

Appendix 2
IMS-Roche NDC Patient Methodology Comparison

Methodological Comparison: Roche FDA Quarterly Reports and IMS Patient Estimator

Background

Over the years as more Dermatologists utilized Accutane for patients with severe recalcitrant nodular acne, Roche in conjunction with the U.S. Food and Drug Administration wanted to gauge how effective these programs were in preventing and recording adverse events. In order to accomplish this, in 1991 Roche contracted with National Data Incorporated (NDC), then called Walsh America, to estimate the number of patients receiving Accutane each year going forward. By doing so, the two parties could monitor the trends in incidence of adverse events as more patients received Accutane as their therapy regimen.

Objective

The purpose of this analysis is to compare and contrast the differences between two products that estimate the number of patients on a certain drug:

IMS's Patient Estimator & NDC's Accutane Patient Projection Model

Results

It is important to point out the nature of these two products is slightly different. Both companies can estimate the number of patients on a given therapy. However, IMS's Patient Estimator is more of an 'on-demand' product where the NDC study is a much larger-scale, longitudinal study that Roche commissions each year with NDC. Both products output is virtually the same: # patients taking Drug 'X' in a given time period.

IMS and NDC both provided a definition of each product's methodology to Roche. These definitions are attached to this report (appendix).

There is one major difference between the two products. The IMS Patient Estimator uses information from *physicians* who are surveyed twice a quarter on their interactions with patients that visit their office on a particular day. The NDC (Accutane model) product is a sampling of *patients* who have filled a prescription.

Results – IMS Methodology

The IMS Patient Estimator uses two of their most prominent products, the National Prescription Audit (NPA) and the National Disease and Therapeutic Index (NDTI) audit. The number of patients is estimated by dividing the number of new prescriptions dispensed nationally (from NPA) in a year by the average number of new prescriptions each patient receives in that same year (from NDTI). Other factors are also taken into account, such as whether the drug being measured is for short-term or long-term therapy.

NPA includes three pharmacy types: retail pharmacies (over 21,000 of the 51,000 pharmacies in the U.S. are in the sample panel), mail order pharmacies (46 of the 101 estimated mail order pharmacies in the U.S. are in surveyed sample), and long-term care pharmacies (251 of the 1937 long-term care pharmacies that exist in the U.S. are in the sample). By utilizing NPA, IMS helps account for pharmacy substitution and patient non-compliance which are events that are different than what the physician intends for the patient.

NDTI is a panel of over 3400 physicians currently. It has included anywhere from 77-92 Dermatologists in its sample over the last 3½ years. NDTI measures myriad demographics and events that take place when a patient visits their physician. For the Patient Estimator, the part of NDTI that is utilized is the estimated number of new prescriptions per patient per year for a particular drug. Physicians indicate, when surveyed, whether an Rx was issued to the patient (written or phoned-in). It excludes situations such as a drug issued to the patient as a sample, hospital order, or dispensed from stock.

Results – Major Caveats IMS

1. Based on a physician audit, NOT patient data
 - a written or phoned-in Rx is not necessarily filled (can lead to higher # patient estimates)
2. Patient is counted multiple times if they see their physician more than once in a year with a prescription.
 - Accutane is considered 'short-term therapy' and assumes one visit per year; >1 visit per year by patient and they are counted as another patient (can lead to over estimation).
3. Patient is counted twice if they see a second physician for their diagnosis in a given year.
4. Only counts total patients; does NOT discern between 'new' patients and 'total' patients.
5. Only goes back to 1995 (attached methodology in appendix is in error on this issue (1993)).
6. Patient Estimator only gives patient totals for a 12-month period.
7. NDTI based on physicians filling out surveys 2 consecutive days per every 3-month period.
8. Less than 1% of practicing Dermatologists are surveyed in NDTI (92 of 9600 Derm's in 2Q2000).
9. Does not count patients whose entire course of therapy is samples, free goods, or hospital orders.
 - Roche does not sample Accutane to MD's
 - IMS does not have access to Roche internal records of free goods (indigent patients, personal use by MD, etc.).

Results – NDC/Accutane Methodology

The Accutane Patient Projection Model combines three distinct data sources to count the number of new patients and total patients on Accutane each month. This patient data is reported to the FDA every quarter.

The three sources are:

- Alpha Database* (Source Prescription Audit measures total retail prescriptions in the U.S.)
- Beta Database from PCS (3rd Party payment program tracks over 45 million patients' Rx's.)
- Roche Factory Shipments (calibrates national Rx volume to a known volume of Accutane.)

*The appendix refers to this as the 'PDS Alpha' database; name changed since.

This model calculates Accutane patients by dividing the number of total prescriptions in the U.S.(Alpha) by the number of prescriptions per active patient (Beta-PCS). An 'Active Patient' has received an Rx for Accutane in the given time period (month, quarter, or year). 'New Patients' are individuals who have not received Accutane in the 365 days preceding their initial prescription. In subsequent time periods, they are considered 'Ongoing Patients' and would be considered part of the total patients, not new patients.

By utilizing individual patient prescription records, NDS harvests large amounts of critical demographics of the Accutane-treated population. This model provides information on specific age groups of patients, sex, and new versus on-going patients. These categories of patients are provided quarterly to Roche by NDC. Because the model is patient-based, if further information is needed on certain issues (patients retreated, for example) Roche is usually able to retrieve such.

Source Prescription Audit® (SPA from NDC) has prescription data from 35,300 pharmacies in the U.S. This captures 71% of prescriptions in the known universe, and almost 61% of pharmacies (35,300 out of 58,000). This 71% of prescription's in the sample is projected to 100% of national prescription activity. In other words, SPA catches over 150 million Rx's per month and projects this to estimated national activity.

