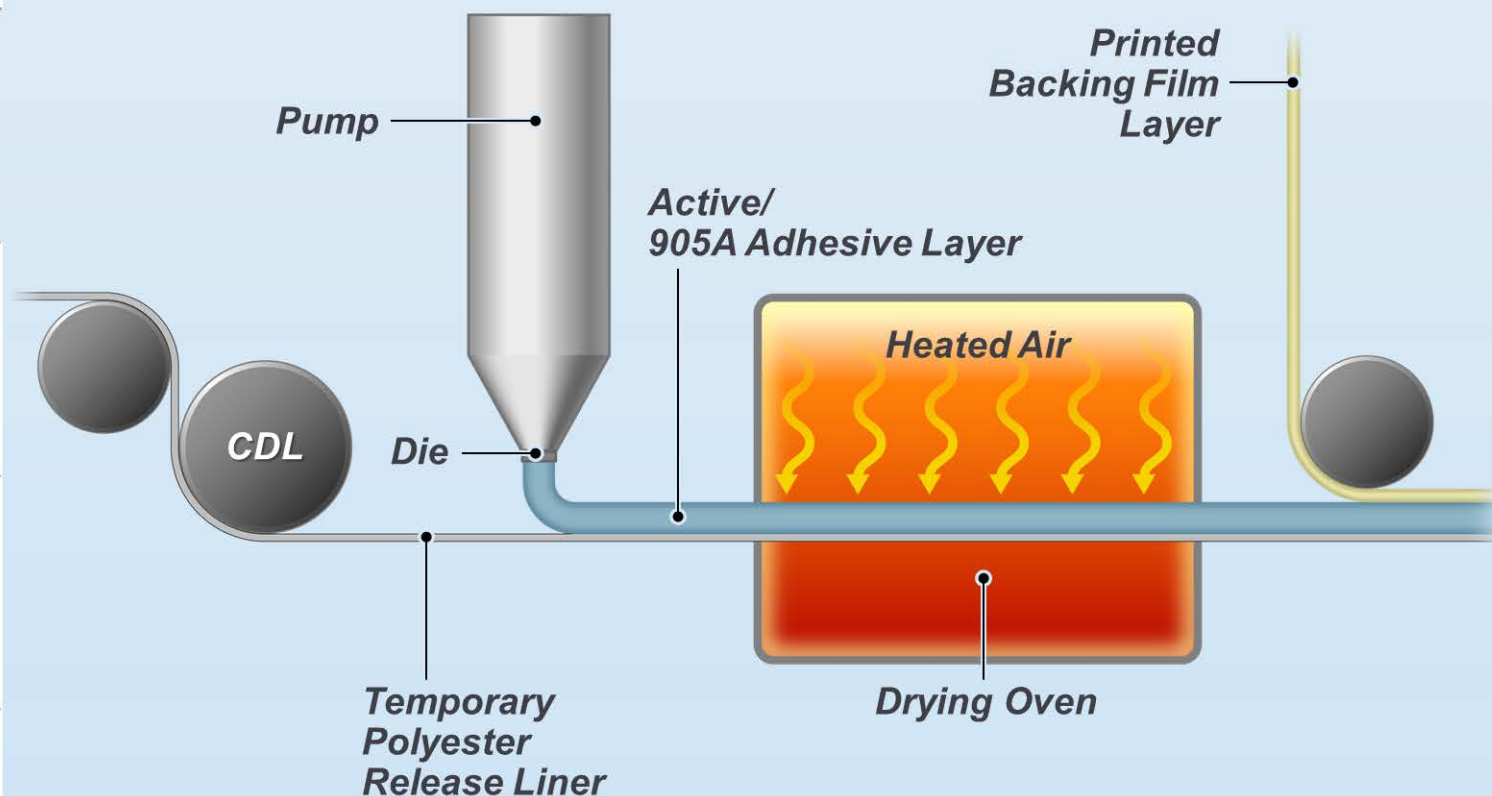
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- ▶ As the coated polyester release liner exits the drying oven, the backing film is laminated onto the exposed, dried adhesive.



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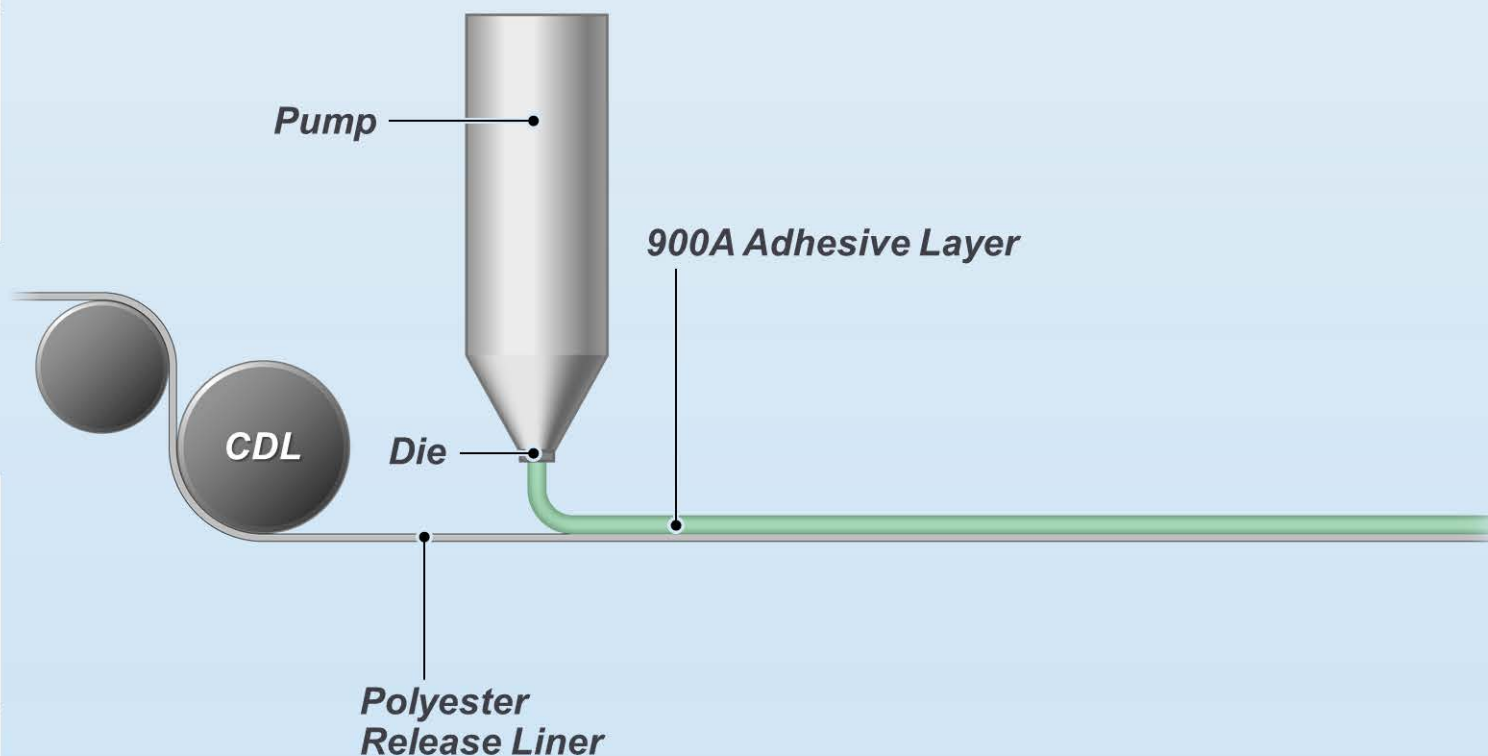
### STEP 4:

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- ▶ Another polyester release liner is coated with a thin, uniform film of DuroTak® 900A adhesive.



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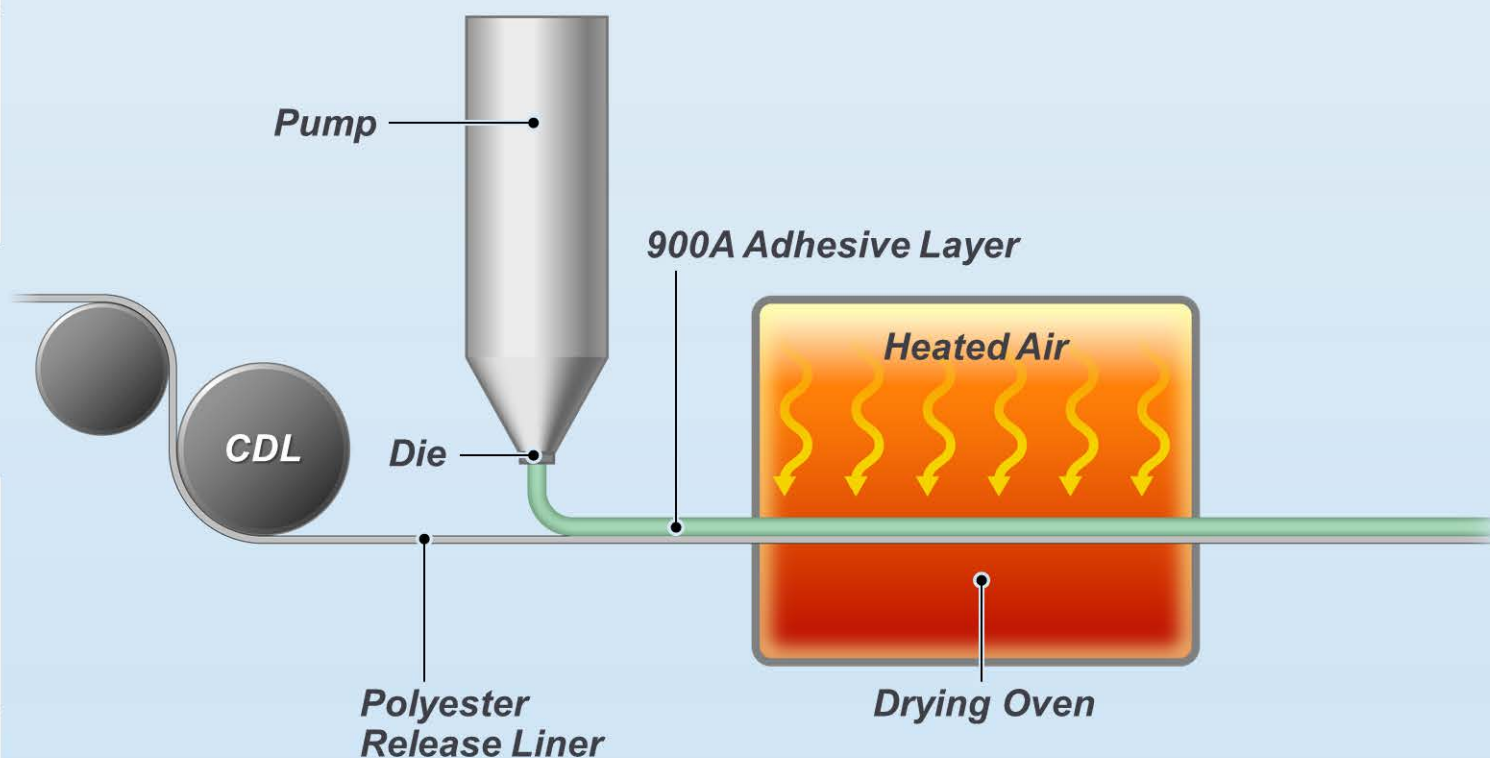
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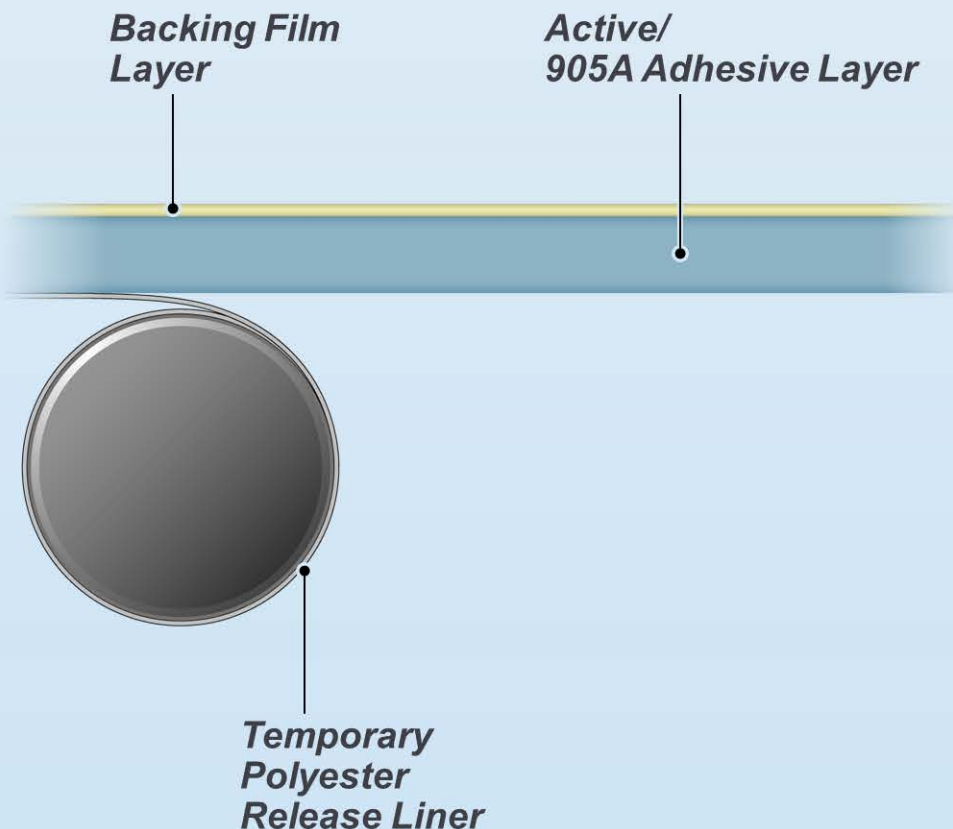
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- The temporary release liner from STEP 2 is removed and discarded, once again exposing the Active/905A Adhesive Matrix.



