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# The Benefits of Chlorine Chemistry in Pharmaceuticals in the United States and Canada

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## Executive summary

Pharmaceutical products are an essential component of the almost \$3 trillion health care systems of the United States and Canada. In 2012, sales of pharmaceutical products in all settings amounted to \$345 billion in the U.S. and another \$30 billion in Canada, or \$375 billion overall. Sales of nutritional products and other sundry products are not included in these figures.

The costs of the other components of the health care system far exceeded the cost of pharmaceuticals, yet the use of pharmaceuticals can be viewed as a critical factor in reducing total health care costs as well as improving the quality of life for those who use them. Without effective and safe pharmaceutical products, patients would place greater demands on physician visits or experience longer lengths of stays in nursing homes and hospitals.

For consumers of pharmaceutical products, the direct economic gain of chlorine chemistry can be measured as the opportunity cost of the next best health care alternative. In other words, what would it cost consumers to purchase a substitute product or utilize a different treatment regime. For this analysis, we have evaluated the composition and manufacturing processes for the top-selling one hundred drugs sold in the U.S. in 2012. Chlorine chemistry is widely used in the production of these pharmaceutical products – 25% of these drugs contain chlorine in the dose form and over 60% of them use chlorine chemistry in the manufacturing process. The manufacturing process may use chlorine-containing intermediates, for example, which lose their identity during the course of building up the molecule from smaller constituents. Thus, chlorine chemistry is employed in the manufacture of 88% of the top-selling drugs – less than 12% have no association with chlorine chemistry.

For U.S. and Canadian consumers, the net direct economic benefit of chlorine chemistry in pharmaceuticals is estimated to be of the order of \$320 billion per year, a mid-range estimate lying between a lower bound of \$230 billion and an upper bound of \$640 billion. At this level, the benefits amount to about 110% of the cost of these drugs. Since effective use of pharmaceuticals improves consumers' wellbeing as well as reducing costs in the healthcare system itself, the total benefits of chlorine chemistry to consumers exceed the direct benefits estimated in this research.

This analysis validates previous research on the economic importance of chlorine chemistry in this sector and suggests that chlorine chemistry will continue to provide substantial benefits to consumers of pharmaceuticals well into the future. The benefits are extremely large relative to the amount of chlorine that is consumed to produce them.

## Introduction

Pharmaceutical products are an essential component of the health care systems in North America and around the world. It has been estimated, for example, that total expenditures for health care in the United States in 2011 amounted to nearly \$2.7 trillion<sup>[1]</sup> and that sales of prescription drugs in all settings amounted to about \$326 billion.<sup>[2]</sup> Sales of over-the-counter medicines in 2011 added a further \$19 billion to health care expenditures.<sup>[3]</sup> Total expenditures for health care in Canada in the same period amounted to about \$200 billion and sales of prescription and non-prescription drugs in all settings amounted to about \$30 billion.<sup>[4]</sup> Sales of nutritional products and other sundry products are not included in these figures.

The costs of the other components of the health care system, primarily hospital and nursing home care, medical supplies and the services of physicians and other health care professionals, far exceeded the costs of pharmaceuticals. Indeed, the use of pharmaceuticals can be viewed as a critical factor in reducing total health care costs as well as improving the quality of life for those who use them. The outpatient use of antibiotics to control bacterial infections, for example, is far less costly than the requirements for repeated visits to physicians or extended hospitalization to treat such infections. It has been estimated that appropriate use of pharmaceuticals reduces the cost of other components of the health care system by two to four times the cost of the drugs used.<sup>[5]</sup> It is also known that chlorine chemistry is heavily involved in the manufacture of pharmaceuticals and other health care products, and that consumers would incur significant costs if they were deprived of access to them.<sup>[6]</sup>

In this analysis Whitfield & Associates seeks to answer the question: what do consumers of pharmaceutical products gain by using chlorine chemistry?

## Benefits estimation methodology

For consumers of pharmaceutical products, the direct economic gain of chlorine chemistry can be measured as the opportunity cost of the next best alternative. In other words, how much would it cost consumers to purchase substitute products or utilize different treatment regimes? This cost includes not only the cost of the pharmaceuticals themselves but the cost of other components of the health care system that would be used as substitutes. Consumers of chlorine-based pharmaceuticals would have a range of health care choices if the pharmaceuticals they currently use no longer were available. These choices include:

- **Do Without Option:** Accept the absence of the chlorine-based product without the use of the next best substitute and without reliance on any of the other components of the health care system. Such a choice will decrease the consumers' health care status, reduce the quality of their lives, and will meet a high level of resistance from informed consumers. We do not believe such an option would be accepted by most consumers.
- **Use the Next Best Drug Option:** Use the next best, chlorine-free substitute pharmaceutical appropriate for the condition, without reliance on any other of the components of the health care system. In some therapeutic classes there are very few, if any, alternatives to chlorine-based pharmaceuticals, and there may be contraindications involved with the chlorine-free alternatives, meaning that there is no assurance that

1 Centers for Medicare and Medicaid Services, "National Health Expenditures – 2012."

2 Hoffman, J. et al., "Projecting future drug expenditures in the U.S. nonfederal hospitals and clinics – 2013," *American Journal Health-System Pharmacy*, Vol 70, March 15, 2013.

