Testimony of William P. Kennedy: Owner
Nephron Pharmaceuticals Corporation
FDA-Approved Manufacturing Facility/Orlando, FL
Registered Pharmacist, State of Florida since 1967
Senate Committee on Health, Education, Labor & Pensions
Hearing on Pharmacy Compounding
October 23, 2003

Mr. Chairman and Members of the Committee, thank you sincerely for your efforts to shed public light on the phenomenon in the country today of pharmacies boldly compounding massive quantities of prescription drugs. I believe that I am uniquely qualified to speak to you on this topic. I am both a licensed pharmacist who was involved in large scale compounding and I am now the owner of an FDA-approved manufacturing facility in Orlando, Florida. I know this issue inside out. The American public is at risk and you are to be commended for your interest in and pursuit of non-FDA compliant compounding.

In 1966 I graduated from the University of South Carolina's College of Pharmacy and became a registered pharmacist in that state. A year later, I moved to Florida and began to pursue my career in pharmacy in earnest.

In 1972 I purchased my own retail drugstore, Thayer's Colonial Pharmacy, Inc., located in Orlando, Florida. This drugstore had been in Orlando for many years with a reputation for finding unique prescription drugs and compounding various discontinued formulations. Included in this were many combinations of two or more drugs. For example, dermatological preparations and respiratory drugs were commonly compounded.

In the mid-1980's we began compounding various respiratory medications on a broader scale. This business grew rapidly, including a large portion of mail order transactions. We attracted much attention within the industry.

Around 1990, the FDA paid us a visit. Their mission was to investigate my compounding pharmacy. After two weeks of intense scrutiny, they determined that I should be "labeled" a manufacturer, and **ordered that I cease and desist this compounding** division of Thayer's. The FDA representatives said, *"If you want to be in the manufacturing business, then you must have an FDA-approved manufacturing facility"*. Of course, the back room of my drug store did not qualify.

In 1991, following the FDA's instruction, I set out to secure the approvals and financing necessary to open a proper manufacturing facility. Although I was a bit naive at the outset, I soon learned that I was involved in a daunting process. In my case, it took over six years to secure approval for my first new drug product, and my plant. It was arduous, capital intensive and certainly the most challenging endeavor of my career in health care. However, I now understood the rules and knew this was necessary to begin providing prescription drugs on a large scale to the public. I knew this because the FDA had told me so.

In 1997 Nephron Pharmaceuticals was up and running as an FDA-approved and registered facility. Our focus is oral inhalation solutions used to treat asthma, bronchitis

and Chronic Obstructive Pulmonary Disease. Nephron owns six approved Abbreviated New Drug Applications (ANDA's) for prescription drugs:

- Albuterol Sulfate Inh. Sol., 0.083%
- Albuterol Sulfate Inh. Sol., 0.5%
- Ipratropium Bromide Inh. Sol., 0.02%
- Isoetharine Inh. Sol., 1%
- Metaproterenol Sulfate Inh. Sol., 0.4%
- Metaproterenol Sulfate Inh. Sol., 0.6%

Now, by national pharmaceutical standards, we are little guys. Even so, here is what is entailed in the manufacture of our drugs:

Our 76,000 square foot facility is designed for full FDA compliance. Our production room design houses controlled environment rooms, based on the 1997 ISPE Sterile Manufacturing Facilities Guideline that was developed with the help of the FDA.

- Main Room classified as "Pharmaceutical" "D Grade", Class 100,000 in operation;
- Gown Room, Class 100,000
- Mix Room, Class 10,000
- Filling Room, Class 10,000 with Class 100 HEPA Shrouded fill nozzle systems
- All rooms use positive pressure, cascading air filtration systems.

The attached exhibits show the design of this facility (Attachment #1), the structured materials flow chart (Attachment #2), the complex HVAC system required (Attachments #3 and #4), and one of the Water for Injection systems required for operation (Attachment #5).

