2005 Ephedrine / Pseudoephedrine Legitimate Medical Use Methodology and Final Report

U. S. Drug Enforcement Administration

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Executive Summary

The Combat Methamphetamine Epidemic Act of 2005 requires the Drug Enforcement Administration (DEA) to develop annual quotas for the manufacture and importation of Ephedrine, Pseudoephedrine, and Phenylpropanolamine products for legitimate utilization in the U.S. No direct estimate for the volume and use of these products is available. At the request of the DEA, IMS Health (IMS) developed an approach to estimating legitimate need for Ephedrine and Pseudoephedrine utilizing IMS Health (IMS) data sources augmented by data from ACNielsen.

The methodology employed develops three (3) estimates for each product, and then produces a composite weighted average of the three (3) estimates. The weighting factors for the composite are derived from the relative uncertainty in each of the three (3) separate estimating models. The estimating models were developed by examining three (3) measures of the market: sales into outlets (e.g., chain drug stores, food stores, mass merchandisers); product sales to consumers; and patient prescription healthcare claims. In all cases, data from 2005 were used, and for consistency, a standard product list was employed across the three (3) models.

The project approach and methodology called for producing a preliminary estimate and a final estimate. The results of the preliminary estimates were utilized by DEA along with information relating to inventory and export requirements to propose the United States assessment of annual needs which DEA published in the Federal Register for public comment for proposed rule making. The final estimates incorporate planned additional analysis not included in the preliminary estimates as well as refinements to the models based on public comments received. The DEA published the preliminary estimates in Federal Register Notice FR Doc E6-17526 [Federal Register: October 19, 2006 (Volume 71, Number 202)]. IMS reviewed the comments pertaining to the preliminary estimates and in coordination with the DEA, developed several enhancements for inclusion in the final estimates.

The final estimate of the legitimate need for Ephedrine for 2005 is 4.096 metric tons and the estimate for Pseudoephedrine is 280.268 metric tons. These estimates represent a slight increase from the preliminary estimates for Ephedrine and a small decrease in the estimates for Pseudoephedrine. The increase in Ephedrine is primarily due to adjustments made to capture sales made exclusively through convenience store outlets. Preliminary estimates were primarily decreased by factoring out the weights of base salts to derive for each product a weight reflecting only the molecule of interest (Ephedrine, Pseudoephedrine). Additional sensitivity analysis in the final estimate and contained in this report provide further insights into the stability of each of the three (3) estimating models and the weights given each for the final composite estimates.

Methodology Used in Developing Estimates of

Ephedrine and Pseudoephedrine 2005 Legitimate Medical Use

The Drug Enforcement Administration (DEA) is required, as part of the Combat Methamphetamine Epidemic Act, to develop annual quotas for the manufacture and importation of Ephedrine, Pseudoephedrine, and Phenylpropanolamine products for legitimate utilization in the U.S. At the DEA's request, IMS Health (IMS) identified an approach for generating estimates of 2005 usage for Ephedrine and Pseudoephedrine based upon the integration of the data assets IMS Health (IMS) has available, which include outlet sales, consumer purchases, and medical claims. Due to the veterinary use of phenylpropanolamine, consideration of approaches for this product will be addressed in a later document. This report documents the methodology used in developing preliminary estimates of Ephedrine and Pseudoephedrine usage. The results obtained yield values of 280.3 million grams of Pseudoephedrine and 4.1 million grams of Ephedrine as the estimated 2005 legitimate medical use volumes.

Concept

The DEA requires a best estimate of the magnitude of the legitimate medical use of Ephedrine and Pseudoephedrine for 2005. Although no direct estimate for this measure is currently available, IMS has access to a variety of data sources that provide differing insights about the marketplace, and which can be used in developing an appropriate estimate. These data sources can be utilized to develop multiple estimates of the legitimate medical use of Ephedrine and Pseudoephedrine, each derived using databases providing a view of the market from a different perspective. These estimates can then be integrated by taking into account information about the uncertainty associated with each estimate in order to develop a best estimate.

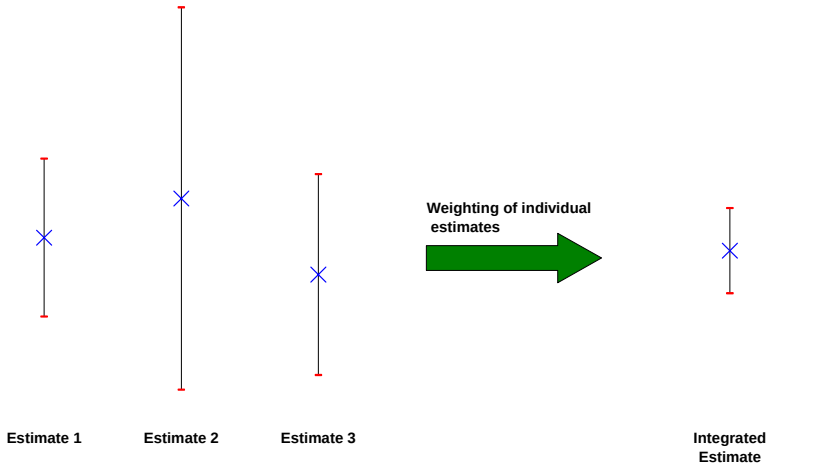
The first estimate is based upon product sales to outlets, from IMS' National Sales Perspective (NSP) service, supplemented with information from IMS' Drug Distribution Database (DDD) and National Prescription Audit (NPA), and ACNielsen's Scantrack (ST) and Homescan (HS) services. The second estimate is based upon product sales to customers, from NPA, ST, and HS services, supplemented with information from DDD and NSP services. The third estimate is based upon patient prescription claims data from IMS' ReferencePoint (RP) database, supplemented with information from U.S. Census Bureau population estimates and IMS' National Disease and Therapeutic Index (NDTI), NSP, DDD, ST, and HS services.