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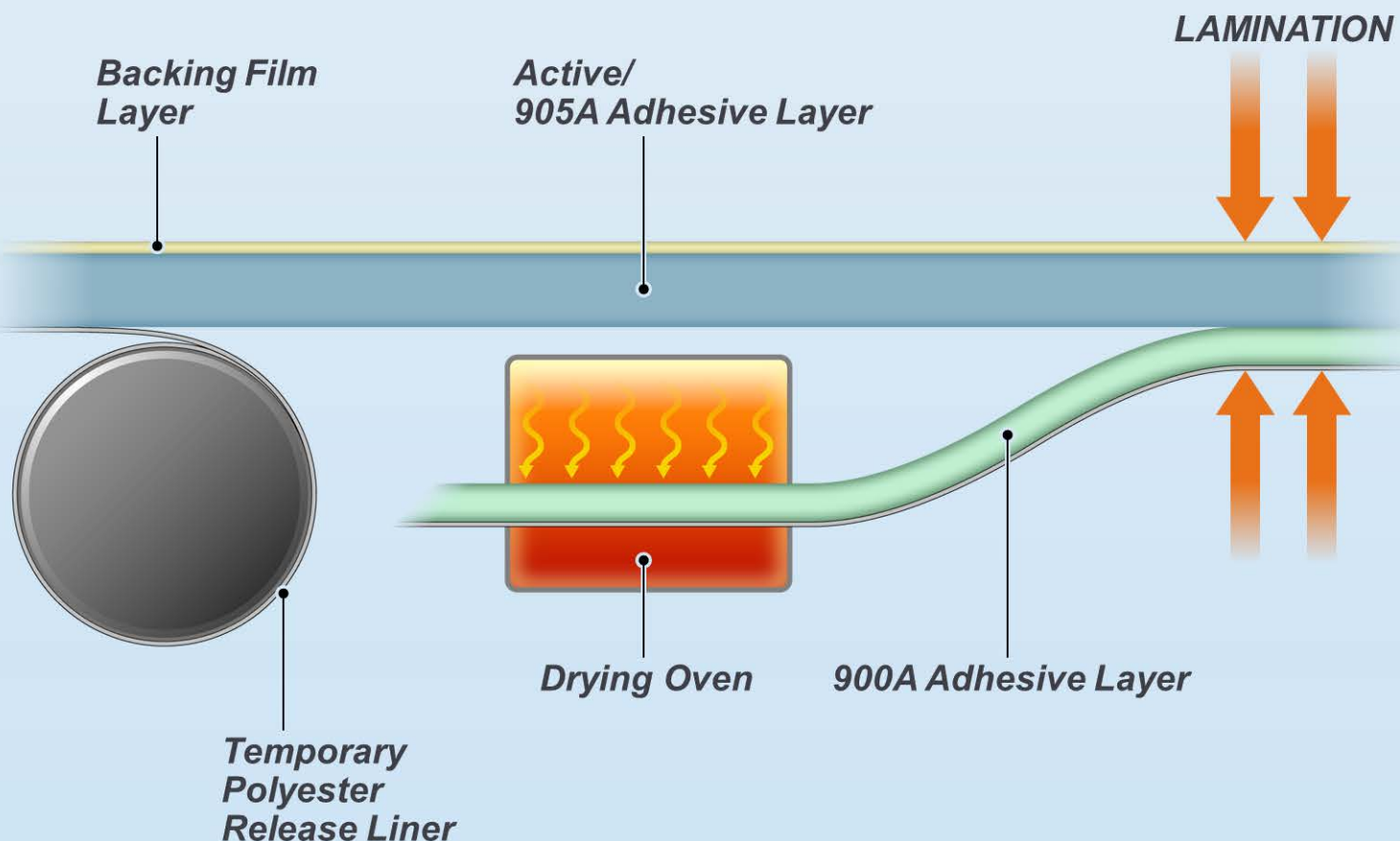
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- ▶ **Active/905A Adhesive Layer** is then laminated onto the **900A Adhesive Layer** to form the **905A/900A Adhesive Bilayer**.