3 American College of Preventive Medicine, "Over-the-counter medications: use in general and special populations, therapeutic error, misuse, storage and disposal," 2011. [http://www.acpm.org/?page=OTCMeds\\_ClinRef&hhSearchTerms=otc+and+medications](http://www.acpm.org/?page=OTCMeds_ClinRef&hhSearchTerms=otc+and+medications). Accessed August 30, 2013.

4 Canadian Institute for Health Information, "National Health Information Trends, 1975-2012. Canadian costs are converted to U.S. dollars based on the average exchange rate for 2011 of 0.989.

5 F. R. Lichtenberg, *American Economic Review*, Vol 86, May, 1996, pg 384 and *Health Affairs*, Vol 20, Number 5, 2001, pg 241.

6 "Assessment of the Economic Benefits of Chlor-Alkali Chemicals to the United States and Canadian Economies," Charles River Associates, April, 1993 and "The Benefits of Chlorine Chemistry in Pharmaceuticals," Global Insight, Inc., December, 2006.

physicians would be able to prescribe a perfect substitute for the chlorine-based compound. Thus, some decrease in consumers' health care status is likely. Like the previous case, this choice would not be the preferred option for informed consumers.

- **Seek Other Options Within the Health Care System:** Use the next best pharmaceutical substitute as well as increased reliance on the remaining components of the health care system to restore patients' health care status to their previous level. This choice could involve more frequent visits to physician's offices, clinics, and hospital emergency rooms, increased lengths of hospital stays or use of nursing home facilities, increased use of home health care providers, and increased reliance on homeopathic remedies.

We believe that the third option would be the choice preferred by most consumers. This choice will lead to increased costs in the non-pharmaceutical components of the health care system as consumers attempt to restore the health care status quo ante. As we will show, these cost increases will exceed the cost savings resulting from a decrease in the cost of prescribing a smaller suite of pharmaceutical compounds.

This conclusion is based on the view that total health care costs are minimized when each component of the health care system is used most efficiently. The current availability of numerous options within each therapeutic class of pharmaceuticals insures that physicians are able to prescribe the most appropriate compound for each patient's condition, given the specific facts and circumstances of the situation. Any decrease of the range of choices for appropriate pharmaceuticals will lead to increased reliance on the use of other, less efficient components of the health care system as consumers strive to maintain their health status. It has been shown repeatedly that appropriate pharmaceutical use is more efficient economically than the unnecessary use of the other components of the health care system.<sup>[7]</sup>

The net gain by using chlorine can be estimated through the use of an appropriate economic model of the health care system. For this analysis, we use a specific economic model, the Cobb-Douglas model, to estimate the extent to which the level of the other components of the health care system would have to change in order to maintain the same level of output, if the input level from pharmaceuticals were to decrease. We describe this model in more detail in Appendix A. It should be noted that this methodology does not recognize the indirect benefits that consumers enjoy through access to chlorine-based pharmaceuticals. Indirect benefits include elements that are not considered part of the health care system such as reductions in lost work time due to prolonged illness, reduced worker compensation costs, improved productivity, improved wellbeing due to more rapid and complete recoveries from illness, improved pain management, and other quality of life benefits.

To use the Cobb-Douglas model in this manner, we need to know the current distribution of costs for pharmaceuticals and the other components of the health care system, and the extent to which the pharmaceutical cost inputs would change if chlorine chemistry were not employed.

The involvement of chlorine chemistry in pharmaceutical manufacturing is described in the next section.

**Estimated distribution of health care expenditures in the United States and Canada, 2011**  
(millions of dollars)

	<b>United States</b>	<b>Canada</b>	<b>Total</b>
Prescription Pharmaceuticals	345.0	31.6	376.6
Hospital & Nursing Home Care	1,233.9	89.6	1,323.5
Physicians and Other Costs	779.4	49.9	829.3
<b>Total costs</b>	<b>2,358.3</b>	<b>171.1</b>	<b>2,529.4</b>

Notes: (1) Prescription drug sales include sales in retail and mail-order pharmacies, clinics, nonfederal hospitals, long term care facilities, federal facilities, staff-model HMOs, home health care, and other.

(2) We exclude health care spending for government and insurance administrative costs and investment in research and development. When these costs are included, the total health care spending for the U.S. amounts to \$2,700.7 billion and C\$200.6 billion for Canada.