In this facility we have the following Departments/Personnel required to comply with drug manufacturing regulations (21 CFR §210/211)

- Regulatory Department: **4 people** responsible for all **FDA compliance**/reporting

- Quality Assurance Department: **41 people** involved in document control, validation, training, batch record review and production line control;
- Quality Control: **9 degreed chemists**/technicians to analyze all active and inactive ingredients and finished product stability studies; **19 degreed microbiologists**/technicians who do environmental monitoring of all clean room, samples of WFI and Pure Steam condensate, sampling of raw materials and production components;
- Production Department: **117 production personnel**;
- Engineering Department: **4 Blow/Fill/Seal specialists** whose technology requires no human contact with the product or its immediate container during filling and is recognized by the US Pharmacopoeia (USP) as an advanced technology for the manufacture of liquid solution in unit-dose forms; **22 production equipment assistants.**

And these personnel operate at this facility in compliance with Federal Regulations (21 CFR §210/211), which requires the following:

- 517 Production Standard Operating Procedures (SOP's);
- 30 Microbiology SOPs;
- 47 Chemistry SOPs;
- 29 Microbiology Validated Test Methods;
- 20 Chemistry Validated Test Methods;
- 219 Equipment Installation/Operation Qualification Procedures;
- 310 Performance Qualifications/Validated Processes.

As you can see, this is a highly complex industry. The FDA requirements, which are incredibly demanding, seem never-ending. However, as a manufacturer, I have the comfort of knowing that all FDA-approved facilities are subject to the same sets of regulations and requirements. These rules are not frivolous; they are there for a purpose. And that is to protect the public by insuring a uniform standard of integrity in the prescription drugs produced in our country.

Let me give you an example. We have to test the raw ingredients used in the manufacture of a batch of drugs at the beginning of the batch and at the end of the batch. If the

composition of the raw ingredients does not meet their predefined specifications at the end of the batch, all the drugs in that batch MUST BE DESTROYED.

And yet, while these high standards are uniform with the FDA facilities, there is another sphere of drugs, in my case, inhalation drugs, which are produced throughout the country today with no similar level of accountability. Pharmacies, like Thayers, are producing drugs that should be identical to those produced by my company, but fall far short.

I have attached four reports (Attachments #6 to #9), of pharmacy-produced products sent to my chemistry lab at Nephron for analysis. As you can see, they miss the mark on potency and quantity. A recent study by the FDA itself showed a failure rate of more than 34%. These failures result from inadequate facilities as well as inadequate testing of raw ingredients.

Perhaps to attack this problem, the FDA instituted a rule that ***all*** *oral inhalation drugs have to be* ***sterile***. Initially, receipt of this ruling reconfirmed to me that I had made the correct decision in 1991 to pursue FDA certification. However, in my trips around the country marketing my products, I encounter time after time non-FDA approved companies in the inhalation drug market willfully mass compounding their products. Let me assure you, their product is rampant. I know. I ran a similar operation in the 80's. I can tell you there is no comparison to the way I produced Albuterol in the back room at Thayers to the way Albuterol is now produced at Nephron.

Which brings us to the importance of the hearing you are holding today. Americans across the country believe that the drugs they purchase to fill a doctors prescription are the same… the same chemistry, the same sterility, the same integrity. This is certainly the ideal toward which the FDA and its registered manufacturers work. However, this is far from the reality. The consumer is at risk and does not even know it. The consumers do not know how to protect themselves from non-FDA drugs, or that they even do.