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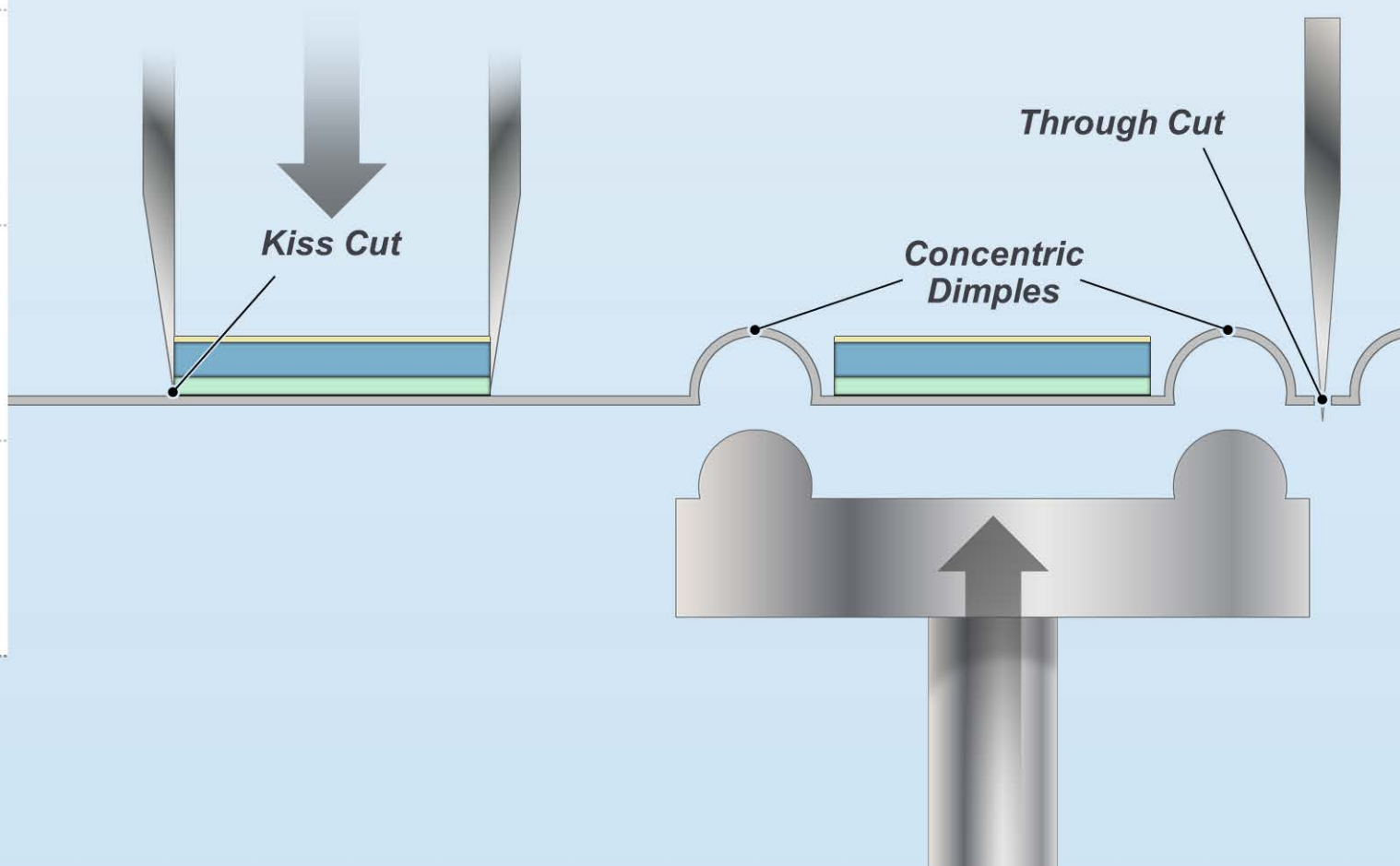
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ADHESIVE BILAYER

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- The Adhesive Bilayer is fed through a cutting machine that “kiss cuts” the backing film and adhesive layers, and makes concentric dimples on the release liner.



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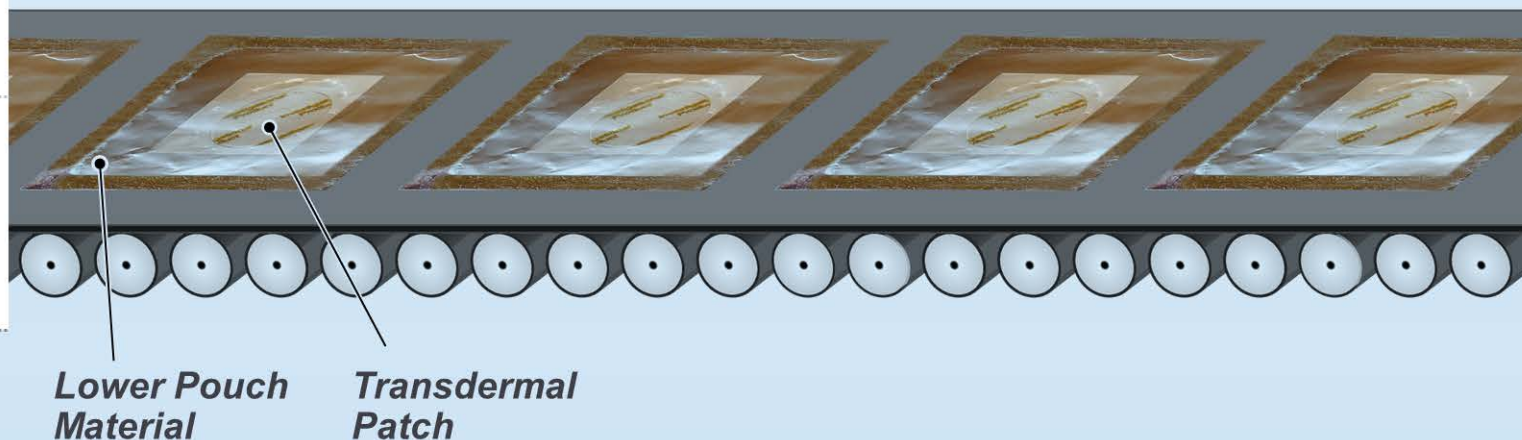
### STEP 4:

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- ▶ The transdermal systems are then carried to the pouching portion of the machine, where they are transferred onto the lower pouching material.