(3) All cost data are expressed in current U.S. dollars. Canadian costs are converted to U.S. dollars using the average exchange rate for 2011 (US\$/C\$ = .989).

Source: Centers for Medicare and Medicaid Services; Canadian Institute for Health Information; Hoffman, James et al., "Projecting future drug expenditures in U.S. nonfederal hospitals and clinics -2013, American Journal Health System Pharmacy, Vol 70, March 15, 2013; interviews with industry experts, and Whitfield & Associates estimates. © 2016 ACC

<sup>7</sup> Lichtenberg, op. cit.

## Chlorine chemistry in the manufacture of pharmaceutical compounds

The pharmaceutical industry is a dynamic and innovative industry in which companies are driven to develop new products for health care that improve upon the properties of existing compounds and extend the range of conditions that can be treated effectively with drugs. While thousands of patent-protected and generic pharmaceuticals are available to consumers, a list of the most heavily prescribed ones changes remarkably within a short time span. Not one of the top twenty selling pharmaceuticals in 1990 was among the top twenty sold in 2004, a fourteen year time span – in fact, only three of them were among the top two hundred list of 2004.<sup>[8]</sup> In the eight year time span from 2004 to 2012, only seven of the top-selling fifteen pharmaceuticals in 2004 (or their generic equivalents) were still ranked in the top one hundred in 2012. Therefore, although chlorine chemistry was shown to be very heavily involved in pharmaceutical manufacturing in 1990 and 2004, the goal of this research is to determine the extent of its current role.<sup>[9]</sup>

Whitfield & Associates obtained information on the sales of the top one hundred prescription pharmaceuticals in all settings in the United States in 2012.<sup>[10]</sup> The brand names were linked to compound names, chemical compositions and the compound's primary medical uses or indications.<sup>[11]</sup> This information was sufficient to assign each compound to the appropriate therapeutic class and to identify those with chlorine in their structure, but not to determine the extent to which chlorine chemistry may have been involved in the manufacture of the compound.

For so-called “small molecule” pharmaceuticals, information on the manufacturing processes proposed in the compound's patent was available for all but the most recently approved compounds.<sup>[12]</sup> It was necessary to search the patent literature to obtain such information on the biologics and some of the newer small molecules in the top-selling drug list.<sup>[13]</sup> Small molecules are drugs such as Lipitor® that have relatively low molecular weights and are synthesized using the techniques common in organic chemistry. Biologics are drugs such as Enbrel® and Epogen® that are produced from proteins or synthesized using recombinant DNA techniques common in biology. In some cases, the patents listed a number of possible routes for the synthesis of the compound that did not necessarily identify chlorine chemistry in the same way, or even at all. In these cases, information from other sources and judgment were used to identify the most likely route and the involvement of chlorine chemistry, if any.

The compounds in the list were then sorted into one of four groups based on the specific role of chlorine chemistry:

- Compounds that contained the hydrochloride salt in the therapeutically active form or whose dosage form contained HCl to adjust its pH;
- Compounds that contained either chlorine or bromine covalently bound to the structure of the therapeutically active form;
- Compounds for which chlorine chemistry was involved in their synthesis, either through the use of chlorine or bromine-containing intermediates or through the use of chlorine-containing solvents or other chlorine-based materials; and
- Compounds for which chlorine has no association based on information in the available sources.

8 Whitfield & Associates project files.

9 Charles River Associates, op. cit.. and Global Insight, op. cit.

10 Sources include drugs.com and IMS Health. www.drugs.com reports the retail sales for the top 100 drugs sold in the U.S. <http://www.drugs.com/top100sales>. Accessed August 13, 2013.

11 Physicians' Desk Reference, 66th edition, Medical Economics Company, 2012.

12 Pharmaceutical Manufacturing Encyclopedia, 3rd edition, William Andrew Publishing, 2006.

13 Patent information can be found at [www.uspto.gov](http://www.uspto.gov).

Bromine contained on the molecule or in the synthesis of a compound is associated with chlorine since bromine is produced commercially from bromine-rich brines using chlorine gas. The use of hydrochloric acid to neutralize basic compounds to form the hydrochloride salt is done because of its stability and availability; however, many other acidic anions might be and are used for this purpose. In addition to inorganic anions such as nitrate, phosphate, or sulfate, use of organic anions such as acetate, citrate, maleate, mesylate, oxalate and xinafoate might be physiologically acceptable alternatives, but the hydrochloride is preferred where it is used. The same logic applies to the use of HCl to control the pH of the dose of pharmaceuticals that are supplied in aqueous media suitable for injection.

