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SUMMARY

Currently, AstraZeneca and Gensia Sicor/Baxter have the only propofols on the U.S. market, but Faulding/Mayne plans to introduce another within the next 3 years, and several aqueous interesting formulations are in development. However, true generics are not expected until 2015.

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PROPOFOL UPDATE

Currently, AstraZeneca and Gensia Sicor/Baxter have the only propofols on the U.S. market, but there are other propofols on the market elsewhere in the world, and a number of new formulations and generics are in development. Sources doubted that AstraZeneca and Gensia, which both use lipid-based formulations, would be very vulnerable to a new propofol unless it was a non-lipid formulation. Baxter/Gensia and AstraZeneca are both viewed as strong marketers, and they split the market almost equally. Sources speculated that a new product could sell based on a cheaper price, but a new formulation might make a new product attractive and help it take market share.

Propofol is a general anesthetic commonly used for the induction and maintenance of anesthesia during surgical procedures and as a sedative for patients who are mechanically ventilated. One of the advantages of propofol over other anesthetics is the ability to quickly adjust the amount of sedation because of propofol's short half-life. It also has a very good safety profile. As a result, propofol has become the preferred anesthetic agent for out-patient surgery.

Annual U.S. sales of propofol are estimated at about $500 million. Total global sales of propofol have been relatively flat since 1999, and sources indicated this will continue this year and beyond. A new generic entry in the U.S. market could expand the market or force prices lower – or both, depending on how it is priced.

A key issue in developing a propofol for the U.S. market is the choice of preservative. European regulators don't require that propofol have a preservative in it, but the FDA does. AstraZeneca's Diprivan uses EDTA and Gensia's Propofol uses sodium metabisulfite. Another preservative some companies have considered is benzyl alcohol (BA). A GensiaSicor source said, "The issue with BA is that it is not allowed in the pediatric market, so we always thought the constraint could be that if Bedford came with BA, it might not get an A/B rating, which is very important for substitutions. One would have to have special labeling that it is not allowed in pediatrics, which would make it very difficult logistically for hospitals. Pharmacies would have to carry two formulations, and that is where confusion and medical errors could increase. But the preservative is mostly a marketing issue."

A true generic propofol is unlikely in the U.S. before 2015, when the AstraZeneca patent expires, because all propofol in the U.S. require a microbial retardant (preservative). A Guilford researcher explained, "You could never sell a non-preserved propofol in the U.S. There were clusters of deaths from propofol contamination, and that is the reason a preservative is required. AstraZeneca worked first to educate physicians to use Diprivan according to the label – which would have prevented the deaths -- but then added EDTA and took non-preserved propofol off the market, and the clusters were no longer reported. We're not sure if deaths are still occurring, but there are not deaths at the cluster level with preserved propofol."

Gensia's propofol was filed through an ANDA and is a branded generic. A Gensia source said, "AZN helped us by pulling the original non-preserved formulation so anyone with a generic has to have a propofol formulation with a microbial retardant. The FDA does not recognize non-preserved propofol, though the rest of the world does not require a microbial retardant…What AstraZeneca didn't do which it should have done is say in its patent filing, 'Our EDTA preservative works but nothing else does.' So, we were able to make our preservative work." Thus, everything in development so far is thought to be a branded generic.

The price of propofol has been relatively stable for the last few years, and the market is growing about 10% a year. A GPO source said propofol is so cheap that it is not an especially attractive market for new entrants, but that doesn't seem to be deterring companies from working on new propofols. A Gensia source admitted there is no ability to raise pricing.

The market for lipid-emulsion propofols may evaporate within three years, making this area less appealing for new entrants, sources suggested. Several new formulations are on the horizon, and sources indicated they are likely to capture huge market share. A GPO source said, "An aqueous propofol would be a big advance." Anesthesiologists already are excited about aqueous and other new propofols. A Connecticut doctor said, "Guilford's prodrug will be an exciting advance." A Florida doctor said, "I think the new, short-acting propofol will be a lot cheaper." A Maryland doctor said, "Propofol is a wonderful drug, but there is no difference between the Baxter and AstraZeneca propofols. We'll buy the cheapest." An Alabama doctor said, "Most people are pretty much stuck on Diprivan, but price could drive use of a new product."

Several companies were thought to be working on a new propofol, but officials denied those rumors. These include:

- Teva Pharmaceuticals USA
- Roxane Laboratories. An official said, "We have no pain medications in development. We sold our pain franchise."