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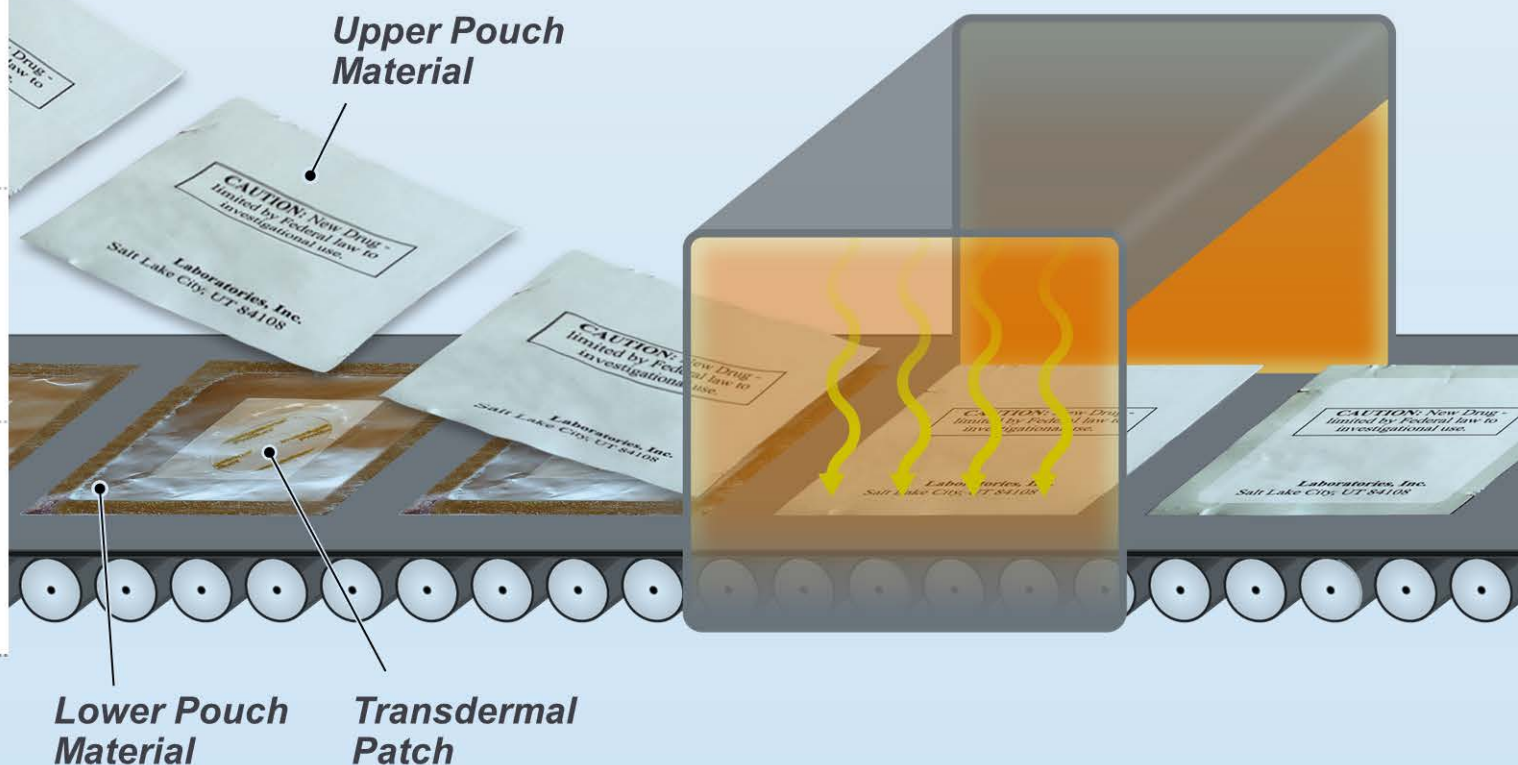
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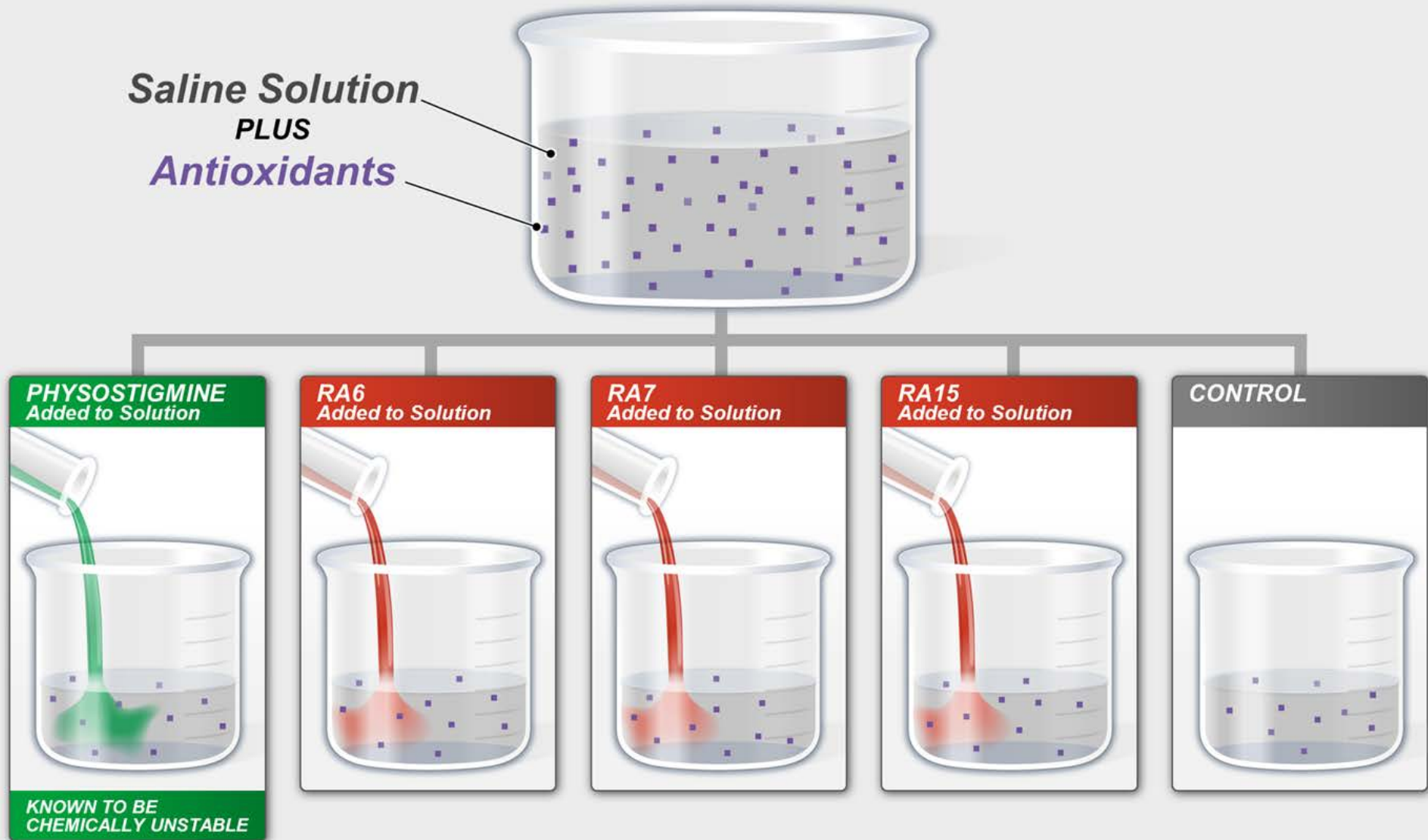
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POUCHING