Each of these estimates is derived by starting with the core information available from the data assets, then developing a model that explains the relationship between the measure represented by the core information and the estimate of interest (legitimate medical use of Ephedrine and Pseudoephedrine). The model will be based upon a combination of knowledge about the data asset and outside information.

The individual estimates are integrated based upon assessments of the uncertainty associated with each estimate. In this fashion, greater weight is given to that estimate determined to provide the greatest accuracy. Combining estimates in this way yields an overall estimate with greater accuracy than any individual estimate, and can be represented in the following illustration, with the "X"

representing the point estimate, and the "-" representing the upper and lower confidence intervals for the estimate. (Note: Confidence intervals are not available for the estimates, rather a measure of uncertainty based upon knowledge of the data source and the modeling necessary to derive the estimate will be used in determining the weights.)

Illustration of Estimate Integration



Methodology

The following are descriptions of the methodology employed to develop each preliminary estimate.

A. Outlet Purchase Data-based Estimate (Base Source: NSP; Ancillary Sources: NPA, ST, HS, DDD)

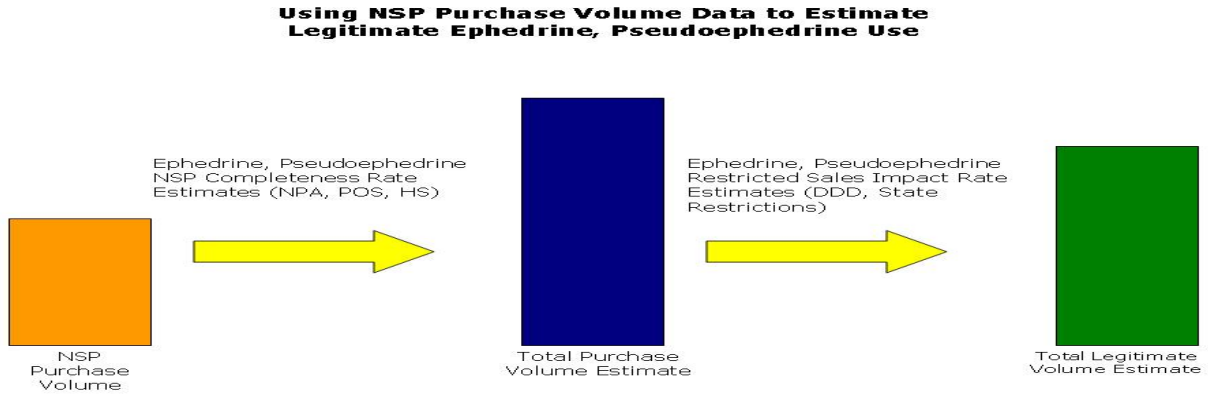
IMS Health's National Sales Perspective (NSP) provides national level monthly estimates of pharmaceutical product purchases, in units and dollars, made by outlets that dispense products through prescriptions and/or physician orders. Estimates are generated at the product package level within each of a number of channels (chain – including mass merchandiser – pharmacies, independent pharmacies, food stores with pharmacies, mail service pharmacies, non-federal hospitals, federal facilities, long-term care facilities, clinics, HMOs, home healthcare, and miscellaneous – including universities, prisons, and miscellaneous other facilities). IMS Health (IMS) obtains data from two basic sources encompassing roughly 85% of the total U.S. pharmaceutical sales volume: approximately 265 Drug Distribution Data (DDD) warehouses that supply indirect pharmaceutical purchases by outlets; and approximately 100 manufacturers that report direct purchase by outlets. The data are projected to represent national totals at the product package level within each channel.

The reported data include purchases of OTC as well as prescriptions products within the covered channels, although coverage for OTC products is substantially less than that for prescription products, due to warehouses that do not handle prescription products and are thus not in scope for NSP. NSP

estimates for OTC products have been assessed to represent roughly 50% of the total OTC purchases in the covered channels.

NSP estimated product sales to outlets include any product purchased by outlets that is diverted for non-legitimate use.

NSP thus provides a foundation from which to develop a total Ephedrine/Pseudoephedrine usage estimate, given appropriate adjustments for completeness and legitimate use. The following illustrates the approach utilized for generating an estimate of legitimate Ephedrine and Pseudoephedrine use from NSP purchase volume estimates.



The steps used in generating the Outlet Purchase Data-based Estimate of Ephedrine and Pseudoephedrine 2005 legitimate use are as follows:

1) Extract NSP Ephedrine/Pseudoephedrine Unit Estimates by Product Package

All product packages containing Ephedrine and/or Pseudoephedrine were identified from IMS Health's (IMS) product master file. This file contains a total of 400 NDCs for product packages containing Ephedrine and 4,792 NDC's for product packages containing Pseudoephedrine (see Excel file attached – NDCs with Ephedrine Compound Weight/pEphedrine Compound weight >0). Of these product packages, there were a total of 54 NDCs for product packages containing Ephedrine and 2,029 NDC's for product packages containing Pseudoephedrine for which either sales or prescription activity was seen in NSP or NPA (see Excel file attached – NDCs with Activity=Y). NSP monthly estimates of unit (e.g., pills) outlet sales by channel for the period of January 2004 through March 2006 were extracted for all Ephedrine and Pseudoephedrine product packages.

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2) Convert Estimated Units to Estimated Weight (in grams) by Product Package

Measures across product packages were normalized using the base weight, in grams, of the Ephedrine or Pseudoephedrine molecule (e.g., the weight, in grams, of Pseudoephedrine in Novafed), using information from IMS Health's (IMS) product master file as to the weight of the Ephedrine or Pseudoephedrine compound contained in the product and information from DEA as to the proportion of the compound attributable to the Ephedrine or Pseudoephedrine molecule (see Excel file attached in section A1 above).