EXISTING PRODUCTS

ASTRAZENECA'S DIPRIVAN

Diprivan, the first in a new class of IV anesthetics, alkylphenols, was the first propofol on the U.S. market; it was FDA approved in 1989, and it remains the market leader. It is not indicated for use in Pediatric ICU sedation, but it is approved for:

- Induction of general anesthesia in adult patients and pediatric patients ≥3 years of age.
- Maintenance of general anesthesia in adult patients and pediatric patients >2 months of age.
- Intensive Care Unit(ICU) sedation for intubated patients.

Diprivan caught on quickly with anesthesiologists and post-op nurses because it reduced post-operative nausea and vomiting and shortened recovery time, all of which also increased patient satisfaction.

GENSIA SICOR'S PROPOFOL (marketed by Baxter)

GensiaSicor had manufacturing problems last year, but officials did not expect them to affect sales. A source predicted that Gensia could meet future demand, but only by emphasizing the larger vial sizes. A Gensia official said, "We figured we would have competition, but we didn't, so we had to ramp up in several places. First, we ramped up the line. We had issues in compounding (mixing things together), and we found we needed a new compounding suite to make larger batches, so we built that. Then, bottlenecks occurred in packaging and inspection, so we increased that. So, now we can service quite a bit. (In 2001) we did 15 million units, and I think that is where we will stay, but we can produce 16 million to 18 million units a year, so we could still ramp up a little. However, we can make substantially more by converting those units to larger vials."

Gensia offers propofol in three sizes: 20 ml, 50 ml and 100 ml. In 2001, GensiaSicor had 46% market share, selling 14.1 million units, with 800,000 units in the channel. Last year, the 50 ml SKU reportedly was on back-order for several months. The company claimed its propofol sales growth is mostly in the 100 ml size. A source said, "I'm hearing from the field that this is from anesthesiologists using propofol more often in longer-term sedation, where the larger vial size is used. At first, propofol was used mostly for outpatient surgery – quick surgeries like knee operations – but now it is being used for longer sedation."

This is particularly interesting since in March 2001, AstraZeneca sent a Dear Doctor reminding doctors that Propofol is not FDA-approved for sedation.

It is easier for Gensia to produce 100 ml vials, and they can produce more of these. A source explained, "We can make two batches of 100s in a single day, but only one batch of 20s. It is easier for us to produce bigger batches of 100s." Gensia is predicting that its unit sales will remain flat but volume will go up as more 100 ml vials are sold.

GensiaSicor's marketing contract with Baxter expires on January 1, 2005. The company probably will continue to have Baxter sell the product. A Gensia source last year said, "We and Baxter have to decide what to do. Baxter has been able to capture almost half the market the last couple of years. They did a good job, and they have strong relationships with

hospitals and GPOs. We haven't done the analysis to decide what to do, but if another product were coming out by 2005, we may want the Baxter muscle behind this. We always thought we would have competition, and it made sense to have their muscle in a competitive environment. We could still be in that position in 2005."

However, Gensia also has its own sales force, and it is bringing some products back in house. An official said, "Going forward, we really do want to build our own sales force, and long-term we want that control. And selling to hospitals and GPOs doesn't require a huge sales force. But we are happy, so internally there is more a feeling of 'Why rock the boat?' If we sell it alone, we would have a higher margin, but could we keep the market share?"

GENERIC/BRANDED GENERIC PRODUCTS IN DEVELOPMENT

Faulding/Mayne may have the next propofol on the U.S. market, and Abbott, Bedford, and Baxter all have ANDAs that are tentatively approved by the FDA, which means that they can market their products as soon as the AstraZeneca patent expires in 2015. There also has been speculation that one or more of these companies might try to launch its propofol prior to that time.

A Baxter official said he believes both Bedford and Abbott are going forward with their propofols – but not until the AstraZeneca patent expiration in 2015, "I thought they were both still plugging along. To me, they still have the products, but I haven't seen any evidence of them working on them. We (Baxter) have had a tentative ANDA approval since 1998 on an EDTA-preserved propofol for when the AstraZeneca patent expires in 2015, and we will decide then if there is any market and whether we should really introduce it. Bedford and Abbott both have tentative ANDA approvals. The Abbott tentative approval was with EDTA as a preservative, though Abbott could be working on another version."

ABBOTT

Abbott has filed an ANDA for a generic propofol, and it has not given up on that, though most sources thought it had, perhaps because it has been very quiet about it. An Abbott source said, "We're exploring our options to bring a generic propofol to market, but I haven't heard anything about it in some time. I confirmed our filing is still active with the agency (FDA), and we are in discussions regarding questions the FDA had." Another official said the company is still committed to this product, but there is no evidence that it intends to try to break the AstraZeneca patent and launch this before 2015, "This continues to be an area we are working on, but obviously we haven't done anything beyond a regulatory perspective…The timing is up in the air at this point, but the filing is still active."