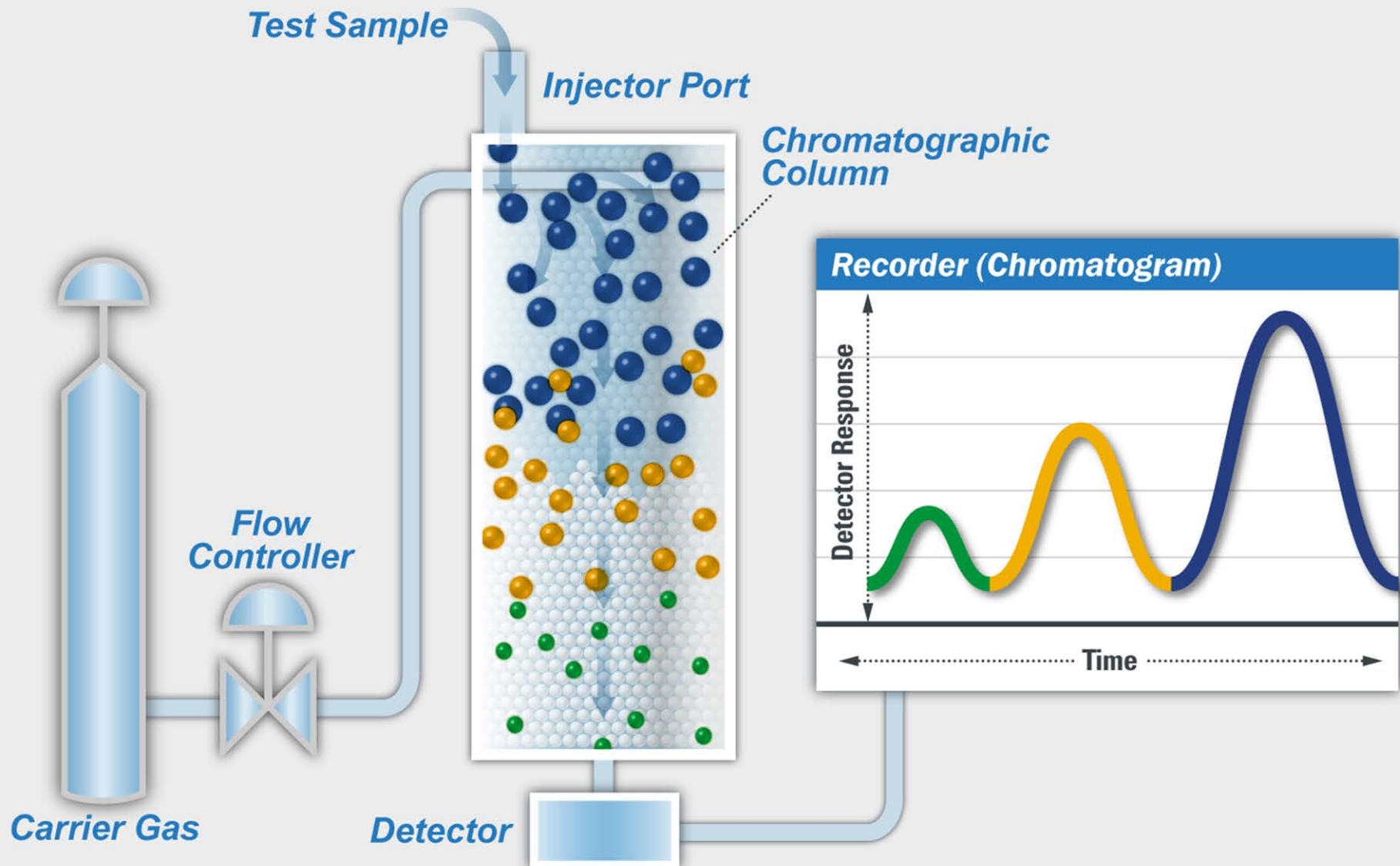
- ▶ The lower pouch carrying the transdermal system is drawn under another web of pouching material and passed through a heat seal station.