Small molecule synthesis is traditionally carried out using the well-established techniques of organic chemistry. Many of the pharmaceutical compounds have complex structures involving aliphatic and aromatic components with a wide variety of side chains, heteroatom constituents and acidic and basic regimes. Many also have requirements for specific stereochemistries or crystalline forms that complicate and constrain the synthesis and purification routes that might be considered, and multi-step syntheses are usually required. Pharmaceutical chemists have developed rich libraries of approaches to the rational synthesis of such compounds, many of which utilize chlorine-containing intermediates which lose their identity during the course of building up the molecule from smaller constituents. In many cases, the most efficient, lowest cost procedure is to synthesize chlorine-containing fragments of the final compound, or a molecular target for chlorine to react with, and then build up the compound from the appropriate fragments using chlorine as a facilitator in the process.<sup>[14]</sup>

These processes are usually carried out in solution, the solvents being chosen with regard to the solubilities of the components and the requirements of the chemical reactions. Chlorinated solvents are often used as reaction media and are chosen for their chemical compatibility or ease of removal from the reaction products. In other cases, chlorinated solvents are used in the purification of intermediates or of the crude product form, extracting them (or extracting the impurities from them) from aqueous phases or preferentially dissolving the solids. Other chlorine-based materials, such as buffers and chelating agents, may also be used at various steps in the syntheses.

The manufacturing chemistries of biologics are different from those of most small molecules in that they are usually carried out in aqueous solutions and at near ambient conditions. These types of products include such materials as vaccines, polypeptide compounds of relatively low molecular weight, insulin and its various analogs, and a variety of complex compounds made by either solid or solution-phase synthesis or by recombinant DNA technology. Use of organic solvents and chlorine-containing intermediates is far less common in the synthesis pathways for these types of materials. Chlorine chemistry may be employed, however, in those steps that involve use of chlorine-based antibiotics to select for cells that have retained the required DNA-containing plasmids, in the use of HCl to control solution pHs, or in the use of certain chlorine-based detergents and chelating agents. Also, steps that use chlorinated solvents as separating or purification agents and chlorine chemistry that is used in the preparation of affinity-based synthesis or separation columns may be used in the production of biologics.

14 Dr. Alan Goldhammer, Pharmaceutical Research and Manufacturers of America, Washington, D.C.

## Chlorine chemistry in the manufacture of the top-selling 100 pharmaceuticals, 2012

Therapeutic category	Sales in category (\$ billion)	Percent of sales with			
		HCl in product or dose	Cl/Br on molecule	Chlorine in manufacture	No chlorine involvement
Cardiovascular	\$4.7	0.0%	0.0%	100.0%	0.0%
Central nervous system	\$40.9	24.8%	16.2%	41.5%	17.4%
Alimentary-metabolism	\$26.5	3.3%	4.1%	81.7%	10.9%
Respiratory	\$19.4	0.0%	36.9%	63.1%	0.0%
Anti-infectives	\$9.5	0.0%	0.0%	72.3%	27.7%
Musculo-skeletal	\$19.8	3.7%	0.0%	92.3%	3.9%
Genito-urinary	\$2.7	0.0%	0.0%	100.0%	0.0%
Cytostatics	\$12.7	14.1%	8.8%	51.8%	25.3%
Blood agents	\$10.4	7.1%	28.8%	64.0%	0.0%
Hormones	\$13.6	48.9%	0.0%	36.9%	14.2%
Antiretrovirals and miscellaneous	\$8.3	0.0%	33.9%	48.5%	17.6%
<b>Total, all categories</b>	<b>\$168.5</b>	<b>12.5%</b>	<b>12.9%</b>	<b>62.7%</b>	<b>11.9%</b>

Notes: (1) Includes anti-retroviral drugs and diagnostic agents.

(2) We did not consider the use of sodium or potassium hydroxide in this analysis. They are co-products of chlorine production and are widely used as neutralizing agents, for pH control, and for organic synthesis.

Source: IMS Health, www.drugs.com, and Whitfield and Associates estimates.

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The specific compounds in this list have changed almost completely from those evaluated in earlier studies, yet the table above demonstrates the important role that chlorine chemistry continues to play in pharmaceutical manufacture. A comparison of results from earlier studies is instructive:<sup>[15]</sup>

- 85% of the top selling drugs in 1993 use chlorine chemistry,
- 93% of the top selling drugs in 2006 use chlorine chemistry, and
- 88% of the top selling drugs in 2012 use chlorine chemistry.

This is a remarkable achievement given the dynamic nature of drug research and development.

Over 25% of the total sales of the top 100 pharmaceuticals sold in 2012 are for substances that have chlorine covalently bound to the drug compound, are used as the hydrochloride salt, or have HCl in the dose form. Another 63% of the sales are for compounds that use chlorine in their manufacture, and less than 12% of these compounds have no association with chlorine. If we simply counted the number of drugs that depend on chlorine without weighting them by sales value, we reach a similar conclusion: 85.7% of them depend on chlorine chemistry and only 14.3% have no association with chlorine.