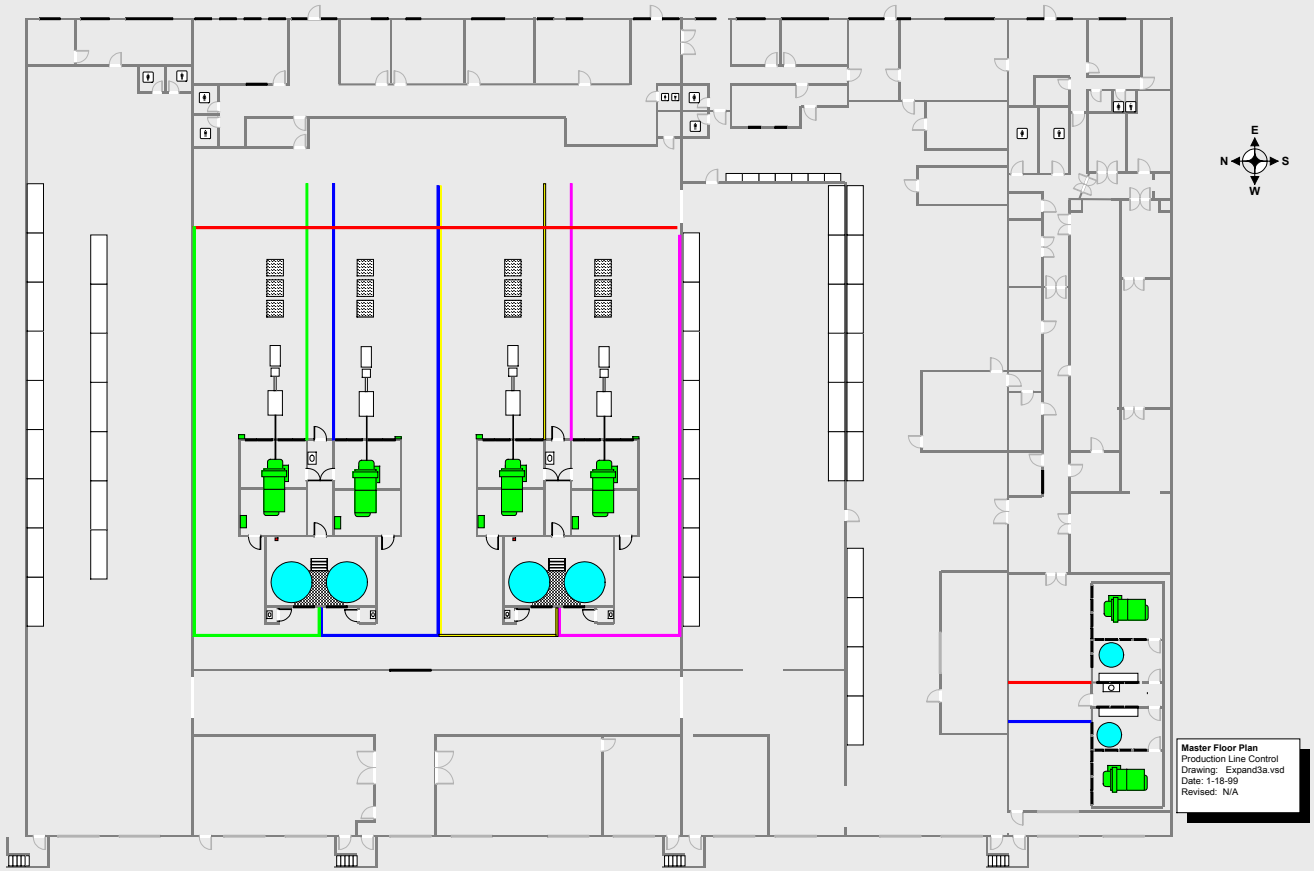
Clearly, the integrity of the prescription drug market in this country is under siege. Companies and individuals are willfully breaking the rules and regulations long established by the FDA. Given my background, and I find this situation is stunning. The consumer, however, should find it frightening. As you know from documented press stories, the result of this mass compounding outside the FDA arena can be lethal.

Again, thank you for providing this public forum to discuss this crisis. I am confident that with your attention, the double standard prevalent in the inhalation drug market will no longer be tolerated.

I would be happy to answer any questions you might have.