Abbott has been very quiet about this product. An expert in the field commented, "We haven't heard anything about it. The company isn't saying anything, isn't answering any questions. It's as if the drug just dropped into a black hole." A Gensia official had thought Abbott ended development of propofol, saying, "At the end of 2000, Abbott was very, very vocal about its propofol, and we thought competition was coming in early 2001. Abbott sells propofol in other parts of the world, but I haven't heard about recently anything it coming here. Abbott was outing its product and then stopped. We heard that Abbott was working on benzyl alcohol as the preservative, and it has a patent on a benzyl alcohol/EDTA mix."

The reason for Abbott to enter the market would be product line extension, allowing the company to better bundle and bid products, not the profitability of propofol, a source speculated. A GPO source who was asked if his firm would be interested in a new generic propofol said, "We thought Abbott's propofol was dead, but Abbott came in and asked if they could get a contract for theirs. We said, 'No, we have a two-year exclusive agreement with Baxter.' Abbott has no reason to enter this market now because the price is so low, but Abbott may just want to do a line extension."

BAXTER

Baxter had a propofol in development, filed an ANDA for it, and was granted tentative approval in 1998. Then, Baxter acquired Wyeth's ESI Lederle division, which also had an ANDA application for a generic propofol. In December 2002, the FTC required that Baxter sell the propofol it got from Wyeth, and Baxter sold it to Mayne, an Australian company, which, in turn, turned it over to its U.S. subsidiary, Faulding (which will soon take the Mayne name).

Baxter still has its own propofol. This was described as "an exact generic equivalent of AstraZeneca's Diprivan," with EDTA as the preservative. However, this propofol will not be on the market until at least 2015, when the AstraZeneca patent expires, if at all. A Baxter official said, "The AstraZeneca patent expires in 2015, and we will decide closer to then if there is any market and whether we really want to introduce it."

Because this propofol is so far from market, it was impossible for sources to estimate manufacturing capability or costs. Strategic planning will begin when and if a decision is made to go ahead with this product. There are no partners at this point.

BEDFORD

Bedford is a subsidiary of one of the premier contract manufacturing firms, BenVenue Laboratories, which is a division of Boehringer Ingelheim. BenVenue is one of the premier contract manufacturing firms in the country, and it is experienced in developing and manufacturing liquid and lyophilized sterilized injectable products. The generic Drug firm Roxane is a sister company to Bedford.

Bedford filed an ANDA for a generic propofol, which resulted in the issuance of the Citizen Response notification to AstraZeneca in October 2001. There was speculation that Bedford had withdrawn its ANDA, but a Bedford official denied that. However, Bedford also does not have any plans at this time to try to market its propofol before AstraZeneca's patent expires in 2015. He said, "I'll be retired before we introduce propofol."

In line with this, sources at major GPOs said they have not been contacted by Bedford about the imminent introduction of a propofol, and they have no reason to believe that Bedford is preparing a propofol entry any time soon. Furthermore, no anesthesiologists questioned were aware of any ongoing studies by Bedford.

If and when Bedford does market propofol, it most likely would be manufactured by another Boehringer Ingelheim subsidiary, BenVenue. A Bedford official said, "BenVenue holds all the ANDAs and does all our manufacturing except one item (glycogen), and we are just the sales and marketing arm. We have no plans to expedite our propofol."

MAYNE/FAULDING

Officials of Faulding, which is owned by Mayne, an Australian company, said they expect to launch the propofol they got from Baxter/Wyeth **in the next 30 months** *at the latest.* They would not discuss the preservative used in this propofol, but an official did say, "We do have patent coverage for our product. None of the propofols in development are straight generics, including ours…In the rest of the world, there is no preservative, and usage is very specific to the procedure. In the U.S., it is slightly different. We plan to do more market research on why people are choosing that size. Was it price? And how are they using it?"

Mayne/Faulding has not decided where to manufacture its propofol, but the two leading options are: (1) their own plant in Puerto Rico, and (2) a contract manufacturing firm. Discussions about this are going on now. A Mayne source said, "Who will make our propofol is still to be determined. Actually manufacturing will not occur until 2005, so that can be decided later. We have a facility in Melbourne (Australia) that could do it, or we might do it in Puerto Rico." A Faulding source said, "Our intention is to achieve a certain (unspecified) market share and to make enough to serve that market share."

The focus of sales, at least initially, will be the U.S. market, but the company is not excluding international sales. "That's what we bought it for," a Mayne source said. "It fits well with our product portfolio that we have internationally, and it is one of our areas of core competence – oncology, anesthesia and cardiovascular." A Faulding official said, "We already have a propofol licensed in various markets, but some places we withdrew from because it got too competitive."