This definition of the use of chlorine in the pharmaceutical sector is conservative since many of the compounds for which no association was found were synthesized from complex starting materials whose own syntheses may have involved chlorine in some way. In addition, we did not consider in this analysis the use of chlorine co-products – sodium hydroxide or potassium hydroxide. These products are widely used as neutralizing agents, for pH control, and for organic synthesis. While chlorine is used in all classes of pharmaceuticals, chlorine consumption for these applications amounts to less than 1.5% of total chlorine production in North America.

As shown, chlorine chemistry is used in all therapeutic categories. About 4% of the compounds evaluated (representing about 3% of total sales) used chlorine in manufacturing and as the hydrochloride. Only 12% of the compounds evaluated did not use chlorine, and almost two thirds of them by sales value were in central nervous system, anti-infective and cytostatic drug categories. More than 82% of drugs in all the other

15 Charles River Associates, op. cit and Global Insight, op. cit.

categories use chlorine chemistry, so it would be quite difficult to prescribe alternatives to them if they were not available due to differences in efficacy for specific conditions and due to possible contraindications. All top-selling drugs in the cardiovascular, respiratory, genito-urinary and blood agent categories are produced with chlorine chemistry, and it is not apparent how consumers could find acceptable substitutes. Clearly, consumers benefit from chlorine chemistry in the great majority of pharmaceuticals that they rely on. Examples of how chlorine is used for the top fifteen selling drugs are shown below.

#### Chlorine chemistry in the manufacture of the top 15 selling pharmaceuticals, 2012

Pharmaceutical product	Sales (\$ billions)	Used for the management of	HCl in product or dose	Cl/Br on molecule	Chlorine in manufacture	No chlorine involvement
Nexium®	6.0	Gastric ulcers			Yes	
Abilify®	5.9	Depression		Yes		
Crestor®	5.1	Cholesterol			Yes	
Cymbalta®	4.7	Depression	Yes			
Humira®	4.3	Rheumatoid arthritis			Yes	
Enbrel®	4.3	Rheumatoid arthritis			Yes	
Remicade®	3.9	Rheumatoid arthritis			Yes	
Copaxone®	3.6	Multiple sclerosis				No
Neulasta®	3.5	Anti-infective			Yes	
Singulair®	3.3	Asthma		Yes		
Rituxan®	3.2	Immune disorders				No
Plavix®	3.0	Blood thinner		Yes		
Atripla®	2.9	HIV		Yes		
Spiriva® Handihaler®	2.8	COPD		Yes	Yes	

Source: IMS Health National Sales Perspectives, Dec. 2012

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While only one hundred prescription pharmaceuticals were evaluated for this research, their sales represent almost 50% of total prescription drug sales in the United States. Furthermore, many of the top selling drugs evaluated in the 2006 study (or their generic counterparts) are now ranked in the remaining 50% of sales, and they have a very similar chlorine use profile. Since the use of chlorine chemistry in these compounds is high in all therapeutic classes, and is the same order of magnitude as the sample evaluated in 1993 and 2006, it is quite reasonable to assume that these results are representative of the use of chlorine chemistry in the sales of all pharmaceuticals in the United States and in Canada.

## Taking a closer look

**Anemia:** Cancers, kidney disease, and various orthopedic surgeries involving blood loss often cause anemia that leads to fatigue and, often, withdrawal from work activities. A bioengineered hormone product, erythropoietin alfa (e.g. Epogen<sup>®</sup>, Procrit<sup>®</sup>), which involves chlorine in its synthesis, helps to correct anemia by stimulating the body's production of red blood cells.

**Stomach ulcers:** Not too long ago, peptic and duodenal ulcers were major indications for surgery, hospitalization, and recovery time, with great economic consequences. Recently, new pharmacologic therapy proton-pump inhibitors (e.g. Nexium<sup>®</sup>, Prevacid<sup>®</sup>) and older drugs with H<sub>2</sub> blockers (e.g. Zantac<sup>®</sup> 75, Pepcid<sup>®</sup> AC<sup>®</sup>) and that control stomach acids, as well as antibiotic therapy for *Helicobacter pylori* infection, found to be chiefly responsible for ulcers, has helped keep people in the workplace and fully productive. All four of these products use chlorine in their manufacturing processes.

**Cholesterol:** Recognizing cholesterol's role in causing cardiovascular disease and the availability of medications to control cholesterol levels (e.g. Lipitor<sup>®</sup>, Zocor<sup>®</sup>) were a major medical breakthrough. These medications help prevent heart attacks, death from heart attacks and strokes, and hospitalizations for interventions to open arteries, and both use chlorine in their manufacturing processes.