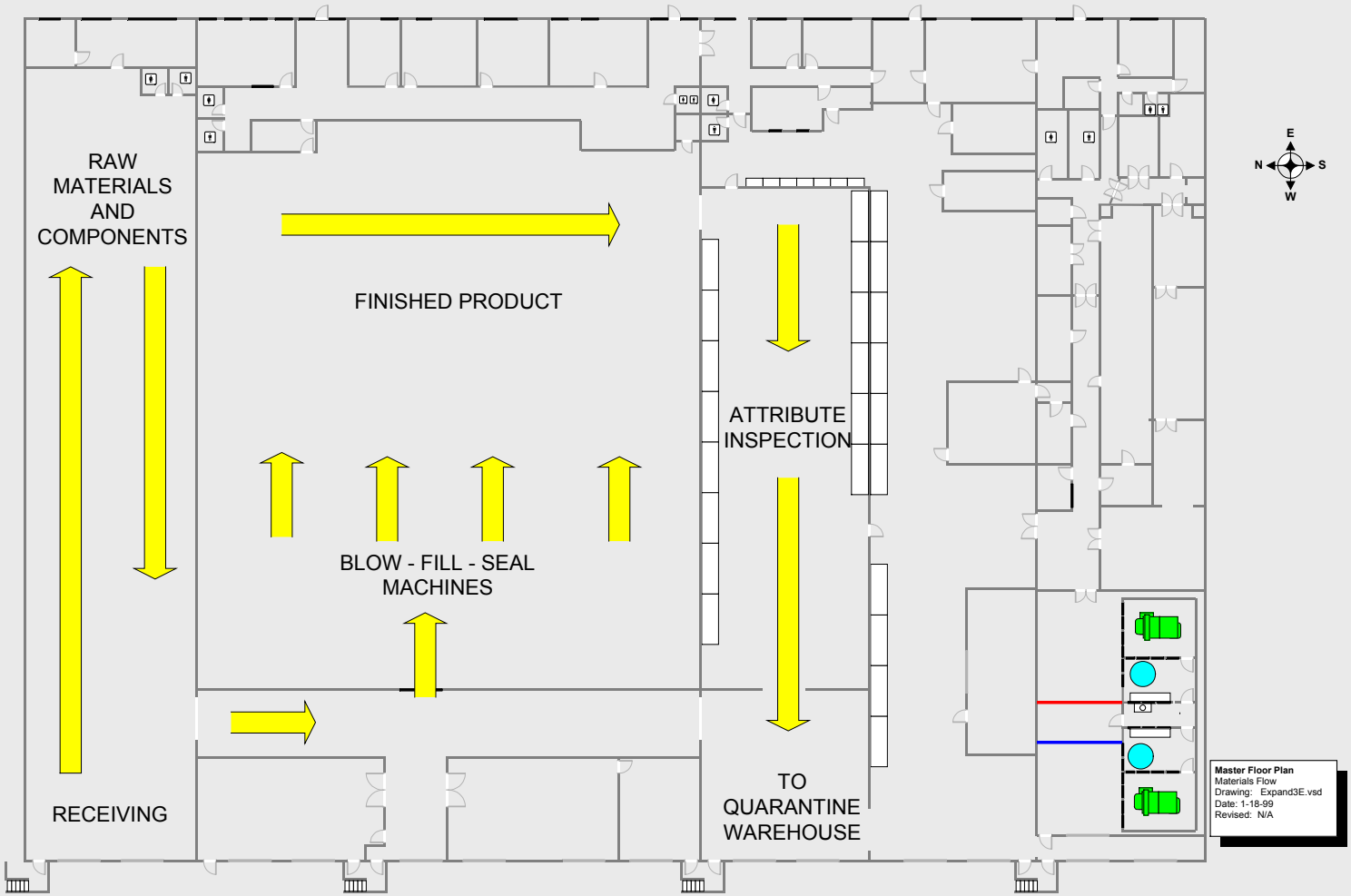
Attachment 1

Production Room #4 Layout



Attachment 2

Production Room #4 Materials Flow



Attachment #3

Production Room #4

- HVAC
  - Primary Filtration
    - FAR 30/30 prefilters
    - 90/95 ASHRAE rated filters
    - 3 air handlers @ 29,000 cfm each
    - Approximately 23 room air changes per hour
  - Secondary Filtration
    - 68 HEPA filters @ 720 cfm each
    - Air supply = 87,270 cfm