Sources said they don't know whether this product will expand the propofol market, and they expect the market to change over the next 30 months. An official said, "If you look at IMS usage on an individual vial basis, there is an increase in usage because there are more older people, more surgeries, more day procedures. So we think the market is expanding somewhat…And there is a move by doctors to more short-acting drugs…Use of propofol is pretty well established, so it will just be a marketing issue between us, Baxter (Gensia) and AstraZeneca."

Asked about the new formulations in development, including aqueous-based formulations, an official said, "That just makes more competition, assuming they are A/B rated or equivalent. Then, there is the issue of price. I'm not sure SkyePharma has the clout to sell their product here."

He also does not expect many competitors to enter this market, even after AstraZeneca's patent protection. He said, "When AstraZeneca's patent expires, there won't be 10-15 competitors. This is an injectable, and I think there will be only five or six competitors after the patent expires, and I don't think there will be that many before the patent expires."

Prior to its purchase by Mayne, Faulding had been working on sustained release formulations and liposomal formulations, but it is not known whether those efforts are still ongoing. In March 1995, Faulding and the Commonwealth Scientific and Industrial Research Organization (CSIRO), Australia's largest scientific research agency, agreed to collaborate on a new drug delivery technology invented by CSIRO. This liposomal drug delivery system uses lipids instead of sugars to deliver toxic drugs. Sources had little information on this technology, which may be referred to as Lipidation in Australia.

Faulding also was a leader in sustained-release technology. The company's sustained release morphine, Kapanol, was approved in Australia in 1994. It also was approved in the U.S., but it has not taken off very well here. Faulding had trouble marketing its Kadian pain reliever against Purdue's MS Contin, which had a more aggressive sales force than Faulding.

NEW FORMULATIONS IN DEVELOPMENT

At least three aqueous formulations of propofol are on the horizon by Guilford, Maelor and SkyePharma, though each uses a different approach.

GUILFORD

Guilford's Aquavan (PQ-1002, GPI-15715) is an injectable, water-soluble pro-drug of propofol. It is rapidly converted in the body into propofol after IV administration. Guilford acquired exclusive worldwide commercialization and development rights to this agent from ProQuest Pharmaceuticals Inc., a privately held pharmaceutical company based in Lawrence, Kansas. It is believed that Ricerca (of Painesville OH) is the contract manufacturer.

Guilford is going the branded generic route, not the generic route, with an NDA filing. A source said, "Any new formulation will be very expensive to develop, and won't be generic because it will have to have a preservative. And you have to do an NDA for a new formulation. If you just change the preservative, you don't have to do full drug development. Baxter never dosed a single person.

The Phase I program, which was conducted in Europe is completed. The results reportedly showed that Aquavan can "rapidly sedate patients within 45 minutes, with no pain at the injection site." This agent is designed to "help in the conscious sedation, general anesthesia and monitored sedation markets, with the hypnotic market the largest for Aquavan."

Phase II rapid-acting sedation trials are underway, in two phases. The first phase will determine safety, tolerability and optimal dosing for use during colonoscopies. The second phase will compare Aquavan to midazolam in 100 patients undergoing colonoscopy. Officials said Guilford has successfully completed a pre-IND review with the FDA. Guilford reportedly is shifting resources to focus on this product and has hired a "very experienced" anesthesiologist to direct the Aquavan program. An official said, " We are trying to find drugs that sell directly into the hospital/ICU marketplace with sales around $50 million."

Guilford hopes that the water-soluble formulation will give its propofol a better safety profile "by smoothing out some of propofol's very rapid actions when you give a quick dose or rapidly change the rate of administration."

Some of Aquavan's advantages over lipid-based propofols are expected to include:

- Increased ease of use.
- Improved stability.
- Reduced risk of bacterial contamination.
- Potentially fewer side effects such as elevated blood lipid levels (hyperlipidemia) and pain upon injection.
- Less pain. There reportedly is no pain with the Guilford prodrug. A researcher said, "We've taken the molecule and made it water soluble. The part that causes the pain is gone." Guilford has concluded that the pain experienced with current propofol formulations is due to the propofol and not the emulsion.
- Perhaps price. Guilford expects Aquavan to be cheaper to produce because the process is simpler than for Diprivan, perhaps giving it a pricing advantage.

Even Guilford officials do not expect Aquavan to completely replace Diprivan, especially in anesthesia induction, where Diprivan was described as "well-liked." A source said, "We see our drug used in other places where it would compete against midalozam (Versed) and Diprivan – for conscious sedation."