3) Summarize Estimated Weight (in grams) Across Product Packages

Estimated weights were summed across product package and months to channel (Retail – Chain, Independent, Food stores – and Other – Mail Service, Non-federal hospitals, Federal Facilities, Long-term Care Facilities, Clinics, HMOs, Home Healthcare, and Miscellaneous) and product type (Rx, OTC) for each molecule. The following are the results for 2005:

2005 Outlet Sales Estimates
Source: IMS Health's National Sales Perspective
Volume in Million Grams

	Ephedrine Product Type		Pseudoephedrine Product Type	
Channel	OTC	Rx	OTC	Rx
Retail	0.928	0.006	168.261	75.826
Other	0.005	0.300	5.626	19.012

4) Estimate NSP Completeness Rates

The underlying assumption is that NSP estimates are unbiased for Rx products and for OTC products within other than Retail channels. Adjustment for NSP completeness is thus limited to the OTC product type within the Retail channel, as this represents the product area and channel where IMS Health's (IMS) data sources do not cover the full universe of interest for this project.

Measures of full coverage for OTC products in the Retail channel are obtained from NPA (restricted to OTC products), ST, and HS (refer to Section B for a description of these data sources).

a) NPA and ST quarterly estimates of unit (e.g., pills) consumer purchases for the period 1Q 2005 through 1Q 2006 were extracted for all Ephedrine and Pseudoephedrine product packages, and normalized to weight (in grams) as described in step A2 above, then summarized to across product packages to source (NPA, ST) for each molecule.

b) ST results were then adjusted to account for completeness (mass merchandisers not included in the ST universe and non-covered channels (e.g., convenience stores)), based upon a comparison to 2005 estimated consumer purchases obtained from HS – completeness was estimated to be 47.6% for Pseudoephedrine products and 61.6% for Ephedrine products.

c) NSP quarterly estimated OTC product weights were compared to combined NPA and adjusted ST quarterly estimated OTC product weights, with the median ratio of NSP to NPA/ST used as the estimated completeness for NSP for 2005. The results were as follows:

2005 Estimated NSP Completeness Rates

	Ephedrine			Pseudoephedrine		
	NSP	NPA/ST	Completeness Rate	NSP	NPA/ST	Completeness Rate
1Q2005	0.233	0.831	28.0%	55.684	77.161	72.2%
2Q2005	0.229	0.789	29.0%	41.953	54.292	77.3%
3Q2005	0.215	0.760	28.3%	29.538	39.545	74.7%
4Q2005	0.252	0.804	31.3%	41.086	48.740	84.3%
1Q2006	0.197	0.753	26.2%	36.457	47.954	76.0%
Median			28.3%			76.0%

5) Adjust NSP for Estimated Completeness Rates

The estimated completeness rates were applied to the NSP estimated Retail OTC product weights, yielding the following:

2005 Outlet Sales Estimates
Adjusted for NSP Completeness Rates
Volume in Million Grams

	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Retail	3.279	0.006	221.324	75.826
Other	0.005	0.300	5.626	19.012

6) Estimate Impact of Sales Restrictions on Usage

The underlying assumption is that trends in Ephedrine and Pseudoephedrine product usage in states that have enacted restrictions on sales of these products provide an appropriate proxy for the relationship between overall and legitimate use of Ephedrine and Pseudoephedrine. State sales data over time were examined using DDD information.

IMS Health's (IMS) Drug Distribution Data (DDD) provides monthly pharmaceutical product purchases, in units and dollars, for outlets that dispense products through prescriptions and/or physician orders. IMS Health (IMS) obtains data from two basic sources encompassing roughly 85% of the total U.S. pharmaceutical sales volume: approximately 265 warehouses that supply indirect pharmaceutical purchases by outlets; and approximately 100 manufacturers that report direct purchase by outlets (the same data source as is used for NSP). Data are reported and maintained at the product package level for each outlet.

a) DDD monthly data on unit (e.g., pills) outlet consumer purchases for the period November 2003 through March 2006 were extracted for all Ephedrine and Pseudoephedrine product packages, and normalized to weight (in grams) as described in step A2 above, then summarized to across product packages and outlets within state to channel (Retail, Other) and product type (Rx, OTC) for each molecule.

b) State level weight data were aggregated to rolling three (3) month levels. Year-over-year ratios were calculated for each molecule/product type/channel/state/month for the period January 2005 through March 2006.

c) Based upon an examination of the year-over-year ratios, in conjunction with information on sales restrictions (see attached Excel file – DEA Enacted Regulations), it was determined that impact of sales restrictions were seen beginning with the rolling three (3) month period ending three (3) months after the quarter in which sales restrictions were enacted.

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To derive an estimated impact of sales restrictions:

i. For each state in which sales restrictions were enacted, the difference between state and benchmark ratios (year-over-year ratios of aggregated weight data for states which had not enacted sales restrictions as of 1Q 2006) were derived.

ii. For each month, September 2005 through March 2006, the median difference across states for which the three month lag period had been passed was calculated.

iii. The median of the monthly median differences was derived and used as the expected impact of sales restrictions. The results were as follows:

Estimated Impact of Sales Restrictions on Ephedrine/Pseudoephedrine Total Outlet Sales

Molecule	Ephedrine				Pseudoephedrine			
Product Type	Rx		OTC		Rx		OTC	
Channel	Retail	Other	Retail	Other	Retail	Other	Retail	Other
Month	Median difference in year-over-year relative outlet sales weights: restrictions - no restrictions							
Sep 05	71.1%	-2.0%	9.6%	-45.2%	5.0%	5.1%	-9.7%	-9.0%
Oct 05	6.7%	0.6%	17.8%	-45.2%	9.6%	0.8%	-22.0%	-18.3%
Nov 05	-18.9%	-2.7%	37.8%	-25.9%	10.5%	4.3%	-23.0%	-17.9%
Dec 05	-14.6%	-4.1%	32.7%	-69.4%	8.6%	4.3%	-21.4%	-15.0%
Jan 06	-18.3%	-5.1%	39.3%	-39.5%	9.2%	7.2%	-25.0%	-10.8%
Feb 06	-11.9%	-5.7%	23.7%	-52.1%	5.4%	6.0%	-22.0%	-10.0%
Mar 06	8.5%	-2.8%	19.9%	-56.7%	1.6%	8.4%	-18.7%	-4.9%
Median	-11.9%	-2.8%	23.7%	-45.2%	8.6%	5.1%	-22.0%	-10.8%

d) As some states had already experienced some part of the impact of sales restrictions, the net impact relative to NSP estimated 2005 national product weights was adjusted based upon distribution of DDD state level product weights and timing of the state sales restrictions. It was assumed 25% of the impact had already been reflected in the sales data

for a state, for each quarter prior to 4Q 2005 that the state enacted sales restrictions. As a result, the overall estimated impact of sales restrictions were adjusted as follows for application to NSP 2005 outlet sales estimates:

Estimated Impact of Sales Restrictions on Ephedrine/Pseudoephedrine NSP 2005 Outlet Sales

Molecule	Ephedrine				Psuedoephedrine			
Product Type	Rx		OTC		Rx		OTC	
Channel	Retail	Other	Retail	Other	Retail	Other	Retail	Other
	Estimated impact of sales restrictions on Ephedrine/Pseudoephedrine outlet sales							
	-11.9%	-2.8%	23.7%	-45.2%	8.6%	5.1%	-22.0%	-10.8%
Sales Restriction Enactment	Estimated distribution of Ephedrine/Pseudoephedrine outlet sales by sales restrictions enactment							
1Q2005	0.6%	1.8%	2.4%	2.5%	2.6%	1.9%	1.7%	1.3%
2Q2005	6.2%	9.0%	7.5%	6.6%	10.6%	14.5%	7.8%	7.5%
3Q2005	54.5%	25.2%	24.4%	27.3%	36.1%	21.8%	24.9%	22.0%
4Q2005 forward	38.8%	64.0%	65.7%	63.5%	50.7%	61.8%	65.6%	69.2%
	Net estimated impact of sales restrictions on Ephedrine/Pseudoephedrine NSP 2005 outlet sales							
	-9.9%	-2.4%	20.9%	-39.7%	7.2%	4.4%	-19.5%	-9.7%

7) Estimate Net 2005 Ephedrine/Pseudoephedrine legitimate Use

The estimated impact of sales restrictions on NSP 2005 outlet sales were then applied to the 2005 outlet sales adjusted for NSP completeness, yielding estimated totals of 284.4 million grams of Pseudoephedrine and 4.3 million grams of Ephedrine as the legitimate medical use volumes for 2005.

2005 Outlet Sales Estimates
Adjusted for NSP Completeness Rates, Restricted Sales Impact
Volume in Million Grams

	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Retail	3.964	0.006	178.182	81.294
Other	0.003	0.292	5.083	19.830
Total Product		4.265		284.389

B. Consumer Purchase Data-based Estimate (Base Sources: NPA, ST, HS; Ancillary Sources: NSP, DDD)

IMS Health's (IMS) National Prescription Audit (NPA) provides national level weekly and monthly estimates of dispensed prescription volumes, in prescription, units and dollars, for retail (chain, independent, and food stores), mail service, and long-term care pharmacies. Estimates are generated at the product/form/strength level within each of several channels (chain – including mass merchandiser – pharmacies, independent pharmacies, food stores with pharmacies, mail service

pharmacies, and long-term care pharmacies). IMS Health (IMS) obtains data from roughly 80 chain pharmacy organizations and pharmacy software vendors encompassing over 36,000 pharmacies accounting for over 70% of the total U.S. pharmacy prescription volume. The set of sample retail pharmacy data are sub sampled by pharmacy to represent the universe distribution by state and poverty status within Census division, pharmacy type (chain, independent, food store), and pharmacy size (small, medium, large), yielding a sample size of roughly 22,000 retail pharmacies accounting for approximately 45% of the total U.S. retail pharmacy prescription volume. All sample mail service pharmacies (approximately 80, accounting for roughly 76% of the total U.S. mail service pharmacy prescription volume) and all sample long-term care pharmacies (over 600, accounting for roughly 50% of the total U.S. long-term care pharmacy prescription volume) are included in the NPA sample. Data are projected to represent national totals at the product/form/strength level within each channel.

ACNielsen's Scantrack (ST) provides national and selected market level weekly estimates of product sales (not including prescriptions), in units and dollars, made by retail pharmacies, food stores, and mass merchandisers. Estimates are generated at the product package level. ACNielsen obtains data from over 4,800 stores representing more than 800 retailers in 52 major markets. Data are projected to represent national and market totals at the product package level.

ACNielsen's Homescan (HS) provides national level annual estimates of product purchases (not including prescriptions), in units and dollars, made by households. Estimates are generated at the product package level. ACNielsen utilizes a panel of approximately 125,000 households in the U.S. that reports data on consumer goods purchases for in home use. Data are projected to represent national totals at the product package level.

ST and HS data are collected at the UPC level. The Excel spreadsheet below contains a list of the UPCs for which volume was reported in ST (787) and/or HS (160).