**Diabetes:** Over 20 million people in the U.S. and Canada are diabetic. According to Dr. Andrew J. Drexler, head of the diabetes unit at Mount Sinai Medical Center in New York City, until a few years ago there were only two classes of drugs to stimulate insulin secretion: human insulin and the sulfonylureas (e.g. Amaryl). Today, there are additional classes of drugs that work against diabetes by different mechanisms: biguanides (e.g. Glucophage, Glucovance), thiazolidinediones (e.g. Avanta) and alpha-glucosidase inhibitors (e.g. Glyset). Even the modified insulin (e.g. Humalog, Lantus<sup>®</sup>) that is available today works more quickly than the regular insulin that has been in use since 1922. Of these specific drugs, Amaryl uses chlorine in its manufacture, Glucovance contains chlorine on the molecule, and Humalog and Lantus<sup>®</sup> use HCl in the dose form. Avanta and Glyset do not appear to use chlorine.

**Allergies:** The American Academy of Allergy, Asthma, and Immunology estimates that allergies are the sixth leading cause of chronic disease in the United States: over 50 million people suffer from allergies, including allergic asthma. Some estimates suggest that employers can save \$2 to \$4 for every dollar spent when non-sedating antihistamines are used rather than sedating antihistamines. Leading drugs in this category that contain chlorine on the molecule include Nasonex and Singulair<sup>®</sup>; Advair<sup>®</sup> Diskus<sup>®</sup> and Spiriva<sup>®</sup> use chlorine in the manufacturing process.

Sources: Robert H. Rubin, M.D., Health Care & Productivity (2000), pp. 2-3.; Centers for Disease Control and Prevention; National Heart Blood and Lung Institute; American Heart Association; Medstat; American Diabetes Association; American Academy of Allergy, Asthma, and Immunology.

## The benefits of chlorine chemistry in pharmaceuticals manufacture

If we assume that only 11.9% of pharmaceuticals are available (those with no association with chlorine chemistry), we can apply the Cobb-Douglas model to predict that the net gain to consumers. For consumers in the United States and Canada, the net gain amounts to about \$640 billion per year, or almost twice the cost of the affected pharmaceuticals. This multiplier is at the lower range estimated by other researchers of the general direct economic benefits of new pharmaceuticals.<sup>[16]</sup>

The magnitude of the benefits of chlorine chemistry in pharmaceuticals manufacture is sensitive to the price of pharmaceuticals, and prices can differ significantly between Canada and the United States. Some researchers estimate that prices of prescription pharmaceuticals in Canada are between 30% to 40% less than comparable products in the United States.<sup>[17]</sup> At 2012 prices, the direct gain of chlorine chemistry in Canada amounts to about \$60 billion per year, and the gain to consumers in the United States amounts to about \$580 billion per

<sup>16</sup> See F. R. Lichtenberg, *Journal of Occupational and Environmental Medicine*, Vol 47, Number 4, p. 377.

<sup>17</sup> Professor Steven Schondelmeyer, Department of Pharmaceutical Case & Health Systems, University of Minnesota.

year. This is equivalent to 1.9 times the cost of the pharmaceuticals “lost” to consumers in the United States, and about 2.1 times the cost of the pharmaceuticals “lost” in Canada.

This analysis suggests that current use of pharmaceuticals in Canada is somewhat more efficient vis-à-vis other components of the health care system than is the case in the United States. In the aggregate, a one-third reduction in the cost of pharmaceuticals would reduce the net consumer gain from 1.9 to 1.7 times the cost of the drugs, which would still be a very significant benefit. In any case, consumers would witness severe stresses in the non-pharmaceutical segments of the health care system since these sectors would have to expand their capabilities greatly to cope with the increases in patient care. If the necessary expansions could not be carried out efficiently, we expect that costs would be higher and the direct benefits of chlorine chemistry would be even higher than estimated here.

These estimates may represent an upper bound on the value of the direct benefits, however, since pharmaceutical producers have some flexibility in their manufacturing processes and might be able to take steps to reduce or possibly even eliminate the use of chlorine chemistry in some products, although this could involve significant increases in manufacturing costs and take a considerable amount of time. In fact, pharmaceutical manufacturers strive continuously to improve their manufacturing processes to increase efficiency, reduce costs, and reduce environmental impacts while insuring the production of safe and effective products through the application of current Good Manufacturing Processes.

For those compounds with chlorine on the molecule, it is highly unlikely that suitable alternatives can be found easily. For compounds that use the hydrochloride salt or that are sold with HCl in the dose, it is possible that suitable chlorine-free substitutes can be developed although with some increase in cost. If we assume that the approximately 12.5% of pharmaceutical sales for which chlorine is employed only by the presence of the hydrochloride could be substituted by compounds neutralized by other anions, only 75.6% of pharmaceutical sales would involve chlorine chemistry. Further, if we assume that the sales prices of the affected products would increase by only 2%, the Cobb-Douglas model predicts that the net gain to consumers in the United States and Canada by using chlorine would be about \$320 billion per year. This is over 110% of the cost of the chlorine-based pharmaceuticals in this category.