## Prior Art – Elmalem Paper and the '807 Patent Disclose an Antioxidant for Use with Physostigmine, and As a Control



## Gas Chromatography Is Used to Detect Different Compounds in a Test Sample





## Gas Chromatography Testing: Patch Surrounded by Oxygen, Nitrogen and Room Air

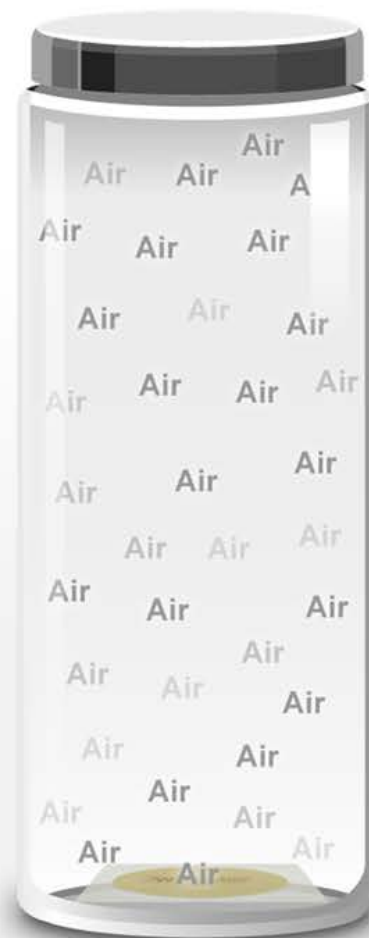
OXYGEN



NITROGEN

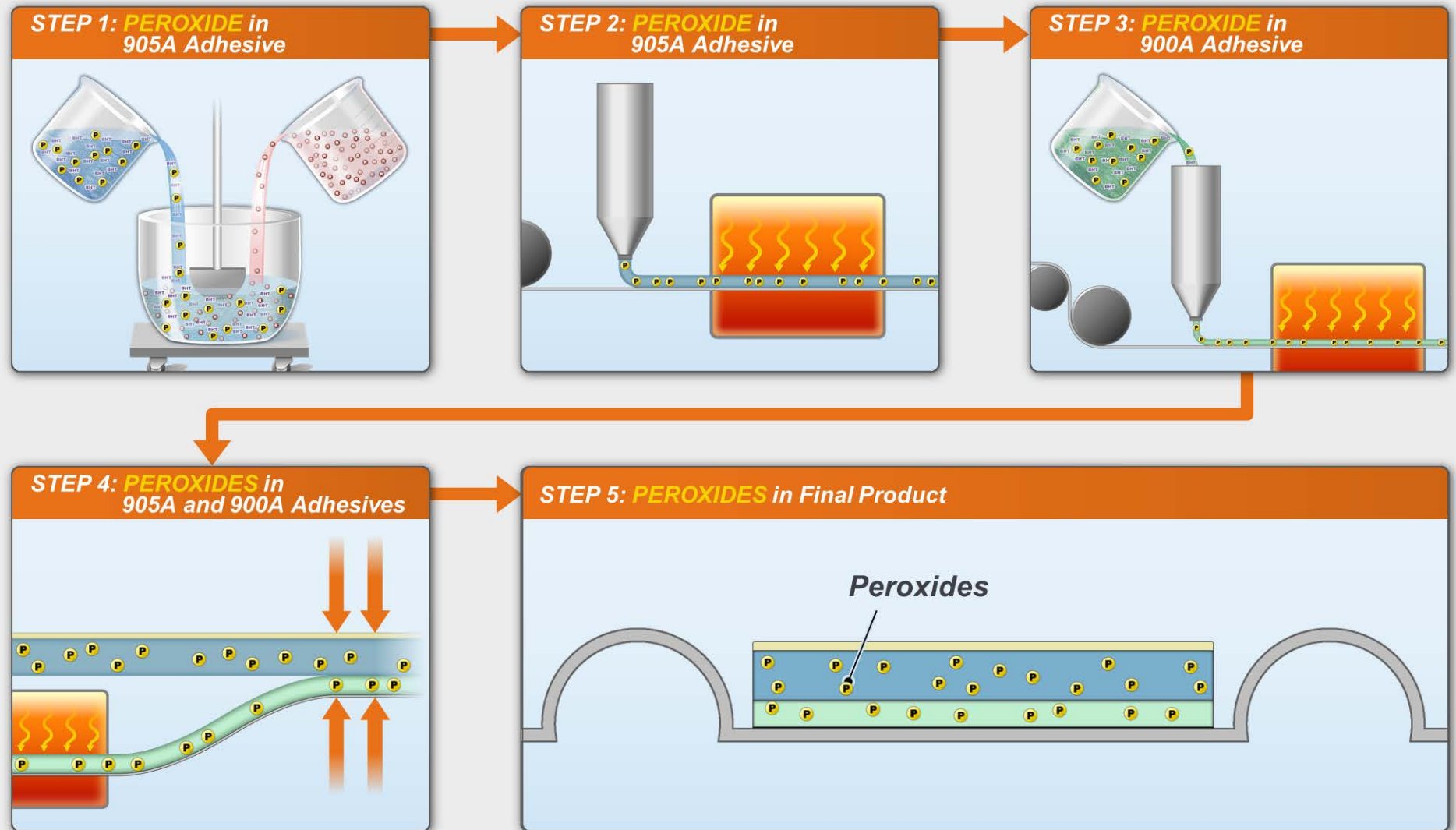


ROOM AIR





## The Peroxides in the 905A and 900A Adhesives Will End Up In the Final Generic Product



# What Is An Enantiomer?

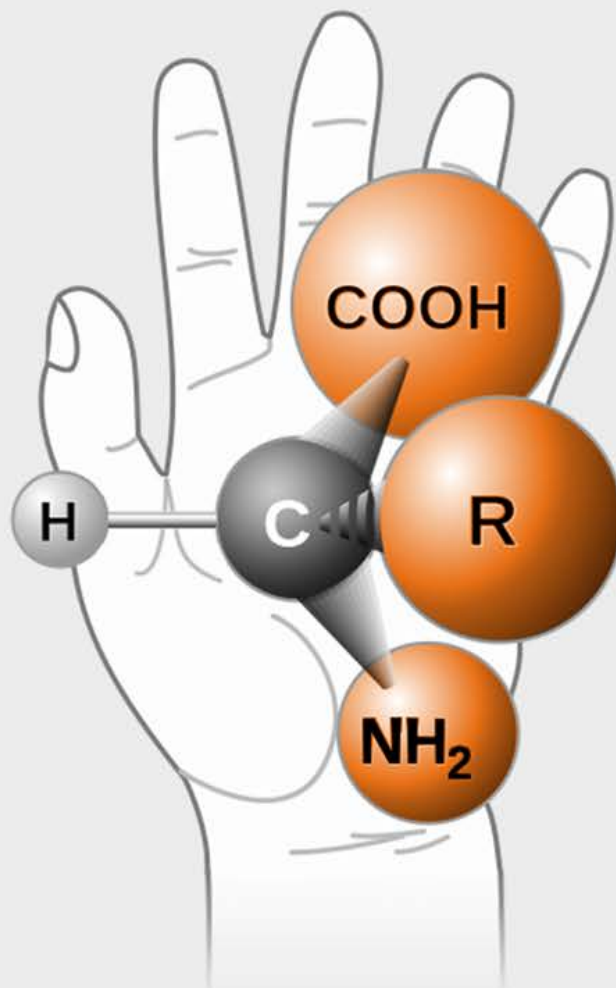
Two molecules that are **non-superimposable** mirror images of each other.