MAELOR

Maelor's Micelle Propofol is another aqueous formulation using a proprietary drug-delivery system (micellar delivery) for water-insoluble drugs (e.g., lipid emulsions). A micelle is an aggregation of polymers which attract one another to form an organized structure. These polymers are "amphiphilic" (i.e., they have a hydrophilic pole and a hydrophobic pole within the same chain.) The hydrophobic poles attract each other, thus forming the interior of the micelle. This interior environment can carry lipophilic substances, while the hydrophilic poles can allow the micelles to disperse in water. In this way, a micelle can be used to "solubilize" materials which have little or no solubility in water.

Micelle Propofol's claim to fame is likely to be the incorporation of lidocaine in the formulation, to avoid the pain of propofol injections. This could make administering the lidocaine easier (right now, anesthesiologists consider this a hassle). An official said, "We are taking one product forward with speed, which is propofol, a very widely used anesthetic agent, notorious for the complexity of its formulation, but which our team has been able to solubilize in a very elegant way. Propofol is therefore the forerunner of what we hope one day will be a large family of agents and we are hoping to inject intellectual property back into materials that are fundamentally off patent. The original protection has gone, but we are hoping to return a degree of protection to those technologies."

The timetable reportedly was:

- 2002 -- find a pharma partner. Maelor has worked with Teva on other agents, but had not, at last check, signed a deal yet with Teva on propofol.
- Late 2002 -- start a Phase III trial. It is uncertain whether this has begun yet.
- Late 2003 – submit to the FDA and European regulatory officials
- Mid-2004 – launch

Maelor was expected to go directly from Phase I to Phase III, skipping Phase II because this is a known product (propofol). Maelor cannot undertake the Phase III trials without a partner. It admittedly does not have the resources on its own.

The company reported that the Phase I data was "essentially comparable with Diprivan. A number of minor differences between Maelor Propofol and Diprivan were noted, with a suggestion that our product was associated with greater pain on injection, and marginally slower times to onset of anesthesia; however, our product appears to leave the patient in a better mental state after initial recovery, and was associated with less hypotension than Diprivan. Within the limitations of a Phase I study design, which precludes large-scale statistical analysis, it is clear that even in this prototype formulation our product has an efficacy and safety profile which is essentially similar to Diprivan…Importantly, this trial has confirmed that our delivery system is safe and effective in taking an insoluble product into an aqueous formulation without any loss in performance of the original compound. This gives us great confidence in the proprietary micelle delivery system, which can be applied to many other products."

Maelor expects that its agent will be approved for pediatric use. In August 2001, the European Committee on Safety of Medicines concluded that emulsion preparations containing propofol "should be contraindicated in children of 16 years and younger" due to reports of serious adverse events such as metabolic acidosis, hyperlipidemia and hepatomegaly. These side effects have been linked to infusion of large quantities of fat. Since Maelor's formulation contains no fat components, the company sees a potential role for its product in the pediatric population.

The Maelor formulation reportedly is thermodynamically stable (and therefore steam-sterilizable), easily formed, and microbially resistant. Manufacturing will be done by a contract manufacturer.

Maelor has patents on this technology – for the micelle system, for the formulation, and for a combination of propofol with lidocaine. A Maelor official, commenting on SkyePharma/RTP's patents (*see SkyePharma below*) said, "We have been aware of the RTP patents for some time, and I know that we reviewed them in depth before proceeding with our own patent applications. There is no technology over-lap at all with our micelle-based approach. This does not mean that we can discount RTP as a competitor, since there are usually several ways of achieving a given goal with drug delivery systems. We only have to consider the vast number of controlled-release mechanisms if we want proof of that principle."

Maelor's propofol, like all other propofols discussed in this report -- except the Guilford prodrug -- is associated with pain on administration, but Maelor has found a way to reduce this pain. According to Maelor: "Up to 70% of patients experience pain at the site of injection during the administration of Propofol. In an attempt to reduce this discomfort, clinicians routinely pre-mix the medication with lidocaine immediately prior to injection. The addition of lidocaine is recommended in official prescribing information for Propofol emulsions, although the materials must not be mixed until immediately before use, due to a fundamental incompatibility between the lidocaine and the emulsion carrier…It is now possible for us to incorporate local anesthetics such as lidocaine into the micelle formulation of Propofol during manufacture, thereby providing a formulation that will reduce the level of pain on injection, in addition to all the other benefits that our aqueous formulation has over the standard emulsion based formulation. We are therefore developing modified formulations, which will shortly be subjected to clinical study so that we can identify the most appropriate candidate formulations for Phase III study and final regulatory submission."