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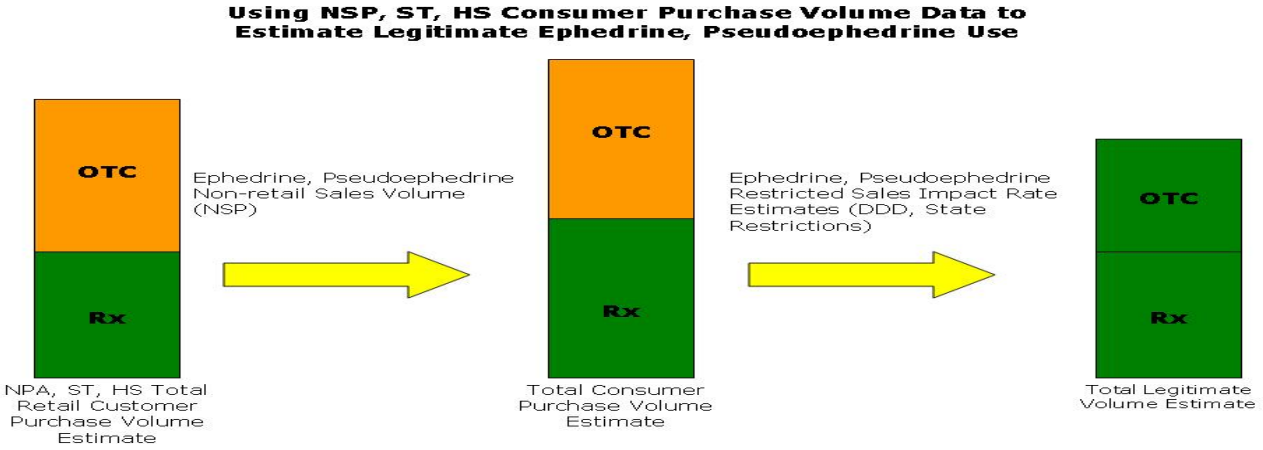
NPA, ST, and HS estimates can be integrated so as to provide a complete picture of consumer purchase activity, encompassing both prescription and over-the-counter purchases, for retail channels (retail pharmacies, food stores, mass merchandisers, convenience stores, etc.). The estimates from these services would not cover purchases in non-retail channels (hospitals, clinics, etc.). In addition, the estimated consumer purchases include any product purchased by consumers that is diverted for non-legitimate use.

NPA, ST, and HS thus provide a foundation from which to develop total Ephedrine and Pseudoephedrine usage estimates, given appropriate adjustments for non-covered channels and legitimate use. The following illustrates the approach utilized for generating an estimate of legitimate Ephedrine and Pseudoephedrine use from combined NPA, ST, and HS purchase volume estimates.



The steps used in generating the Consumer Purchase Data-based Estimate of Ephedrine and Pseudoephedrine 2005 Legitimate Use are as follows:

1) Extract NPA, ST, and HS Ephedrine/Pseudoephedrine Unit Estimates by Product Package

All product packages containing Ephedrine and/or Pseudoephedrine were identified from IMS Health's (IMS) product master file (refer to Section A1). NPA monthly estimates of unit (e.g., pills) prescription volumes by channel for the period January 2004 through March 2006 were extracted for all Ephedrine and Pseudoephedrine product packages. ST Quarterly estimates of unit consumer purchase volumes for retail pharmacies/ food stores/mass merchandisers for the period 1Q 2005 through 1Q 2006 were extracted for Ephedrine and Pseudoephedrine product packages. HS 2005 annual estimates of unit consumer purchase volumes were extracted for Ephedrine and Pseudoephedrine product packages.

2) Convert Estimated Units to Estimated Weight (in grams) by Product Package

Measures across product packages were normalized to weight, in grams, of the Ephedrine or Pseudoephedrine molecule as described in Section A2.

3) Summarize Estimated Weight (in grams) Across Product Packages

Estimated weights were summed across product package and months/quarters to channel (Retail prescriptions – from NPA; Retail over-the-counter – from ST; Convenience, etc. – from HS) and product type (Rx, OTC) for each molecule. The following are the results for 2005:

2005 Consumer Purchase Estimates Based on NPA, ST, HS Estimates Volume in Million Grams				
	Ephedrine Product Type		Pseudoephedrine Product Type	
Channel	OTC	Rx	OTC	Rx
Retail				
Prescriptions	0.002	0.065	2.486	73.913
Over-the-counter	3.029	n/a	188.891	n/a
Convenience,etc	0.134	n/a	5.985	n/a

4) Adjust for Non-covered Channels

As the combined NPA/ST/HS estimated consumer purchase volumes do not encompass non-retail (e.g., hospital, clinic) consumer purchases, NSP estimated outlet sales volumes for other channels as described in Section A3 were used to account for the non-covered channels.

2005 Consumer Purchase Estimates Including Other Channels from NSP Volume in Million Grams				
	Ephedrine Product Type		Pseudoephedrine Product Type	
Channel	OTC	Rx	OTC	Rx
Retail				
Prescriptions	0.002	0.065	2.486	73.913
Over-the-counter	3.029	n/a	188.891	n/a
Convenience,etc	0.134	n/a	5.985	n/a
Other	0.005	0.300	5.626	19.012

5) Estimate Impact of Sales Restrictions on Usage

Impact of sales restrictions on usage was assumed to be the same as those estimated in Section A6.

Estimated Impact of Sales Restrictions on Ephedrine/Pseudoephedrine NSP 2005 Outlet Sales

Molecule	Ephedrine				Psuedoephedrine			
Product Type	Rx		OTC		Rx		OTC	
Channel	Retail	Other	Retail	Other	Retail	Other	Retail	Other
	Estimated impact of sales restrictions on Ephedrine/Pseudoephedrine outlet sales							
	-11.9%	-2.8%	23.7%	-45.2%	8.6%	5.1%	-22.0%	-10.8%
Sales Restriction Enactment	Estimated distribution of Ephedrine/Pseudoephedrine outlet sales by sales restrictions enactment							
1Q2005	0.6%	1.8%	2.4%	2.5%	2.6%	1.9%	1.7%	1.3%
2Q2005	6.2%	9.0%	7.5%	6.6%	10.6%	14.5%	7.8%	7.5%
3Q2005	54.5%	25.2%	24.4%	27.3%	36.1%	21.8%	24.9%	22.0%
4Q2005 forward	38.8%	64.0%	65.7%	63.5%	50.7%	61.8%	65.6%	69.2%
	Net estimated impact of sales restrictions on Ephedrine/Pseudoephedrine NSP 2005 outlet sales							
	-9.9%	-2.4%	20.9%	-39.7%	7.2%	4.4%	-19.5%	-9.7%

6) Estimate Net 2005 Ephedrine/Pseudoephedrine Legitimate Use

The estimated impact of sales restrictions were then applied to the estimated 2005 consumer purchases, yielding estimated totals of 263.0 million grams of Pseudoephedrine and 4.2 million grams of Ephedrine as the legitimate use volumes for 2005.