The molecules have **all the same properties**

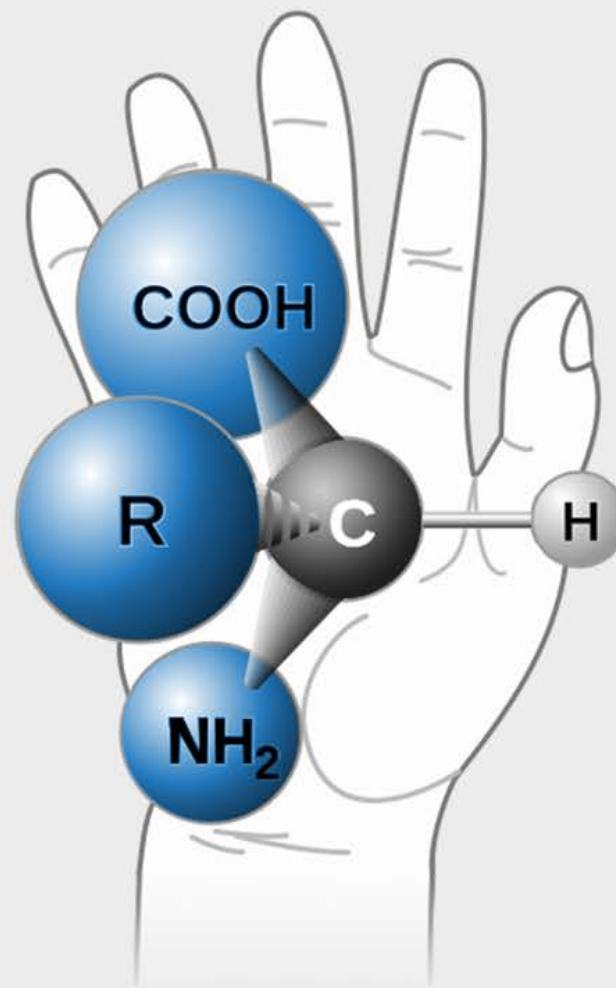
**BUT**

rotate plane-polarized light in **opposite directions**.

R-ENANTIOMER

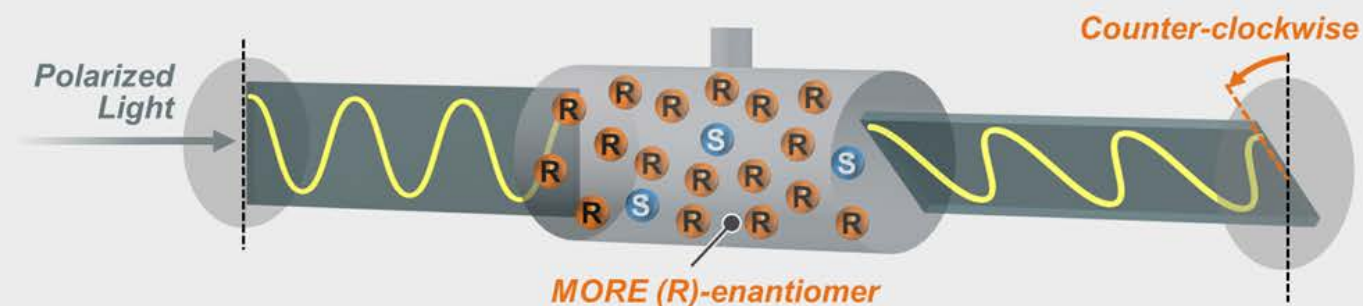


S-ENANTIOMER

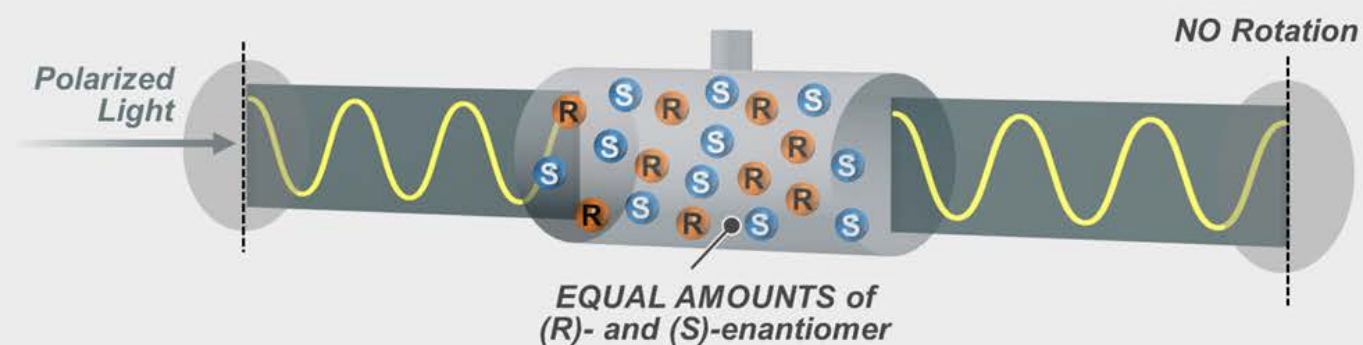


**The Racemate  
and Its Constituent  
Enantiomer Are  
DIFFERENT  
CHEMICAL  
COMPOUNDS**

**(R)-Enantiomer rotates polarized light COUNTER-CLOCKWISE**



**Racemate DOES NOT ROTATE polarized light**



**(S)-Enantiomer rotates polarized light CLOCKWISE**