SKYEPHARMA/RTP PHARMA

A reformulated propofol, combining SkyePharma's nanoparticulate technology with RTP's Insoluble Drug Delivery (IDD) system, is being developed. It is in Phase IIb trials, with a 2005 target launch date. On December 31, 2003, SkyePharma granted Endo Pharmaceuticals exclusive U.S. and Canadian marketing and distribution rights to its Propofol IDD-D intravenous formulation of propofol to maintain anesthesia and sedation in surgery and intensive care settings. SkyePharma was to receive a $25 million upfront payment, up to $95 million in milestone payments, and a share of sales (starting at 20% of net sales and increasing to up to 60% if specific sales levels are met). ENDP is responsible for funding any post-marketing studies.

RTP has patents on technologies for compatibilizing propofol in aqueous formulations via the formation of phospholipid-stabilized micro droplets of propofol. However, Maelor officials believe this formulation should be considered like a conventional oil-in-water emulsion in which the propofol constitutes the dispersed "oil" phase, and therefore, they believe it will suffer from all of the problems associated with classic emulsion formulations.

An earlier (1998) trial of Amrad's IDD propofol (AM-149, which was licensed from RTP) was suspended just six days after it started and was then discontinued as an active project because of problems.

RTP has signed an agreement with Baxter, but that agreement does not make it clear whether Baxter is licensing the IDD technology for use with propofol. Rather, it is thought that Baxter is using the technology for other Baxter compounds.

THE INTERNATIONAL PERSPECTIVE

Several companies sell propofol outside the U.S., including AstraZeneca, Fresenius/Kabi, B. Braun and Schering Oy (a division of Schering AG). Fresenius/Kabi makes some of AstraZeneca's propofol.

Propofol sales continue to increase -- slowly -- as worldwide demand for propofol increases, and that is driven more by medical need for the product than by marketing efforts, sources generally agreed. A source said, "Propofol is increasing in use world wide and is gradually replacing older methods of anesthesia and sedation, such as inhalation.

Dr. Keith Anderson, a clinical lecturer in anesthesia at Glasgow University, doesn't believe any further useful developments can be made in the propofol area. He has commented, "We use propofol extensively, and it is extremely safe. It has very few side effects, and these are minor. You would be lucky to get an intravenous anesthetic that is better than propofol. I am confused as to why there is so much attention given to developing it further."

Dr. Anderson's department is a top research facility for propofol, and its head, Professor Gavin Kenny, is known worldwide for his work with propofol. This department collaborated with AstraZeneca to develop AstraZeneca's microprocessor-controlled syringe pumps, which are regarded as a convenient safety system for propofol delivery.

In Europe, propofol is almost impossible to deliver by hand because it involves complex mathematical calculations, sources explained. They said the AstraZeneca system prevents a stronger concentration than necessary being delivered. There are ID tags on the AstraZeneca syringes so that the machines recognize them and only that propofol can be used. These machines have been on the market since 1998 and are used all over the world except the U.S.

From 60%-70% of patients suffer from pain when propofol is injected, sources estimated. Most companies stress pain minimization strategies, such as warming the propofol or using a local anesthetic, but Braun officials believe their formulation causes less pain. A Braun official said, "We are successful because of our application techniques and our whole system." However, Dr. Anderson doesn't agree, "Just putting in a local anesthetic before injecting propofol, or warming the propofol, is quite effective. Patients only feel pain for a few seconds anyway."

One new use for propofol was announced at the dental school in Glasgow in January 2003: as a self-administering sedative for dental patients.

The price of propofol is much lower outside the U.S., because preservatives are not required elsewhere. The importance of price in determining market share for the various companies is a matter of debate. Leiras/Schering Oy's strategy for selling its propofols is based on competitive prices, quality reputation, delivery system and reliability. A source said, "Quality and reputation are important. We also made the first generic propofol after the (AstraZeneca) patent expired. I think this has given us the edge."

Braun officials said they do not consider price the key market driver for propofol. They cited reliability and marketing as the major sales factors. An official said, "To be known as a company, and to be known as reliable, is important."

In contrast, A Fresenius/Kabi official insisted that price drives the whole propofol market, "In hospitals, propofol now costs $.08 per ml, which is 50% less than it was three years ago." Instead, a source said Fresenius/Kabi's success has been due to its (1) long experience in lipid solutions, (2) longevity in the market, and (3) long-standing production for AstraZeneca, one of its biggest customers. A Fresenius official said, "We are strong. We have produced for AstraZeneca for a long time. We have long experience in lipid solutions, so customers know we understand the product and their needs." However, Fresenius/Kabi shipments to AstraZeneca have been declining. Two years ago, Fresenius/Kabi provided AstraZeneca with 20 million units, but this year only 4.5 million units are planned.