2005 Consumer Purchase Estimates
Adjusted for non-Covered Channels, Restricted Sales Impact Rates
Volume in Million Grams

	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Retail				
Prescriptions	0.003	0.058	2.002	79.243
Over-the-counter	3.662	n/a	152.071	n/a
Convenience,etc	0.163	n/a	4.818	n/a
Other	0.006	0.270	4.530	20.383
Total Product		4.161		263.046

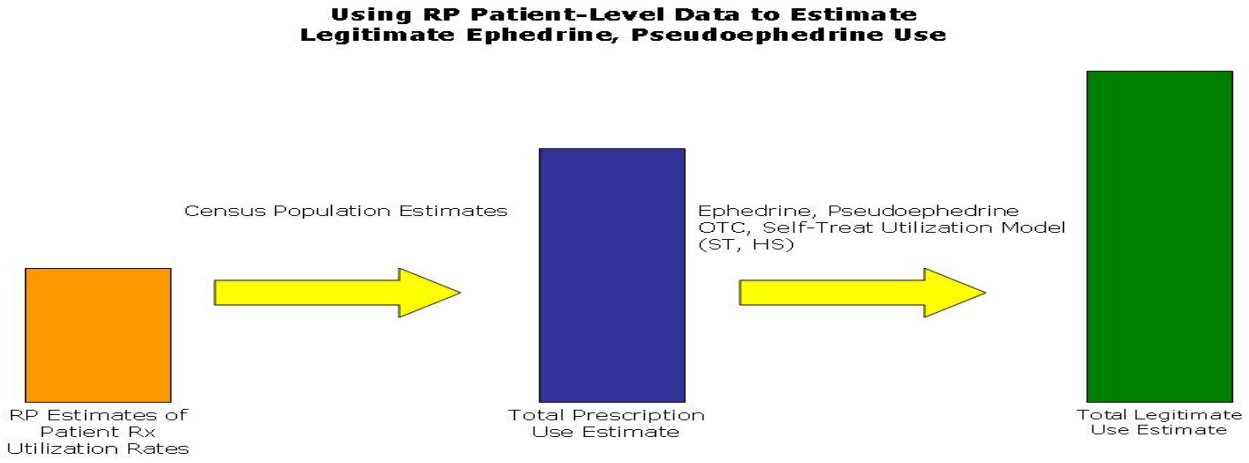
C. Patient Data-based Estimate (Based Source: ReferencePoint, Ancillary Sources: NDTI, Census Population Estimates, ST, HS, and DDD)

IMS Health's (IMS) ReferencePoint (RP) provides de-identified, patient-level data obtained from a federal health plan encompassing HMO, PPO, and fee-for-service, and includes information relative to health encounters and prescription drug use that is specific to over 9 million beneficiaries, located in both the continental U.S. as well as federal facilities abroad. The database consists of de-identified patient longitudinal Encounter, Enrollment & Eligibility, and Pharmacy data, as well as a subset of Laboratory and Radiology resultant information. The ReferencePoint (RP) database contains, prescription drug and biologic utilization information, including the generic and brand name of the product, strength, dosage form, days supply, all dates dispensed, initial/continuing therapy indicator, quantity dispensed, and prescriber specialty, and prescribing location for every outpatient fill in a federal facility or any retail pharmacy transaction in which the federal health plan was billed all or any part of the prescription cost.

RP data can be used to estimate Ephedrine and Pseudoephedrine prescription utilization rates for the covered population. The utilization rates would not cover over-the-counter purchases.

RP thus provides a foundation from which to develop total Ephedrine and Pseudoephedrine usage estimates, given adjustments to the full population and for over-the-counter purchases associated with legitimate use. The following illustrates the approach utilized for generating an estimate of legitimate Ephedrine and Pseudoephedrine use from RP patient-level data.

The following illustrates the approach planned for generating an estimate of legitimate Ephedrine and Pseudoephedrine use from NDTI estimates.



The steps used in generating the Patient Data-based Estimate of Ephedrine and Pseudoephedrine 2005 Legitimate Use are as follows:

1) Identify Diagnoses for which Ephedrine and Pseudoephedrine Products are Prescribed

To provide detailed utilization rates, examination by diagnosis is desired. A list of diagnoses was developed through use of NDTI information.

IMS Health's (IMS) National Disease and Therapeutic Index (NDTI) provides national level monthly and quarterly estimates of disease and treatment patterns occurring in physician offices. In addition, estimates of the total number of patient visits for diseases associated with legitimate Ephedrine and Pseudoephedrine use are available. Estimates of diagnoses and prescription drug treatment are generated for each of 30 group specialties that primarily diagnose and treat disease. IMS Health (IMS) obtains data from a sample of 1,373 office-based physicians per month, for a total of 4.120 per quarter. The total universe of office-based physicians in the specialty groups of interest is roughly 462,000. Data are projected to represent national totals by group specialty.

ICD-9 CM diagnosis codes associated with therapeutic categories containing Ephedrine and Pseudoephedrine products were identified using 2005 NDTI estimates. When multiple 4-digit diagnoses within the same 3-digit diagnosis, the 3-digit diagnosis code was identified, with all 4-digit diagnoses in-scope. The resulting list of ICD-9 CM's is contained in the attached Excel file.

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2) Extract RP Patient Data

All patients within the RP database with either a diagnosis record for FY 2005 (October 2004 - September 2005) in the in-scope list or a prescription transaction for FY 2005 in the list of product packages containing Ephedrine and/or Pseudoephedrine as identified from IMS Health's (IMS) product master file (refer to Section A1). Total RP FY 2005 unit (e.g., pills) prescription volumes for the period Oct 2004 through Sep 2005 were extracted for all Ephedrine and Pseudoephedrine product packages, and linked with diagnoses of interest.

3) Convert Units to Weight (in grams) by Product Package

Measures across product packages were normalized to weight, in grams, of the compound containing Ephedrine or Pseudoephedrine as described in Section A2.