Attachment #4

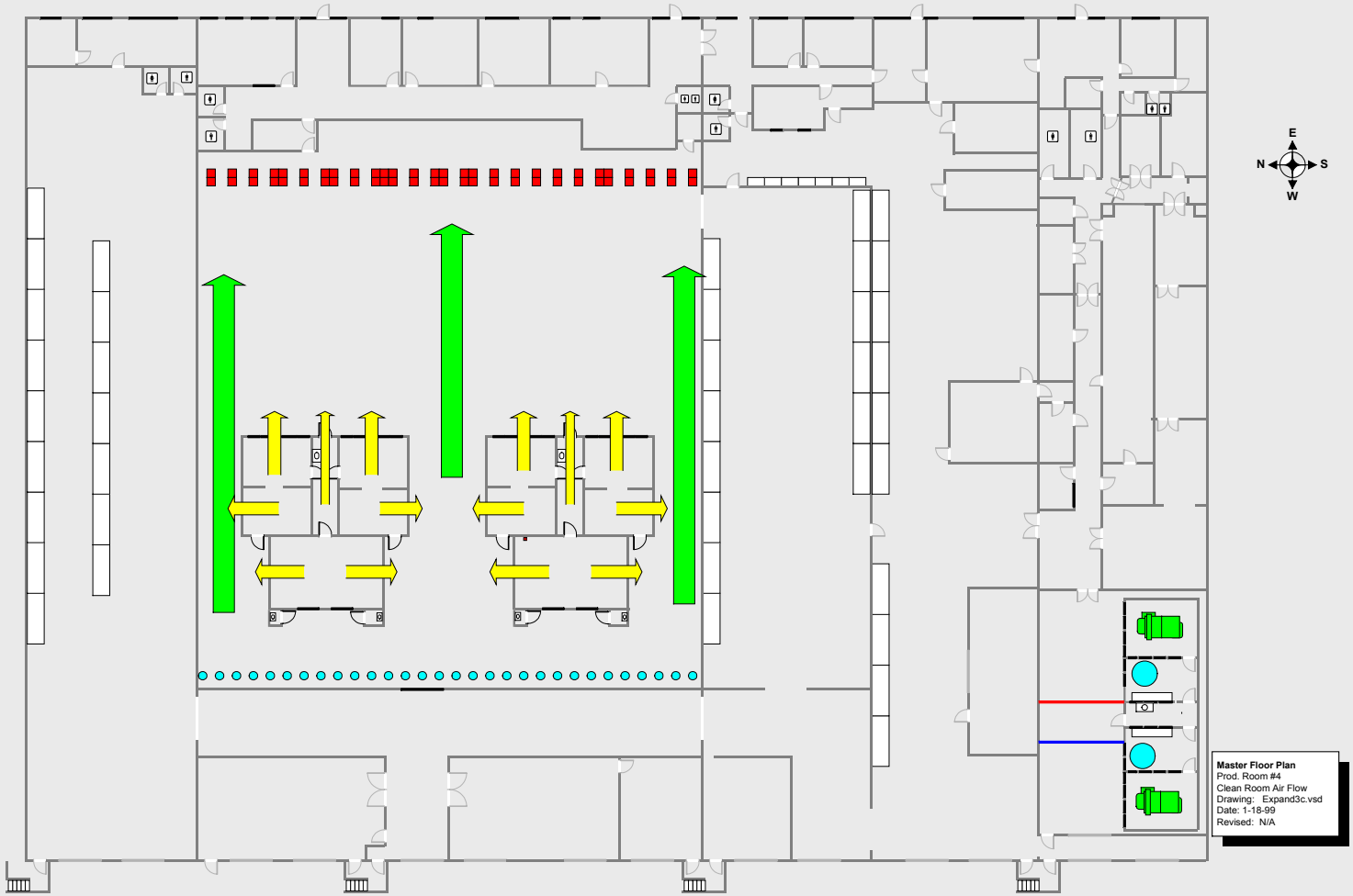
Production Room #4
Room Air Flow Design

HEPA Filtered Air

Air In

Room Air Flow

Air Return



Attachment #5

Raw Materials Control

- Water for Injection
  - Water Distillation and Storage System showing 1 of Nephron's 4,000 gallon storage tanks.