Reducing the use of chlorine chemistry in pharmaceuticals manufacture still further would require altering the procedures used in the synthesis of the active compounds, an extremely difficult task for those processes that are based on the use of chlorine-containing intermediates. Fewer, lower cost modifications might be made to processes that use HCl for pH adjustment, chlorine-based compounds such as chelating agents, or chlorinated solvents for separation or purification where suitable substitutes could be found. This might be accomplished more easily for biologics than for small molecule compounds, and could affect from 15% to 25% of these types of pharmaceuticals.

Making such changes would require that the safety and therapeutic equivalence of the compounds manufactured with chlorine-free chemistry be demonstrated, and that the necessary investments and operational changes be implemented in the production facilities. This would require some time and increase costs in most cases. If we assume that: (a) 20% of all compounds that currently use chlorine in their manufacture fall into this category (b) that the price increases associated with the new routes are no more than 5%, and (c) the hydrochlorides can be eliminated, then the Cobb-Douglas model predicts that the net gain by using chlorine under these circumstances would be about \$230 billion per year. This amounts to almost 90% of the cost of the currently available chlorine-based pharmaceuticals in these categories, and probably represents a lower bound on the benefits of chlorine in pharmaceuticals manufacturing.

This analysis is conservative because we did not consider the indirect gains for consumers of using chlorine. These indirect benefits include reductions in lost work time due to prolonged illness, reduced worker compensation costs, improved productivity, improved wellbeing due to more rapid and complete recoveries from illness, improved pain management, and other quality of life benefits. Thus, the total gain by using chlorine is larger than those developed in this research. It has been estimated, for example, that access to pharmaceuticals for the treatment of 47 selected medical conditions provides benefits in terms of reduced

lost time in the workplace that amount to more than eight times the cost of the drugs consumed.<sup>[18]</sup> Clearly, if such broader benefits are considered, the benefits of chlorine chemistry would far exceed \$1 trillion even at substantially lower pharmaceutical prices.

## Conclusion

Chlorine currently is used in the manufacture of at least 88% of the prescription pharmaceuticals currently sold in the United States and Canada. It is used in the production of all therapeutic classes of pharmaceutical products and in the manufacture of both small molecule and biologically-based compounds.

The net gain to consumers of prescription pharmaceuticals in the United States and Canada by using chlorine could be as high as \$640 billion per year within the health care sector alone, assuming pharmaceutical manufacturers could make no alterations to the compositions or manufacturing processes to produce these compounds and the remaining components of the health care system would not be used less efficiently. This estimate may represent an upper bound of the direct benefits of chlorine chemistry.

If pharmaceutically-active hydrochloride salts and HCl-containing dosage forms could be replaced by chlorine-free substitutes at very low cost, the net gain to consumers would total about \$320 billion per year. This gain amounts to about 110% of the costs of the affected pharmaceuticals, which is somewhat lower than earlier studies. This estimate represents a mid-range estimate of the net gain to consumers.

If we assume that pharmaceutical manufacturers could successfully eliminate the need to produce compounds such as hydrochloride salts and could modify manufacturing processes to eliminate the use of chlorine at relatively low cost, the direct gain to consumers by using chlorine would amount to about \$230 billion per year. This estimate represents a lower bound of the benefits of chlorine chemistry to United States and Canadian consumers. In all three cases, the total benefits – which include the indirect benefits – are even larger since the health, well being, and quality of life is enhanced by the appropriate use of pharmaceutical products.

The use of chlorine in the manufacture of pharmaceuticals has remained very high since the first such analysis was carried out over twenty years ago, even though the specific compounds that constitute the top-selling pharmaceuticals have changed almost completely over this time span. This suggests that chlorine will continue to provide substantial benefits to consumers of pharmaceuticals well into the future, and that the benefits are extremely large relative to the amount of chlorine consumed to produce them.

18 F.R. Lichtenberg, *Journal of Occupational and Environmental Medicine*, Vol 47, Number 4, pg 377.

## **Antibiotic resistance provides a case-in-point regarding the costs of losing access to pharmaceuticals**

It has been known for some time that bacteria can develop resistance to the effects of antibiotics, and it is now understood that this occurs by a variety of mechanisms involving either vertical or horizontal transmission of elements of one antibiotic resistant organism's genome to another. The changes acquired by these mechanisms permit formerly susceptible microorganisms to become resistant to new classes of antibiotics relatively rapidly. Resistance to tetracycline and cephalosporins became widespread within about 5 years of their introduction, for example, and acquisition of drug-resistant infections in hospitals has become a major concern.

A recent (2013) report from the U.S. Centers for Disease Control and Prevention estimates that treatment of antibiotic-resistant infections is responsible for \$35 billion of the health care costs in the United States and results in 8 million hospital day stays per year. Outbreaks of illness due to drug-resistant Salmonella and deaths due to the "superbug" methicillin-resistant Staphylococcus aureus have occurred because physicians cannot treat them effectively.