The PCS database includes at any one time 45-50 million patients. Although not all fill prescriptions in a year, approximately 15-18 million people in this database do fill a prescription. All of these patients are accounted for and then this patient activity/information is projected to the universe. In the upcoming quarter, NDC will improve their database by not capturing only PCS patients. They will use prescription card, 'point-of-sale' information. With this change Roche, through NDC, will now have prescription information on 25-30 million people that fill prescriptions each year. This new sample will include patients using various methods of payment (3rd party, Medicaid, Cash).

Results - Major Caveats NDC/Accutane Model

1. Patient prescription data comes from a third-party prescription database (PCS). Cash and Medicaid patients are projected and accounted for in TOTAL number of Accutane patients reported to the FDA, but they are not in the original sample.
 - For 3Q2000, Roche and NDC will be using a new database of patients that fill their prescriptions with all forms of payment (Cash, Medicaid, 3rd Party). It will have approximately 25-30 million patients in it as opposed to the 15-18 million that are in it now. These are patients filling ALL types of prescriptions.
2. Formulary bias may effect drugs in certain, competitive therapeutic areas when utilizing a PBM's database.
 - Accutane does not currently have generic competition and does not face large-scale competition as 3rd or 4th line therapy for severe, recalcitrant nodular acne. Therefore, this is not an issue.
3. Similar to IMS, NDC does NOT account for patients whose entire course of therapy would be provided without a prescription. However, Roche does have these measures in place.

Results – Comparison Table

<u>Measurement</u>	<u>IMS Patient Estimator</u>	<u>NDC Accutane Model</u>
Data Available Since-	1995	1991
Simple Methodology	NRx's national / (NRx/Pt./Yr.)	TRx's national / (TRx/Pt./Month)
(Sources Used)	NPA / NDTI	SPA & Roche Data / PCS
(Sample Size Numerator)	21,235 pharmacies+MO+LTC	35,300 Pharmacies+Roche data
(Sample Size Denominator)	92 Derms (3671 MD's Total)	18,074 Accutane Patients
Projected # Accutane Patients		
1998	402,760	498,799
1999	397,699	566,335
2000 (most current)	473,631 TOT.(MAT July, 2000)	542,492 Projected for 2000*
Time Periods Measured	12 month periods only	*Used New Pt's Q1 and Q2 x historical ratio Total to New Pt's.
How Sample is Surveyed	MD surveyed 2 days / quarter	Monthly, quarterly, yearly, more
Events Double-Counted	1. Patient retreated in same year 2. Patient sees a 2nd MD in year	Patient filling Rx is captured 1. Patient treated >13months ago -special run eliminates this.
Types of Patients	Total Patients	New Patients and Total Patients
Patient Method of Payment	Anyone diagnosed is included	Sample includes 3rd Party only

Conclusions

Roche continues to use the Accutane Patient Projection Model from NDC for a number of reasons, many of which relate back to the fact that NDC can track individual patient prescription information.

The current model provides more accurate information because it is using both a more *appropriate* source of information (patients who have filled Rx's) and a *larger, more representative sample* (+18,000 patients versus 80-90 physicians). Also, as it is patient-based, it helps provide more in-depth demographics on critical issues concerning trends of patients taking Accutane (new v. continuing therapy, age groups, etc.).

Since 1991 no major changes have occurred to the methods of measuring amounts of patients taking Accutane. This helps Roche and the FDA keep better track of the behaviors of the physicians prescribing, and the patients benefiting from Accutane therapy. IMS' Patient Estimator cannot look back any further than 1995.

The NDC Accutane Patient Model has three other major methodological advantages versus the IMS Patient Estimator: a smaller projection factor, variability in time periods measured, and the frequency with which subjects are measured.

Projection Factor – In the 2nd Quarter of 2000, IMS(NDTI) surveyed 92 Dermatologists and 303 Family Practitioners, the two specialties most likely to prescribe Accutane. There are a total of 9603 Dermatologists and 83,808 Family Practitioners in the United States as of March 15th, 2000 according to Clark-O'Neill. Therefore, a major factor in the equation that IMS uses to determine patients is based on a sample of less than 1% of total physicians.

In the 2nd Quarter of this year, NDC had a sample of over 18,000 Accutane patients. In this same quarter they estimated that there were almost 114,000 new Accutane patients. In other words, a significantly larger sample size is used by NDC to determine how many patients are new to Accutane therapy. This is the information that Roche submits to the FDA each quarter.

Time Periods Measured – Currently IMS' Patient Estimator can only report the number of patients on a certain drug therapy during a rolling 12-month period. Because NDC captures prescriptions being filled each day, Roche is able to report numbers of Accutane patients by various time periods be it month, quarter, year and others.

Frequency Subjects are Measured – To determine the number of new prescriptions per patient per year for a product, IMS uses NDTI. NDTI data is based on *physicians filling out surveys on two consecutive days* per quarter. For each patient a physician sees on those days, they record information on the patient, the primary diagnosis, drug therapies mentioned or prescribed, and other pertinent information.

With the NDC model, *Any day of the year* when an Accutane prescription is filled by a patient in the sample database, information is captured and used to project the number of total and new Accutane patients nationwide.

Appendix Items

1. IMS Patient Estimator – Product Level Patient Estimates Methodology
2. Accutane Patient Projection Model Review Session (NDC – ACNielsen Bases)
3. New Patient Projections – Walsh America (from most recent FDA Quarterly Report)