MEMORANDUM

To: Steve Simmons

From: Angel R. Perez
Chemistry Department

Date: 4-29-99

Subject: *Albuterol sulfate / Ipratropium bromide*

Albuterol Sulfate

The molecular formula for albuterol sulfate is $(C_{13}H_{21}NO_3)_2{\cdot}H_2SO_4$ with molecular weight of 576.71. To obtain a concentration of 0.083% of albuterol the formulation should be corrected for a molecular factor. Albuterol sulfate contains two molecules of albuterol ($C_{13}H_{21}NO_3$) with molecular weight of 239.32. According to this the formulation should be corrected as follow:

Actual formulation:

$$\frac{\text{8.34g Albuterol sulfate}}{\text{10,000 mL}} \times 2 \times \frac{\text{239.32 Albuterol}}{\text{576.71 Albuterol sulfate}} \times 100 = 0.069\% \text{ (actual concentration)}$$

Correction:

$$\frac{\text{10.0g Albuterol sulfate}}{\text{10,000 mL}} \times 2 \times \frac{\text{239.32 Albuterol}}{\text{576.71 Albuterol sulfate}} \times 100 = 0.083\% \text{ Albuterol}$$

The correct amount for albuterol sulfate is 10.0g in 10 liters of solution. Using 8.34 g in this formulation the recovery of albuterol will be of 83% of the label claim.

Ipratropium Bromide

An amount of 1.67g of ipratropium bromide is used in the formulation to obtain a total 0.5 mg of this active ingredient in the final solution (3 mL). Ipratropium bromide contains water between 3.9 to 4.4%. If the water content is not considered in the formulation the final concentration will be about 0.48 mg in the final solution instead of 0.5 mg of ipratropium bromide. This means a recovery of 96% of the label claim.

Comment: *A water content of 3.9% can be used to adjust the formulation. Use an amount of 1.74g instead 1.67g of ipratropium bromide in this formulation to have a recovery about 100% of the label claim.*

Assay Test

Two different method were used to determine the potency for each active ingredient. The HPLC was used to determine the peak area and the samples were compared with a standard solution. The samples had a retention time about 4.4 min. for albuterol sulfate and 9.4 min. for ipratropium bromide and were compared with standard solution. The samples had a recovery of 77% for albuterol and 87.8% for ipratropium bromide. Chromatographic conditions were the following:

Albuterol Sulfate		Ipratropium Bromide	
Chart speed:	2 cm/min	Chart speed:	1 cm/min
Run Time:	6 min.	Run Time:	12 min.
Attenuation:	128	Attenuation:	128
Sensitivity:	0.05 AUF	Sensitivity:	0.05 AUF
Flow:	1.0 mL/min	Flow:	1.3 mL/min
Injection volume:	20 uL	Injection volume:	20 uL
Wavelength:	280 nm	Wavelength:	210 nm
Column:	250 mm X 4.6 mm Allsphere ODS-2 5u S/N: 96100648 Alltech	Column:	4 mm X 0.125 m Lichrosphere SRP- Select Phenomenex 5u S/N: 298086
Pressure:	2,200 psi	Pressure:	1,120 psi

MEMORANDUM

To: Steve Simmons

From: Angel R. Perez
Chemistry Department

Date: 5-04-99

Subject: *Albuterol sulfate / Ipratropium bromide*
2.5 mg / 0.5 mg in 3 mL
Lot no: PH99012101 – PH99022401

Samples of Albuterol Sulfate / Ipratropium Bromide were received on April 30, 1999 from Pulmo Dose to be tested. Two different methods were used to determine the potency of each ingredient by HPLC. Chemistry Lab performed the assay test and the results were less than 90% of the label claim.