As shown in the table titled "Chlorine chemistry in the manufacture of the top-selling 100 pharmaceuticals, 2012", sales of anti-infective drugs amounted to \$9.5 billion in 2012, of which \$6.9 billion was for compounds that use chlorine in their manufacture. These drugs are still effective against a range of microorganisms, although treatment protocols may be more complex than was necessary formerly. The \$35 billion in health care costs due to the loss of previously effective antibiotics illustrates the value of those still in use, and the benefits of chlorine chemistry in pharmaceuticals.

## Appendix A<sup>[19]</sup>

### Cobb-Douglas economic model

The Cobb-Douglas economic model seeks to understand how various combinations of inputs (or factors of production) can be combined to produce goods and services in the economy. In a simple three-factor model, the production function can take on the following general form:

$$Q = f(K, L, M)$$

where Q represents the quantity of output of a particular industry, K represents the amount of capital employed in the industry, L represents the hours of labor input, and M represents the quantity of raw materials consumed. The functional form, f, represents the technological relationships used to convert the various inputs into final products or services. In more complex situations, there may be other variables as well.

The form of this model suggests that decision makers can choose different combinations of the various factors of production to achieve different levels of output. For instance, if the cost of labor rises dramatically, then capital might be substituted for labor to achieve a particular level of output. The trade-offs between factor inputs and different levels of output define the shape and key characteristics of the production process.

For practical purposes, economists have conducted numerous empirical studies of actual production relationships in a wide variety of industries using various types of production functions. At the aggregate level, these models provide useful insight regarding the inter-relationships between different combinations of inputs and the level of output.

Mathematically, we used a special case of this class of economic models defined below:

$$Q = A K^a L^b M^c$$

where A, a, b, and c are all positive constants. When  $a + b + c = 1$ , the Cobb-Douglas function exhibits two useful and interesting properties: constant returns to scale and constant elasticity of substitution. Constant returns to scale means that doubling all factors of production will result in a doubling of output. The elasticity of substitution is a measure of how easy or difficult it is to substitute one input for another.

In a simple example, suppose there are only two factors of production, labor (L) and capital equipment (K). The trade-off between these two factors of production in a Cobb-Douglas function can be depicted as a set of isoquant curves, where an isoquant curve is defined as the alternative combinations of productive inputs that can be used to produce a given level of output. The different levels of output are represented by the contour lines  $Q_1$ ,  $Q_2$ , and  $Q_3$ .

In IHS's production function model for the agricultural economy, we assume that the coefficients a, b, and c can be defined as the expenditure share of each factor input K, L, and M. This is equivalent to assuming constant elasticity of substitution among the factors of production, and we calculate:

$$a = K / (K + L + M)$$

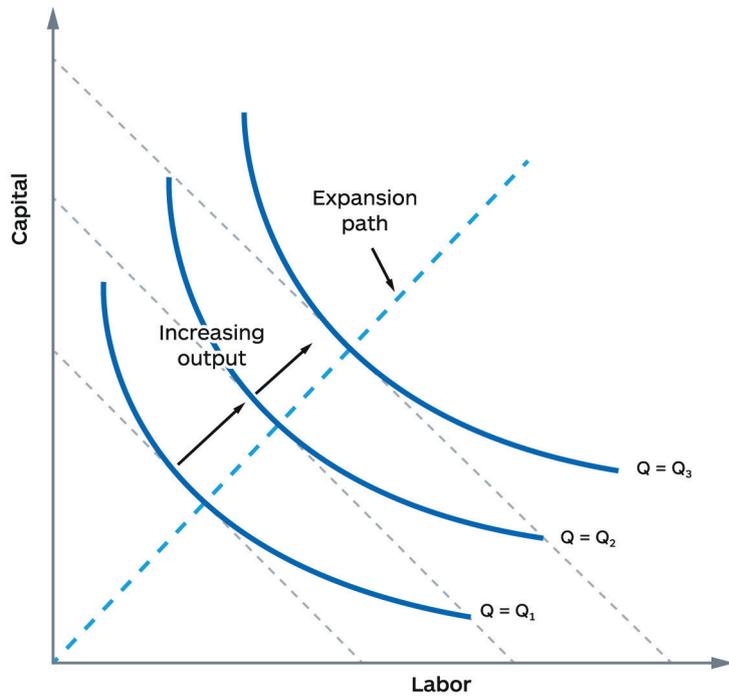
$$b = L / (K + L + M)$$

$$c = M / (K + L + M)$$

If we assume that crop protection products based on chlorine chemistry are no longer available (see text for alternative assumptions), we solve this mathematical model to estimate how much the other factors of production would have to increase in order to compensate for the loss of the chlorine-based products.

<sup>19</sup> This section has been adapted from the authors' previous research at Global Insight, Inc. op. cit.

### Cobb-Douglas production function isoquants



Source: IHS

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