4) Summarize Weight (in grams) Across Product Packages

Weights were summed across product package to diagnosis and total levels within product type (Rx, OTC) for each molecule. Patient counts were also determined for each diagnosis. Following are the FY 2005 results for total and the leading diagnoses associated with Ephedrine and Pseudoephedrine usage within the RP population. Note that patients and utilization could be counted for multiple diagnoses.

Patient Rx Utilization for 12 months Ending Sep 2005
Based on RP Data
Volume in Million Grams, Patients in Thousands

	Ephedrine				Pseudoephedrine			
	OTC		Rx		OTC		Rx	
ICD-9 CM	Patients	Volume	Patients	Volume	Patients	Volume	Patients	Volume
All	0.0	0.0	1.0	0.4	412.4	687.3	841.3	5,088.3
465.9-Acute upper respiratory infections of mulitiple or unspecified sites: Unspecified site	0.0	0.0	0.5	0.1	199.0	281.8	349.3	1,449.5
477.9-Allergic rhinitis: Cause unspecified	0.0	0.0	0.2	0.1	74.7	171.6	151.4	1,378.2
461.9-Acute sinusitis: Unspecified	0.0	0.0	0.2	0.0	41.0	79.4	128.9	879.0
462-Acute pharyngitis	0.0	0.0	0.3	0.1	64.1	97.1	126.3	606.7
466.0-Acute bronchitis	0.0	0.0	0.2	0.0	33.2	59.8	105.4	632.7
473.9-Unspecified sinusitis (chronic)	0.0	0.0	0.1	0.0	29.1	65.8	77.5	595.4
786.2-Symptoms involving respiratory system and other chest symptoms, cough	0.0	0.0	0.2	0.1	41.5	70.2	95.6	581.7
No ICD-9CM of interest	0.0	0.0	0.2	0.2	74.7	134.5	132.3	1,041.1

5) Estimate Per Person Rx Utilization

Per person annual utilization rates were derived within product type for each molecule at the total level, by dividing the total patient utilization by the total number of beneficiaries encompassed by the RP database (9.2 million). The following are results for FY 2005:

Patient Rx Utilization for 12 months Ending Sep 2005 Based on ReferencePoint Data				
Total beneficiaries (000,000)	9.2			
	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Total Rx Usage (000,000 grams)	0.000	0.000	0.558	4.130
Annual Rx Usage per Beneficiary (grams)	0.000	0.000	0.061	0.451

6) Estimate Total U.S. Annual Rx Utilization

Per person utilization rates were multiplied by the July 1, 2005 estimated U.S. population (296.4 million), obtained from the U.S. Census Bureau website, to derive an estimate of the annual Rx utilization for Ephedrine and Pseudoephedrine. Following are the results:

Estimated Total Rx Utilization for 12 months Ending Sep 2005 Adjusted for 2005 U.S. Population Volume in Million Grams				
Total population (000,000)	296.4			
	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Total Rx Usage	0.001	0.011	18.019	133.406

7) Adjust for Over-the-counter Purchase Volume

As the RP data do not encompass over-the-counter consumer purchases, ST and HS estimated consumer purchase volumes, adjusted for legitimate medical use, as described in Section B6 were used to account for over-the-counter legitimate use.

2005 Consumer OTC Purchase Estimates Adjusted for Restricted Sales Impact Rates Based on ACN POS, Homescan Estimates Volume in Million Grams				
	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Retail	3.825	0.000	156.890	0.000

8) Estimate Net 2005 Ephedrine/Pseudoephedrine Legitimate Use

The over-the-counter legitimate medical use estimates were then added to the estimated 2005 patient Rx utilization estimates, yielding estimated totals of 379.1 million grams of Pseudoephedrine compounds and 3.5 million grams of Ephedrine compounds as the legitimate medical use volumes for 2005.

Estimated Total 2005 Utilization
Adjusted for Restricted Sales Impact Rates
Volume in Million Grams

	Ephedrine		Pseudoephedrine	
	OTC	Rx	OTC	Rx
Rx	0.001	0.011	18.019	133.406
OTC	3.825	0.000	156.890	0.000
Total Product		3.836		308.315

D. Integrated Estimate of 2005 Ephedrine and Pseudoephedrine Legitimate Use

The three (3) estimates presented are to be weighted based upon assessment of their relative uncertainty. Based upon the sensitivity analysis (Section E) a weighted average, with the weights differing for Ephedrine and Pseudoephedrine, is recommended. The weights reflect the relative differences in uncertainty among the three (3) models. The recommended weighting yielding totals of 280.3 million grams of Pseudoephedrine and 4.1 million grams of Ephedrine as the estimated 2005 legitimate medical use volumes.

Estimated Total 2005 Ephedrine and Pseudoephedrine Legitimate Use
Volume in Million Grams

Component	**Ephedrine**	**Weight**	**Pseudoephedrine**	**Weight**
Outlet Sales-based	4.265	0.358	284.389	0.588
Consumer Purchases-based	4.161	0.326	263.046	0.309
Patient Data-based	3.836	0.316	308.315	0.103
Simple Average	4.087		285.250	
Weighted Average	4.096		280.268	

E. Sensitivity Analysis of 2005 Ephedrine and Pseudoephedrine Legitimate Use

The three (3) estimates presented (Outlet Sales, Consumer Purchases, Patient Utilization) are based upon observed data and models assumed to hold for Ephedrine and Pseudoephedrine usage. To provide some quantification of the level of uncertainty in the estimates, further assessment was carried out using additional information and modifying model assumptions. Modifications were made generally to offer more conservative (larger) estimates, one at a time, and then cumulatively (i.e., all of the modifications made at once).

In summary, the sensitivity analysis indicates that the Pseudoephedrine legitimate medical use estimate is very stable, as the sensitivity estimates differ from the simple average of the component final estimates by at most 7.7%. The Ephedrine legitimate medical use estimate is relatively unstable, as the sensitivity estimates differ from the final estimate by as much as 46.5%. The majority of this instability comes from taking a conservative view of which products are in-scope. However, even with this broad relative range, the estimated Ephedrine legitimate medical use volume is at most 6.0MM grams.