Lot no: PH99012101 – PH99022401

Active Ingredient	% of the label claim	Strength	mg/mL	mg in 3 mL
Albuterol 0.083%	80.8%	0.067%	0.67	2.01
Ipratropium Bromide 0.0167%	89.2%	0.0149%	0.149	0.447

Suggestions:

- *Verify the water content of the active ingredients in the certificate of analysis from the manufacturer.*
- *Verify the assay result of the active ingredients in the certificate of analysis from the manufacturer.*
- *Calculate the assay value "as is" for albuterol sulfate to determine the correct weight of the active ingredient:*

Example:

water content: 0.5%; assay result: 98.5%

$$\frac{A}{\frac{100 - 0.5}{100}} = 98.5\% \qquad A = 98.01\% \text{ "as is"}$$

Now the formulation should be adjusted using the assay value "as is".

$$\frac{10.0\ g}{98.01 / 100} = 10.2g \text{ Albuterol Sulfate}$$

$$\frac{10.2g \text{ Albuterol Sulfate}}{10{,}000\ mL} \times \frac{98.01}{100} \times 2 \times \frac{239.32 \text{ Albuterol}}{576.71 \text{ Albuterol Sulfate}} \times 100 = 0.083\%$$

- *Calculate the assay value "as is" for ipratropium bromide*:

Example:

water content: 4.4%; assay result: 99.0%

$$\frac{A}{\frac{100 - 4.4}{100}} = 99.0\% \qquad A = 94.64\% \text{ "as is"}$$

Now the formulation should be adjusted using the assay value "as is".

$$\frac{1.67\ g}{94.64/\ 100} = 1.76g \text{ Ipratropium Bromide}$$

$$\frac{1.76g \text{ Ipratropium Bromide}}{10{,}000\ mL} \times \frac{94.64}{100} \times 100 = 0.0167\%^*$$

*A concentration of 0.02% will produce 0.6 mg of ipratropium bromide in 3 mL. Normally, Ipratropium Bromide Inhalation Solution, 0.02% is in 2.5 mL with a total of 0.5 mg of ipratropium bromide. To obtain 0.5 mg in 3 mL the final concentration will be 0.0167% instead of 0.02%.

- *According to this example, use **10.2g** of albuterol sulfate and **1.76g** of ipratropium bromide in the formulation.* ***You can use this amount as standard in the formulation. Using these amounts will ensure a 100% of the label claim.***

- *Verify the scale calibration.*

- *Make sure about the final volume (10,000 mL) of the solution. Use a graduated cylinder (Class A) or a calibrated container.*

- *Make sure about the pH of the solution. Normally, a pH of 4.7 for albuterol sulfate and 3.4 for ipratropium bromide the solution is stable. I recommend adjusting the pH with concentrated sulfuric acid to about 4.0. You will need to determine how many drops are necessary to adjust the pH. Maybe only one drop is enough to reach the desired pH.*

- *Keep the solution in cold and dark storage. Albuterol sulfate is sensitive to the light and high temperature.*

MEMORANDUM

To: Steve Simmons

From: Angel R. Perez
Chemistry Department

Date: 8-26-99

Subject: *Albuterol sulfate / Ipratropium bromide*
2.5 mg / 0.5 mg in 3 mL
Lot no: PH99012101 – PH99022401

Samples of Albuterol Sulfate / Ipratropium Bromide (lot no: PH99012101 – PH99022401) from Pulmo Dose were received in the chemistry department to be tested for each active ingredients. Two different methods were used to determine the potency of each ingredient by HPLC. Chemistry Lab performed the assay test and pH. The results is within specification.

Finished Product
Lot no: PH99012101 – PH99022401 (samples received on 5-25-99)
pH = 4.97 Reference: NL9911 p. 2, 15; NL9906 p. 190

Active Ingredient	% of the label claim	Strength	mg/mL	mg in 3 mL
Albuterol 0.083%	97.5%	0.0809%	0.809	2.43
Ipratropium Bromide 0.0167%	95.1%	0.0159%	0.159	0.48

1 MONTH OF STABILITY (samples received on 6-22-99)
pH = 4.86 Reference: NL9914 p. 147, 154; NL9911 p. 159

Active Ingredient	% of the label claim	Strength	mg/mL	mg in 3 mL
Albuterol 0.083%	98.8%	0.0820%	0.820	2.46
Ipratropium Bromide 0.0167%	98.0%	0.0164%	0.164	0.49