FRESENIUS/KABI

Fresenius/Kabi's international market share of propofol has been growing, sources claimed. In Germany, for example, it is 44% (approximately $38 million). The company has overtaken AstraZeneca in propofol sales in Germany and Austria. However, there are questions as to whether the international market for propofol is growing. One Fresenius/Kabi official said, "The propofol market is huge, but it's not growing. I think the generics -- with some modification to the formulation -- will be able to gain some market share. The European market may be growing slowly, but more units may not mean more revenue." Another official claimed the propofol market is growing.

Fresenius/Kabi will produce about 25 million units of propofol this year, including all sizes. This figure has increased each

year for the last two years. The company's current production capacity is 30 million units, which a source said could be reached within another two years. If further capacity is needed, the plant could add more filling lines and packing lines to increase production.

Fresenius/Kabi has been reorganizing its manufacturing facilities. The factories in Limoges, France, and Potenza, Italy, were sold, and the production facility in Stockholm and the infusion plant in the U.K. were closed. Manufacturing was restructured in Sweden, Germany, Asia and South Africa. Fresenius also made significant changes to its sales organization, completing the merger of the Fresenius pharma sales team with that of the sales employees taken over from Kabi in all countries.

There now are two plants that make propofol: the main one in Graz, Austria, and another in Uppsala, Sweden, which is brand new and just started producing propofol at the end of 2002. Production is not outsourced, except for the packaging of ampoules (but not vials) produced in Graz. However, the Swedish plant will be taking over propofol production from the Graz plant within a couple of years, and even that limited outsourcing will cease.

The production process reportedly is cheaper and more efficient in Sweden – because the plant there can make the whole product, from preparation through to packaging. A source explained, "This business is volume, not price, so you have to have capacity."

To start this shift in production, a few million units are expected to be sent from Graz to Uppsala for packaging by the end of this year. A source said that, even with the added freight costs, it is cheaper to do this than to package in Graz.

Fresenius/Kabi does not make propofol in PVC-free bags, only glass vials and glass ampoules. Plastics generally cannot be used for propofol, as the compound tends to diffuse into plastic materials, a source explained.

Fresenius/Kabi official said they are not seeing a trend to larger-sized vials or ampoules, as has been noted in the U.S. A source said, "It is much easier to have glass. And there is no trend for larger-sized vials or ampoules because they can't be stored properly. You can only use one ampoule per patient, and only 10% of our sales are the 100 ml size. The majority is 20 ml and 50 ml." Another official commented, "In the German market they want to switch from 20 ml ampoules to 20 ml small vials. The market wants it, maybe because of problems breaking the ampoule." A third source said, "I'm aware that people would fancy larger sizes, even 250 ml, but we are not happy (with that) because of issues of clinical safety. People would draw one dose from a larger bottle (and then store it for future use, whereas it should be for single use only), and that could have side effects. So we are reluctant to make them any bigger. Instead, people could use the 2% propofol and stick with the 100 ml size."

Fresenius/Kabi reportedly is investigating reformulations, rather than additional formulations. One source said the company is nowhere near developing a reformulation, but another official said that it is changing its formulation of the lipid emulsion part from LCT to MCT, and that will be on the market in May 2003. A source said the change of formulation is considered necessary because the current one can cause problems in some clinical conditions – e.g., if the patient gets too much lipid emulsion. The ultimate goal is to get rid of lipid emulsion in the propofol formulation altogether, but a source suggested that Fresenius/Kabi might decide that this would be too costly. "We are investigating alternatives to the current system. In some clinical conditions it causes problems. In ICU, lipid emulsion is delivered within artificial nutrition, but lipid emulsion is also the matrix for propofol, so the patient can get too much fat. We have to change the formulation, and we are looking to see if this is clinically and economically feasible. The ultimate goal would be to get rid of the lipid emulsion. Hypothetically speaking, it would take us two years from now to reach the clinical phase, but my colleagues might decide that it is not worth the money."

B. BRAUN

B. Braun separates its business into four sections, and propofol falls in its largest division, the Hospital Products Group. While B. Braun has parlayed its internal expertise and long history of customer service into market leading positions around the globe, the one geographic market that has remained elusive is the U.S. The company first entered the U.S. market in 1979, with the purchase of Burron Industries, a leading manufacturer of regional anesthesia kits and IV administration supplies, but Burron's line of products was too narrow and failed to take advantage of the scope and breadth of Braun's resources.