Examining the variability among the alternative estimates indicated that, for Ephedrine volume, there was little difference in the stability among the models while, for Pseudoephedrine, the Outlet Sales model was much more stable than the other two models and the Patient Utilization model was much less stable than the other two models. The observed differences led to the weights provided in the previous table, with roughly equal weighting for Ephedrine and weight ratios of roughly 6:3:1 (Outlet Sales, Consumer Purchases, and Patient Utilization) for Pseudoephedrine.

Estimated Total 2005 Ephedrine and Pseudoephedrine Legitimate Use Volume in Million Grams		
Component	**Ephedrine**	**Pseudoephedrine**
1. Assuming NSP Completeness Rate is Minimum across 5 Quarters		
Outlet Sales-based	4.592	293.916
Consumer Purchases-based	4.161	263.046
Patient data-based	3.836	308.315
Simple Average	4.196	288.426
2. Including non-matched Products Possibly Containing Ephedrine		
Outlet Sales-based	5.765	284.389
Consumer Purchases-based	5.622	263.046
Patient data-based	5.296	308.315
Simple Average	5.561	285.250
3. Assuming Convenience Stores, etc., Channel = 7.7% of Retail + Convenience		
Outlet Sales-based	4.412	292.063
Consumer Purchases-based	4.304	270.914
Patient data-based	4.577	356.075
Simple Average	4.431	306.351
4. Assuming Convenience Stores, etc., Channel = 15% of Retail + Convenience		
Outlet Sales-based	4.762	305.865
Consumer Purchases-based	4.903	285.064
Patient data-based	4.577	330.333
Simple Average	4.747	307.087
5. Assuming Patient Utilization is Diagnosis Related		
Outlet Sales-based	4.265	284.389
Consumer Purchases-based	4.161	263.046
Patient data-based	3.840	317.181
Simple Average	4.089	288.205
6. Assuming All Scenarios (7.7% Convenience Store Percentage)		
Outlet Sales-based	6.512	302.453
Consumer Purchases-based	5.886	270.914
Patient data-based	5.565	325.049
Simple Average	5.988	299.472

The first modification made was to the estimated NSP completeness rate (labeled “1. Assuming NSP Completeness Rate is Minimum across Five (5) Quarters“). While the implementation model used the median completeness rates across five (5) quarters (28.3% for Ephedrine and 76.0% for Pseudoephedrine), the sensitivity model used the minimum completeness rates across the five (5) quarters (26.2% for Ephedrine and 72.2% for Pseudoephedrine). This modification yielded increased estimated legitimate medical use volumes from the Outlet Sales data-based model for both Ephedrine and Pseudoephedrine.

The second modification (labeled “2. Including non-matched Products Possibly Containing Ephedrine”) was include volume for products on the ST file with a product name indicating they possibly contained Ephedrine, but which were not found on the list of UPCs containing Ephedrine (e.g., Stacker 2, Slimspa EPH TB AS,), yielding an additional 1.2MM grams of Ephedrine use. This modification also affected

the NSP Ephedrine completeness rates (20.5%). This modification yielded increased estimated legitimate use volumes for Ephedrine from all three (3) components.

The third modification (labeled "3. Assuming Convenience Stores, etc., Channel = 7.7% of Retail + Convenience") was to adjust the volume in the convenience store, etc., channel to be 7.7% of the total retail + convenience store, etc., channels, This is the percentage determined by Robbins to represent sales of non-prescription medications in outlets other than drugstores, supermarkets, and discount stores (from Federal Register Document 04-4127, February 25, 2004 (Volume 69, Number 37)). This increased the volume for the convenience stores, etc., channel to 0.2MM grams for Ephedrine and 9.3MM grams for Pseudoephedrine, and changed the NSP Ephederine and Pseudoephedrine completeness rates (27.3% for Ephedrine, 72.9% for Pseudoephedrine). This modification yielded increased estimated legitimate use volumes for both Ephedrine and Pseudoephedrine from all three (3) components.

The fourth modification (labeled "4. Assuming Convenience Stores, etc., Channel = 15% of Retail + Convenience") was to adjust the volume in the convenience store, etc., channel to be 15% of the total retail + convenience store, etc., channels, or roughly twice the Robbins percentage. This increased the volume for the convenience stores, etc., channel to 0.6MM grams for Ephedrine and 26.3MM grams for Pseudoephedrine, and changed the NSP Ephederine and Pseudoephedrine completeness rates, for which the minimum was used (18.6% for Ephedrine, 69.8% for Pseudoephedrine). This modification yielded increased estimated legitimate use volumes for both Ephedrine and Pseudoephedrine from all three (3) components.

The fifth modification (labeled "5. Assuming Patient Utilization is Diagnosis Related") was to adjust the Patient Utilization model to reflect per patient utilization by diagnosis, for the 8 most dominant in-scope diagnoses. This increased the total Rx volume estimate to 0.2MM grams for Ephedrine and 160.3MM grams for Pseudoephedrine. This modification yielded increased estimated legitimate use volumes from the Patient Utilization data-based model for both Ephedrine and Pseudoephedrine.

Finally, all but the fourth modification were used in combination (labeled "6. Assuming All Scenarios (7.7% Convenience Store Percentage)"). This increased the volume for the convenience stores, etc., channel to 0.4MM grams for Ephedrine and 15.8MM grams for Pseudoephedrine, and changed the NSP Ephederine and Pseudoephedrine completeness rates, for which the minimum was used (18.1% for Ephedrine, 69.0% for Pseudoephedrine).

Additionally, consideration was given to a modification using the ST data for estimating impact of sales restrictions on usage, rather than the original approach (utilizing DDD sales data). However, the estimated impact derived from the ST data yielded somewhat lower estimated usage than the original (i.e., the impact of restrictions was estimated to constrain usage more that estimated through the DDD data); therefore it was determined the original approach was providing the more conservative estimate (i.e., larger) of legitimate use.