2 MONTH OF STABILITY (samples received on 7-22-99)
pH = 4.94 Reference: NL9920 p. 7; NL9912 p. 155, 158

Active Ingredient	% of the label claim	Strength	mg/mL	mg in 3 mL
Albuterol 0.083%	98.5%	0.0818%	0.818	2.45
Ipratropium Bromide 0.0167%	97.9%	0.0163%	0.163	0.49

MEMORANDUM

To: Steve Simmons

From: Angel R. Perez
Chemistry Department

Date: 2-10-00

Subject: *Albuterol sulfate / Ipratropium bromide*
2.5 mg / 0.5 mg in 3 mL
Premixed Solution
Lot Number: 12818; Expiration Date: Jul 01, 2000

Vials with premixed solution of Albuterol Sulfate / Ipratropium Bromide were received on February 8, 2000 from International Therapeutic Service to be tested. Two different methods (MA-007 and MA-016) were used to determine the potency of each ingredient by HPLC. Chemistry Lab performed the assay test and the results were the following:

Active Ingredient	% of the label claim	Strength	mg/mL	mg in 3 mL
Albuterol 0.083%	81.2%	0.0674%	0.677	2.03
Ipratropium Bromide 0.0167%*	114.0%	0.0190%	0.190	0.57

*0.5 mg in 3.0 mL contains a concentration of 0.0167% in the solution.

Ten vials were taken for the minimum fill test and the results were the following:

Vial	Volume, mL
#1	2.6
#2	2.55
#3	2.6
#4	2.6
#5	2.6
#6	2.6
#7	2.6
#8	2.6
#9	2.6
#10	2.6

Observations:

1. The fill volume for each vial were less than 3.0 mL.

2. Apparently, the solution was prepared to contain 2.5 mg of albuterol sulfate in 3 cc normal saline. In my opinion, they are not using the molecular factor to convert albuterol sulfate; $(C_{13}H_{21}NO_3)_2$ H_2SO_4 in albuterol; $C_{13}H_{21}NO_3$. To make this conversion they need to multiply the weight of albuterol sulfate by 576.70 / 2 X 239.31 because we have two molecule of albuterol in albuterol sulfate.

3. If our observation is correct then is obvious to found a low concentration in the sample of albuterol.

   For example:

   To contain 2.5 mg of albuterol in 3 cc normal saline we need to have 3.01 mg of albuterol sulfate in this solution. If they are not following this procedure we have about 83% of albuterol when the solution is prepared.

4. Normally, ipratropium bromide inhalation solution is prepared to contain 0.5 mg of ipratropium in 2.5 cc normal saline. In my opinion they are following this normal procedure but when this solution is placed in vials to contain a volume of 3.0 mL the concentration in mg is higher. This produce a value of 0.6 mg of ipratropium in 3.0 mL instead of 0.5 mg of ipratropium. If this is correct then we have about 120% of the label claim.

5. Normally, ipratropium bromide contain about 4.4% of water content. If they are not taking in consideration the water content then we have an initial concentration of 114.7% when the solution is prepared.

6. The pH of the solution was taken and found as 5.55. This pH is normal for 0.9% sodium chloride. This mean that the solution was not adjusted with acid to have a pH about 4.0. A pH of 4.0 make the solution more stable.

7. Vials with 2.6 mL of solution contains a total of 1.76 mg of albuterol and 0.49 mg of ipratropium per vial. If they are using this amount (2.6 mL) as a normal filling process then the result per vial is the following:

   Albuterol: 70.4%
   Ipratropium: 98.0%

   All results reported before were based on a volume of 3.0 cc normal saline for each vials.

My conclusion is the following: they are following two normal procedure to prepare this premixed solution. They are not instructed to convert albuterol sulfate in abuterol and they don't know that ipratropium bromide in 3 cc normal solution contain more mg of active ingredient. Ipratropium bromide was used as 100% when initially this raw material content about 4.4% of water. They are not using this water content in the sample weight.