Three years ago, Braun acquired the McGaw IV solutions business. However, the company has had limited success in leveraging McGaw with its other niche products. It has been able to gain contracts and relationships with many leading groups, but primarily because of clinician demand for its market-leading regional anesthesia kits. Less successful have been attempts to extend those contracts and relationships to its other lines, including IV solutions. Indeed, the company actually has lost market share in IV solutions over the past couple of years, as a handful of leading GPOs have signed contracts with Braun's competitors.

Outside the U.S., Braun sells Propofol-Lipuro 1% (10 mg/ml) for induction and maintenance of general anesthesia (for patients over the age of 1 month), short-term sedation for surgical diagnostic procedures, and long-term sedation. It also sells Propofol-Lipuro 2% (20 mg/ml) for induction and maintenance of general anesthesia, short-term sedation for surgical diagnostic procedures, and long-term sedation of ventilated patients on propofol.

At this time, Braun has the only propofol with an LCT/MCT (long chain triglycerides/medium chain triglycerides) emulsion mix; the others only have LCT. While the pain level will never be zero with a lipid emulsion, this product has had "remarkable" success in reducing pain, compared to competitors' products, sources insisted.

Braun makes all of its own propofol in Melsungen, Germany, which is also the site of the company's headquarters; no production is outsourced. Braun has a partnership with Datex-Ohmeda and perhaps other companies, but those were not identified.

Germany is by far the largest market for Braun, and there is a big gap between market share there and in other countries. An official said, "We are much less important in other markets outside Germany. We have a huge product range and we have to set priorities. The product certainly deserves it and has potential."

No new formulations are believed to be in development by Braun. An official said the market would not pay more for propofol just for a reformulation or new formulation, and he pointed out that development costs are high. A Braun official said, "We are the cream of the crop and we don't have to go any further with the formulation than we have done already. Propofol isn't right for every patient in every situation, but to resolve that we need potentially new compounds, not a new propofol formulation. People will think twice before investing. $16 million is nothing when it comes to development costs, and it can take another ten years to recoup the costs. Most complicated surgery can be undertaken using propofol. We have reached the ceiling with it." Another official laughed at the idea of the market paying any more money for a reformulated propofol, adding, "The economic cost (of development) is high, and it can take up to nine years to get a product to market. We have a different formulation to others anyway."

SCHERING OY (formerly Leiras Oy)

Leiras Oy of Finland changed its name to Schering Oy on March 1, 2003. Schering Oy (a division of Schering AG) produces its own propofol – Recofol and Ivofol; it does not outsource manufacturing. Currently, Recofol and Ivofol are still being produced under the Leiras name, and generic propofol is produced at the same plant but under the Schering Oy name. Sources said that generic propofol is then sold to more than 40 third party distributors for sale under various brands around the world. Schering Oy has a marketing agreement with Dexa Medica to sell its Recofol (propofol) in Europe. In China, its propofol is sold exclusively by PUMC Pharmaceutical Co. Leiras/Schering Oy officials claim to have many other partners world-wide, primarily pharmaceutical companies to whom they supply propofol.

Company officials claimed propofol production is keeping up with demand, and Schering Oy reportedly has the capacity to boost production if world demand increases. A source said, "As a world player we are quite small, but we do supply at least 40 customers world wide with generic propofol."

Sources suggested that new marketing strategies may be instituted now that the company is under the Schering name. One said, "Now that Leiras is Schering, a very big name in German-produced pharmaceuticals, there might be some changes to marketing and (some) thoughts on how we might increase market share of propofol." Another source said, "Perhaps we will see some changes in marketing as well as changes in name, but at the moment it is not possible to say. I think that propofol has been very successful, and that is due to excellent quality and excellent company policies."

According to sources, Schering Oy has no current plans to release new formulations of propofol. In Finland, propofol is only approved for induction and maintenance of sedation and anesthesia, sedation during surgical and diagnostic procedures and sedation of ICU patients.

The core competency areas of Schering/Leiras has been prevention and therapy of coronary disease, women's health and flu ***and pain.*** However, a source said Leiras' strategic focus is on prescription pharmaceuticals, self-care products and consumer health products. Leiras/Schering has approximately 40 sales representatives operating in Finland. "Our aim is to attract new business partners…We have a solid and strong foundation for further growth in the total Nordic area," an official said.

There has been speculation that Leiras could use its polymer-based delivery system in the future to deliver Refecol, but there is no evidence they plan to do this. Furthermore, a senior expert in polymer technology for another, non-competitive firm does not think this is likely. Polymer-based delivery could be good for post-surgical pain management, he pointed out, but not for anesthesia. He reviewed Leiras technology and concluded this speculation is fantasy.